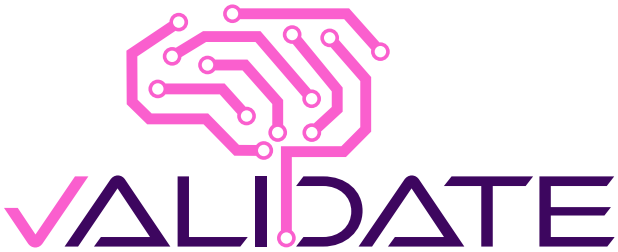

DELIVERABLE

Project Acronym: **VALIDATE**

Grant Agreement number: **101057263**

Project Title: **"Validation of a Trustworthy AI-based Clinical Decision Support System for Improving Patient Outcome in Acute Stroke Treatment"**

D4.1 – Study Initiation Package

Revision: 1.0

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Dissemination Level		
PU	Public, fully open	x
CO	Confidential, restricted under conditions set out in Model Grant Agreement	
CI	Classified, information as referred to in Commission Decision 2001/844/EC	

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Revision History, Status, Abstract, Keywords, Statement of Originality

Revision History

Revision	Date	Author	Organisation	Description
0.1	06.07.2022	Marta Rubiera	VHIR	Research protocol draft
0.2	19.06.2022	Marta Rubiera	VHIR	Study description
0.3	04.10.2022	Marta Rubiera	VHIR	Informed consent; preparedness status
1.0	30.10.2022	Malte von Tottleben	Empirica	Final editorial review

Date of delivery	Contractual:	31.10.2022	Actual:	31.10.2022
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Abstract (for dissemination)	Artificial intelligence (AI)-powered prognostic tools and clinical decision support systems can predict the outcome of certain diseases based on a multitude of patient data at high speed, facilitating decisions by healthcare professionals. In acute ischemic stroke, the overall treatment effect and population-wide outcome benefit of treatments such as IV thrombolysis and mechanical thrombectomy are well established. However, in individual patients it is difficult to predict the prognosis in the acute phase of stroke: some patients are candidates for these treatments, but may have poor clinical outcomes (no improvement of stroke or even worsening). Our aim in this study is to validate an artificial intelligence (AI)-based prognostic tool to provide accurate real-time outcome prediction in patients with acute ischemic stroke. During the study, all patients admitted to the emergency room with an acute ischemic stroke will receive the usual treatment for acute stroke in accordance with the stroke neurologists in charge. A “shadow” clinical researcher, without interaction with treating physicians, will collect the data required by the AI model in vivo. These data will be obtained by filling in clinical data through an App on a hospital mobile/tablet, and by a connection with your electronic medical record. The AI models will estimate the outcome of an acute stroke patient, and this prediction will be compared with the real outcome of the patient after 3 months of follow-up. This document presents the first draft of the study initiation package of the study “Validation of a Trustworthy AI-based Clinical Decision Support System for Improving Patient Outcome in Acute Stroke Treatment””. The study aims to develop a demonstrator to provide accurate prognosis for acute ischemic stroke patients during the hyperacute phase. It has a preclinical phase with the development of the artificial intelligence (AI) models based on retrospective data, and a prospective phase to test these models in real time through a prospective multicenter shadowing observational non-

	interventional study. The predicted outcomes of the patients will be compared with real clinician and patient reported outcomes (PROs and CROs). Here we provide the protocol of the clinical study, the information form and informed consent form for patients/families and the interaction with the Institutional Review Board (IRB) in the different international centers. Now, an IRB approval from the pre-clinical retrospective study has been received, and we are waiting for the complete (pre-clinical and prospective data) IRB approval. The clinical study is also being evaluated for registration in clinicaltrials.gov.
Keywords	Artificial Intelligence, Acute Stroke, Prognosis, Prediction

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation, or both.

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Executive Summary

Background

Artificial intelligence (AI)-powered prognostic tools and clinical decision support systems can predict the outcome of certain diseases based on a multitude of patient data at high speed, facilitating decisions by healthcare professionals. In acute ischemic stroke, the overall treatment effect and population-wide outcome benefit of IV thrombolysis and mechanical thrombectomy are well established. However, the outcome still differs significantly for individual patients, where some are eligible for treatment but may have catastrophic outcomes. Multiple prognostic variables and their combination in a single patient make it difficult to predict individual outcomes after stroke treatment. We aim to validate an AI prognostic tool to provide accurate outcome prediction in patients with acute ischemic stroke in a prospective observational follow-up study.

Hypothesis

AI-based models can be applied in real-time in acute stroke patients and provide an early accurate prediction of their outcome.

Objectives

Primary objective: to demonstrate that the application of AI models in real-time patients with acute ischemic stroke accurately predicts the functional outcome of patients measured by the modified Rankin scale (mRS) at 3 months (trichotomized into the following categories: 0-2, 3-4 and 5 -6)

Secondary objectives:

- Evaluate the accuracy of AI models to predict additional predefined clinician and patient reported outcomes (CROs/PROs)
- Demonstrate the feasibility of applying AI models in real life: AI-based forecast synchronization, problems with system integration, ...

Methodology

The study complies two phases.

Phase 1: retrospective study

While technological readiness will be achieved for the clinical validation study further model refinement on heterogeneous data will be performed based on existing models that have been developed on extensive high-quality medical data. VALIDATE will analyze retrospective databases from the 3 clinical sites involved in the study to test and validate the previously generated AI models. Encrypted data of all acute ischemic stroke patients admitted to the centres during 2018-2021 period will fed the AI models to validate the model's accuracy comparing the outcomes predicted by the AI modelling with those of the actual patients. The dataset includes demographics, baseline clinical characteristics, risk factors, neuroimaging data, acute treatments, clinical evaluation (National

Institute of Health Stroke Scale (NIHSS)), functional evaluation at 3-6 months (mRS), patient reported outcome measures (PROMs), etc. The interaction between these data sets and the AI models will be done through a federated learning procedure, that is, the data will be analyzed on our hospital servers, and they will not be transferred to any other center.

Grading the contribution of the progressively complex diagnostic procedures to the AI models and establishing a set of the minimum relevant variables for the AI model able to accurately predict functional outcome will also be achieved.

Phase 2: Prospective multicenter observational shadowing study

Consecutive acute stroke patients admitted to 3 high-volume comprehensive stroke centres will be evaluated. All patients will receive the usual stroke work-up and standard of care treatment according to the treating physicians. A shadow clinical researcher with no interaction with the treating physicians will recollect in vivo the data required by the AI modelling. These data will be obtained by filling of clinical data through an app and by connection with the electronical medical record of the patient to obtain additional baseline and neuroimaging data. The real outcomes of the patients will be measured through CROMs and PROMs, and they will be compared with the estimated outcomes according to the AI model. PROMS after 7 days, 1 and 3 months will be obtained through the implementation of an innovative nudging-based digital platform (NORA) to improve patient-clinician communication and follow-up. An eCRF will be designed to recollect KPI and CROMs, which will be integrated in the NORA platform.

The **subjects** of the study will be consecutive acute ischemic stroke patients admitted to 3 comprehensive stroke centres during 1.5 years of recruitment.

Inclusion criteria: Subject is 18 years of age or older, or of legal age to give informed consent per state or national law**; i**nformed consent for the use of data, obtained from patient or his or her legally designated representative (if locally required). Given the observational characteristics of the study, inform consent can be obtained any time during follow-up (before the data inclusion in the eCRF)

Exclusion criteria: Neuroimaging (CT/MRI) with signs of acute intracranial haemorrhage; **s**erious, advanced, or terminal illness with anticipated life expectancy of less than 3 months; unlikely to be available for 90-day follow-up (e.g., no fixed home address, no telephone, etc.)

The **sample size** calculation has been based on the results of a clinical dataset of consecutive code stroke patients admitted to Hospital Vall d'Hebron during the year 2020. It has been used as an example of the usual mRS distribution at 3 months in a cohort of consecutive acute stroke patients.

In a test for agreement between two raters using the Kappa statistic, a sample size of 182 subjects achieves 95% power to detect a true Kappa value of 0,7 in a test of H0: Kappa = κ0 vs. H1: Kappa ≠ κ0 when there are three categories with frequencies equal to 0,58, 0,34, and 0,08. This power calculation is based on a significance level of 0,05 and a minimum acceptable kappa (κ_0) of 0.6 (moderate

agreement) and an expected kappa (κ_1) of 0.8 (substantial agreement). Assuming a drop-out rate of 20% for the 90-day follow-up the Dropout-Inflated Expected Enrolment (DIEE) Number would be 218 patients with acute ischemic stroke.

1 Description of the clinical study

Title: Validation of a Trustworthy AI-based Prognostic Tool for Predicting Patient's Outcome in Acute Stroke

1.1 Study rationale

Our aim is to validate a prognostic tool based on artificial intelligence (AI) models to provide accurate outcome prediction in acute stroke patients in a prospective observational shadowing study. The hypothesis of the prospective clinical validation study is that AI-based models can be applied in real-time in acute stroke patients and provide an early accurate prediction of their outcome.

To validate this hypothesis, consecutive acute stroke patients admitted to 3 high-volume comprehensive stroke centers will be evaluated. All patients will receive the usual stroke work-up and standard of care treatment according to the treating physicians. A shadow clinical researcher with no interaction with the treating physicians will recollect in vivo the data required by the AI modelling. These data will be obtained by filling of clinical data through an app and by connection with the electronical medical record of the patient to obtain additional baseline and neuroimaging data.

The real outcomes of the patients will be measured through CROMs and PROMs, and they will be compared with the estimated outcomes according to the AI model.

All hospitals involved in VALIDATE are fully aligned with the Stroke Action Plan for Europe 2030 and follow the ESO clinical guidelines for stroke management, rehabilitation, and recurrence prevention.

1.1.1 Extent and evaluation of current knowledge directly linked to the scientific question(s) to be answered by the clinical study

Machine learning (ML)-enabled AI methods are increasingly adopted in the medical field. In certain areas, such as image segmentation and image diagnostics, they have far surpassed traditional methods and improved performance compared to physicians. With the increasing quantity and availability of medical data, AI-powered Prognostic Tools and Clinical Decision Support Systems (CDSS) also enjoy growing popularity. These novel tools have the capacity to predict outcome in given diseases based on a multitude of patient data at much greater speed facilitating the decisions made by healthcare professionals. Prognostic tools have the potential for safer, faster, more accurate, and evidence-based individualized treatment stratification, improved patient outcomes, and the cost-effective utilization and allocation of health care resources. Prognostic tools can be adapted to the available data and can be deployed in different levels of healthcare. With this, technological innovation will not only reach the top medical centres but potentially can be scaled to more basic hospitals, e.g. in rural areas within the European Union.

A highly promising approach is to develop, test and validate AI-based prognostic tools when stratifying patients for stroke treatment. There is great potential to go beyond the current clinical state-of-the-art as AI excels at finding complex and non-linear relationships across a multitude of prognostic variables for a multitude of patient sub-populations. The field of stroke could highly benefit from the introduction of AI-based prognostic tools and clinical decision support systems.

Current international guidelines recommend endovascular treatment with mechanical thrombectomy in conjunction with i.v. -tPA (recombinant tissue-type plasminogen activator) for the treatment of patients with acute ischemic stroke (AIS) caused by large vessel occlusion (doi: 10.1161/STR.0000000000000211). Overall patients benefit from this treatment approach – often defined as good functional outcome with a modified Rankin Score 0-2 at 90 days post stroke -, but, according to recent randomized controlled trials, only 33% to 71% of patients have this favourable outcome and there are also risks associated with the endovascular procedure (doi: 10.1016/S0140-6736(16)00163-X). Furthermore, outcome still differs significantly for individual patients, where some

patients are eligible for treatment but still can show catastrophic outcomes. Multiple prognostic variables and their combination in a single patient makes individual outcome prognosis after stroke treatment difficult. Predicting which patient benefits from mechanical thrombectomy could improve personalized stroke care and minimize risks while also reducing treatment costs.

Outcomes (efficacy, safety) of completed and number of ongoing clinical studies utilizing the same intervention in the same indication (including review of public registers)

Some examples of retrospective prognostic tools based in AI models are depicted below:

- A machine-learning approach using advanced imaging characteristics before treatment as well as angiographic treatment data and postinterventional clinical and imaging characteristics was used to measure patient outcome (favorable outcome: mRS-90 ≤2 versus unfavorable outcome: mRS-90 >2) of 246 consecutive patients with acute ischemic stroke (AIS) and large vessel occlusion (LVO). The most important parameters resulting in best predictive performance (area under the receiver operating characteristics curve, 0.856 [95% CI, 0.850-0.861]; accuracy, 0.804 [95% CI, 0.799-0.810]; P<0.001) were National Institutes of Health Stroke Scale (NIHSS) score after 24 hours (importance =100%), premorbid mRS score (importance =44%) and final infarction volume on postinterventional CT after 18 to 36 hours (importance =32%). Baseline parameters could only achieve a more moderate predictive performance with an AUC of 0.740 (95% CI, 0.733-0.747) and an accuracy of 0.711 (95% CI, 0.705-0.717)(doi: 10.1161/STROKEAHA.120.030287)
- Another study of 198 patients with AIS due to LVO defined malignant profiles based on Diffusion-Weighted Imaging Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) and Ischemic Core Volume outcomes that have poor response to reperfusion therapy. The unfavorable outcome was defined as a mRS score 5 to 6 at 90 days (area under the curve 0.78, P<0.01; sensitivity 0.71, specificity 0.75) and 71 mL (area under the curve 0.80, P<0.01; sensitivity 0.76, specificity 0.77 (doi: 10.1161/JAHA.119.012558)
- A study on AIS patients from the MR CLEAN thrombectomy study tested different machine learning algorithms and logistic regression models for prediction of reperfusion and functional outcome. All performed poorly in predicting good reperfusion (range mean AUC: 0.53–0.57), and moderately in predicting 3-months functional independence (range mean AUC: 0.77–0.79) using only baseline variables. All models performed well in predicting 3-months functional independence using both baseline and treatment variables (range mean AUC: 0.88–0.91) with a negligible difference of mean AUC (0.01; 95%CI: 0.00–0.01) between best performing machine learning algorithm (Random Forests) and best performing logistic regression model (based on prior knowledge)(https://doi.org/10.3389/fneur.2018.00784)
- Another study included a total of 1,735 patients from 7 hospitals in China. Incorporating age, NIHSS score at admission, premorbid mRS, fasting blood glucose, and creatinine, they found similar predictive performance between different machine-learning models (AUC 0.85-0.86). The AI models were significantly better than known prognostic scores based on logistic regression models (HIAT score, THRIVE score, and NADE nomogram)(https://doi.org/10.3389/fneur.2020.539509)
- Using clinical assessments as well as post-acute treatment image-based biomarkers of 221 subjects pooled from two prospective trials, another group developed nested regression models to predict the 30-days mRS outcome based on clinical data and image-based biomarkers. Combining clinical and imaging data resulted in a better prediction of 30-day mRS, predicted as the exact value, as sliding-window (+1 value of mRS) and as a dichotomous variable (mRS 0-2 or 3-6) (accuracies of exact accuracy of 55.88%, sliding-window accuracy of 82.35%, and binary accuracy of 85.35%)

In conclusion, these previous experiences showed improved accuracy than classical predicting scales based on logistic regression analysis, with areas under the curve (AUC) ranging from 0.7-0.8, using

dichotomic predictions of poor and good outcomes (according to modified Rankin scale (mRS) at 3 months). To date, there are not previous studies of prospectively acquired data of early prediction of outcomes of acute stroke patients in real time based on multimodal AI models.

1.1.1.2 Level of evidence related to the mechanism of action of the intervention in the planned clinical study population

Given the lack of previous prospective studies, we only may estimate an accuracy of our AI models at least similar to those of the referred retrospective studies.

However, after the development of the AI models, clinical and neuroimaging data required for the prediction will be defined. Before the initiation of the clinical study, we plan to analyze retrospective databases from the 3 clinical sites involved in the study to test and validate our own AI models: a retrospective study will then be performed with the available data required for the models, extracted from the electronic medical records (EMR) of 3 high volume comprehensive stroke center (2 Europe, 1 Israel). Encrypted data of all acute ischemic stroke patients admitted to the centers during 2018-2021 period will be prepared by the IT department of each hospital. Interaction between these datasets and the AI models will be performed through an API.

The objectives of the retrospective study will be:

- To validate the model accuracy comparing the outcomes predicted by the AI modelling with those of the actual patients
- To gradate the contribution to the AI model prediction of the progressively complex diagnostic procedures in acute stroke patients (i.e non-contrast CT, CTA, CTP,..)
- To establish a set of the minimum relevant variables for the AI model able to accurately predict functional outcome. These variables will be required to define the dataset to recollect in the prospective study

After this preliminary evaluation we will have our estimation of the accuracy of our own AI models, to test them in real-life scenarios.

1.2 Objectives of the clinical study

The objectives of the prospective study will be:

- Primary objective: to demonstrate that the application of AI models in real-life acute stroke patients predicts accurately the functional outcome of the patients measured by the mRS at 3 months (trichotomized in the following categories: 0-2, 3-4 and 5-6)
- Secondary objectives:
  - To evaluate the accuracy of the AI models to predict additional pre-defined outcomes (clinician reported outcomes (CROs)/ patient reported outcomes (PROs))
  - To demonstrate the feasibility of application of the AI models in real life: timing of AI output, problems with system integration,...

1.2.1 Outcomes and key performance indicators

To determine the objectives fulfillment, the following outcomes/key performance indicators (KPI) will be measured:

1. Acute process KPI: door-to-needle and door-to-puncture times
2. AI model integration KPI: timing of AI model output, integration problems..

3. CROs measurements (CROMS):
    a. 24h and discharge National Institute of Health Stroke Scale (NIHSS)
    b. In-hospital mortality
    c. 3-month modified Rankin Scale (mRS) score

4. PROs measurements (PROMS)
    a. PROMIS-10: Patient Reported-Outcomes Measurement Information System (PROMIS-10) comprises PROMIS-10-PHY to assess physical function, pain, fatigue and general health perception; and PROMIS-10-M to assess emotional distress, social health and general health perceptions. This KPI has been validated by interviews with patients and families and accurately reflects and is related to patient well-being.
    b. HAD: Anxiety and Depression Scale (HADS) provides information about anxiety (HADS-anxiety) and depression (HADS-depression). HADS offers clinicians an acceptable, reliable, valid, and easy-to-use practical tool to identify and quantify depression and anxiety.
    c. EQ-VAS: The EuroQol visual analogue scale (EQ VAS) records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

These 3 PROMS are in concordance with ICHOM (International Consortium of Outcomes, a non-profit institution aimed to define health outcomes and establish benchmarking between international institutions), and will be recorded within 7 days from discharge, 1 month and 3 months after stroke.

In addition to these preselected PROMS, once the prospective clinical trial has started, we will involve our partner SAFE to define needs from specific subgroups of stroke patients to avoid inequalities. Each clinical centre will also engage expert stroke patients and families to identify and cover local patient needs from the physical, psychological, mental and social perspective. These will be multidisciplinary meetings, including also different health-carers along the stroke-care pathway (including nurses, rehabilitation physicians, physiotherapists, social workers, etc) that will provide with additional PROMs to add to our protocol.

1.3 Study population

All consecutive acute ischemic stroke patients admitted to 3 clinical high-volume comprehensive stroke centers (2 in Europe, 1 in Israel) will be analyzed during the 1.5 years of recruitment.

1.3.1 Inclusion and exclusion criteria

Inclusion criteria

- Subject is 18 years of age or older, or of legal age to give informed consent per state or national law
- Informed consent for the use of data, obtained from patient or his or her legally designated representative (if locally required). Given the observational characteristics of the study, inform consent can be obtained any time during follow-up (before the data inclusion in the eCRF)

Exclusion criteria

- Neuroimaging (CT/MRI) with signs of acute intracranial hemorrhage
- Serious, advanced, or terminal illness with anticipated life expectancy of less than 3 months
- Unlikely to be available for 90-day follow-up (e.g. no fixed home address, no telephone,..)

Subjects can withdraw informed consent at any time during the study. If revocal of informed consent is performed after the anonymization process, the already acquired data of the patient will not be deleted in order to ensure validity of the study.

Sites should make multiple attempts (through NORA and/or telephone contact) in order to contact the subject for their 90 days outcome evaluation. In case the patient is lost to follow-up this will be documented and possible reasons, if known, will be recorded.

1.3.2 Sample Size and power calculation

Cohen's Kappa Statistic is normally used to measure the level of agreement between two raters who each classify items into mutually exclusive categories. To validate the hypothesis that AI-based models can be applied in real-time in acute stroke patients and provide an early accurate prediction of their outcome in this study, raters will be defined as:

a: prospective clinical data
b: prediction of AI-based model output

We will compare the ratings in three categories:

Category 1: 90-day mRS 0-2
Category 2: 90-day mRS 3-4
Category 3: 90-day mRS 5-6

The sample size calculation has been based on the results of a clinical dataset of consecutive acute stroke patients admitted to Hospital Vall d'Hebron during the year 2020. It has been used as an example of the usual mRS distribution at 3 months in a cohort of consecutive acute stroke patients, as shown in Table 1.

90-day mRS	**0-2**	**3-4**	**5-6**
Absolut numbers	236 patients	136 patients	33 patients
Proportion	58,27%	33,58%	8,14%

Table 1 Scenarios used for sample size planning

In a test for agreement between two raters using the Kappa statistic, a sample size of 182 subjects achieves 95% power to detect a true Kappa value of 0,7 in a test of H0: Kappa = κ0 vs. H1: Kappa ≠ κ0 when there are three categories with frequencies equal to 0,58, 0,34, and 0,08. This power calculation is based on a significance level of 0,05 and a minimum acceptable kappa (κ0) of 0.6 (moderate agreement) and an expected kappa (κ1) of 0.8 (substantial agreement). Assuming a drop out rate of 20% for the 90 day follow-up, the Dropout- Inflated Expected Enrollment number would be 218 patients with acute ischemic stroke.

For the sample size calculation the R statistical software package "kappaSize" (https://rdocumentation.org/packages/kappaSize/versions/1.2) was used.

After the analysis of the application of out AI models to the retrospective dataset of patients from the 3 clinical sites (described in 1.1.1.3), we will have a better estimation of the accuracy of our AI models, which will be used to adjust our sample size if necessary.

1.4 Design of clinical study

We will perform a prospective multicenter shadowing observational non-interventional study. Given the lack of evidence of the AI models real-time prediction at the moment, and the resistance of physicians to accept treatment recommendations based on IA modelling, we consider that a non-interventional study, with a clinical researcher acting as a shadow of the treating physicians, would be the most appropriate approach. The standard of care procedures for acute stroke patient pathways will be followed.

1.5 Type of intervention

Given the observational nature of the study, no invasive intervention will be performed to patients included in the study, who will receive conventional acute stroke management following international guidelines. However, patients will be offered to download the NORA mobile application as a tool for outcomes recollection. The NORA app and web platform allows communication with clinical and research staff, and health-care education (as described in paragraph 1.6).

1.6 Description and timing of study procedures

Consecutive acute stroke patients will be recruited in the emergency departments of the 3 clinical sites during 18 months.

During the recruitment period, a shadow researcher will accompany the clinical physicians taking care of hyper-acute stroke management. The researcher will register a screening log of all acute strokes arriving to the clinical sites. Those patients who fulfil the inclusion and exclusion criteria will be initially recruited. On-time data recollection of the pre-specified dataset required for the AI models will be recollected by the shadow researcher through an app. Communication through an API to the electronical medical record will also occur, allowing past medical history or neuroimaging data immediate transfer if needed by the AI models. With these multimodal data, an early outcome prediction will be obtained (which will not be shared with the treating physicians).

After the hyperacute stroke phase, patients will receive information of the clinical study by the study investigators, and those patients who sign the informed consent will be definitively included in the study. Where admitted by the Ethics Committee and local laws, a next-of-kin or legal representative may receive and sign the informed consent if the patient is not able to receive the information because of his/her clinical condition. However, if the condition of the patient improves later-on, a re-consent will be required. Only data from those patients with signed informed consent will be included in the eCRF.

Patients who consent to be included in the study will be trained to download and use NORA, an innovative nudging-based digital platform to improve patient-clinician communication and follow-up.

Our technological solution NORA, developed and implemented at VHIR, is an evidence-based tool that provides a holistic approach for improving vascular risk factor control (informative videos, specific diets, physical activity measurement), and treatment adherence, promoting behavioural changes towards healthy lifestyle (nudging) and enhancing patient engagement (alarms for treatment compliance and chat/video-calls between patients and health care providers). It also provides tele-occupational therapy, guided by rehabilitation physicians, to promote return to previous activities or adaptation to disabilities after hospital discharge.. Clinicians and patients/caregivers will be trained on demand and will be continuously supported by VHIR.

In addition, NORA will capture PROs through pre-specified validated scales at baseline, 7-day, 1 month and 3 months after stroke. These results will be integrated into the electronic medical record of each hospital.

In cases when the patient, caregivers or next-of-kin do not have a smartphone to discharge the NORA app, PROMs will be recollected by phone contact by the outcome managers.

The electronic case record file (eCRF) is integrated within the platform NORA. Once the data required for the AI models (demographics, basic clinical characteristics, acute stroke characteristics, neuroimaging data…) will be exactly defined after the pre-clinical retrospective study, they will be incorporated in the eCRF within NORA. The data recollected during the acute treatment phase from the shadow researcher will be transferred to the eCRF, together with KPI and CROMs. PROMs acquired through NORA will automatically be transferred to the eCRF too. An anonymization process will be

later performed to avoid identifiable patient data be shared through our planned open science protocol.

Patients will receive 5 visits: screening, 24 hours, discharge, 1 month and 3 months (final visit) (Figure 1). After discharge, the visits will be virtual through NORA platform or by phone, through a pre-defined accepted interview by mRS-certified researchers.

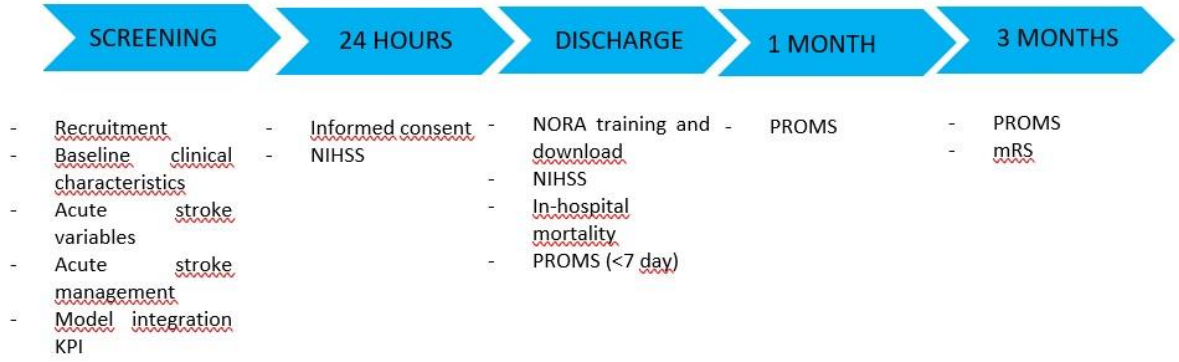


Figure 1 Schematic procedures of the clinical study

2 Preparedness status

Title: Validation of a Trustworthy AI-based Prognostic Tool for Predicting Patient's Outcome in Acute Stroke

2.1 Development of the clinical study protocol

2.1.1 Scientific advice from regulatory and health technology assessment bodies

Continuous advice has been provided for regulatory matters by the Johner-Institut, Konstanz, Germany and by pre-submission inquiry both from the FDA and respective European notified bodies (TÜV, etc.)

2.1.2 Clinical efficacy, safety, and methodological guidelines

We have followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (https://doi.org/10.1161/CIRCULATIONAHA.114.014508; doi:10.7326/M14-0698) for the design of the study.

All 3 clinical sites follow American Heart Association and European international guidelines for the management of acute stroke patients.

2.1.3 Involvement of citizens / patients, carers in drawing up the clinical study protocol

The engagement of stroke patients, families and stroke patients' associations in the design and performance of the clinical study is crucial. This project aims to early engage patients as their feedback can be a differential point to guarantee improving high-value care.

In value-based health care, the new paradigm of health care which we have adopted, the objective is improve the outcomes that really matter to patients. Even if our main objective is based on a clinician-reported outcome (mRS at 3 months), we plan to measure patient reported outcomes (PROMs) in our series, and our AI models will also give prediction of PROs.

To date, we have included in the protocol some PROs to recollect based on ICHOM (International Consortium of Health Outcomes Measurement) recommendations. ICHOM is a non-profit organization, conformed by patients, carers and clinical experts, that has defined a set of PROMs for different health problems that matter most to patients and carers. In addition to these preselected PROMS, we will involve our partner SAFE (Stroke Alliance for Europe) to defined needs from specific subgroups of stroke patients to avoid inequalities. Each clinical center will also engage expert stroke patients and families to identify and cover local patient needs from the physical, psychological, mental and social perspective. These meetings will provide with additional PROMs to add to our protocol.

With the involvement and continuous contribution of SAFE and the communication with patients, family members by the outlined interviews and surveys we will ensure that the patient is at the center while designing the clinical study protocol. We will explicitly focus on patient rights, autonomy and data safety and security.

2.2 Regulatory intelligence

2.2.1 Regulatory expertise to get advice on, and management of, regulatory affairs activities in all concerned jurisdictions

With the Johner-Institut, Konstanz, Germany we have a renowned and excellent partner both for continuous advice during the course of the project and in close collaboration with regard to outreach

to the notified bodies within the European Union and other regulatory bodies such as the FDA, to ensure timely regulatory approval and ethics clearance of the clinical study in all jurisdictions.

2.2.2 Ethics expertise on current proceedings and documentation requirements of all concerned ethics committees

During the course of the project, we will ensure through a variety of measures the adherence to ethical guidelines in the context of AI integration in healthcare.

For outside advice on ethics, we have as an advisory board member Prof. Effy Vayena, ETH Zurich/Harvard who is a renowned expert on ethical implications of AI in healthcare

At the moment, an Institutional Revisory Board (IRB) approval from the pre-clinical retrospective study has been received from the Ethics Committee from the Hadassah Medical Organization in Israel. We are waiting for the complete (pre-clinical and prospective data) IRB approval from the VHIR CEIm in Barcelona.

2.3 Scientific and operational governance

2.3.1 Sponsor(s)

The sponsor is the VALIDATE consortium represented by the clinical institution coordinating the pre-clinical (retrospective) and clinical (prospective) studies, the Fundació Hospital Universitari Vall d'Hebron – Institut de Recerca (VHIR) in Barcelona, Spain

2.3.2 Composition, role and the functioning of the governing bodies.

Each clinical center has a study board conformed by a clinical stroke expert (local Principal Investigator, PI) and a trained in stroke researcher. The PI from the clinical sites are:

- Dra. Marta Rubiera, Hospital Universitari Vall d'Hebron – VHIR
- Prof. Ronan Lecker, Hadassah-Hebrew University Medical Center (HMC-SU)
- Prof. Martin Bendszus, Universitätsklinikum Heidelberg (UKH)

The PI will oversee the patient's recruitment, follow-up and data acquisition (KPI and CROMs) and eCRF fulfilment. The stroke researcher will oversee the PROMs recollection through NORA and communication with patients/caregivers.

Periodical meetings between local study board and staff will be established to monitor study evolution and early identification of problems.

In addition, a clinical research organizer (CRO) will be hired to monitor the global accomplishment of the multicenter study. Periodical on-line meetings between local study boards and CRO will be scheduled. The CRO will be in charge of the fulfillment of the recruitment progress, data recollection, open science adherence, etc.

The Principal Investigator for the whole study, selected by the sponsor, is Dra. Marta Rubiera. Together with each of the local PI, IT, AI experts and a patient representative will conform the steering committee.

Given the observational design of the study, no data safety monitoring board (DSMB) is required.

3 Operational feasibility

3.1 Availability of the intervention throughout the implementation phase

Given the nature of our clinical non-observational shadowing study, no invasive intervention is required.

The 3 clinical sites will receive by mail a tablet with internet access for the data recollection of screening and recruitment of patients during the acute stroke phase through a pre-installed app (in development now).

For the eCRF fulfilment and outcomes recollection, a development of the web-based platform NORA is being performed. NORA has been designed to flexibly adapted to the different electronical medical records of the hospitals. A translation of main contents to German and Hebrew is in process to facilitate use for health professionals and patients/families.

A stroke expert health professional will manage NORA (NORA process manager) in each of the clinical sites. Personal training to each NORA process manager will be performed to ensure platform management and patient's education, training and communication.

3.2 Study population recruitment

Consecutive acute stroke patients will be recruit in the emergency departments of the 3 clinical sites. During the recruitment period, a shadow researcher will accompany the clinical physicians taking care of stroke codes. The researcher will register a screening log of all acute strokes arriving to the clinical sites. Those patients who fulfil the inclusion and exclusion criteria will be initially included. On-time data recollection of the pre-specified dataset required for the AI models will be recollected by the shadow researcher, to obtain an early outcome prediction (which will not be shared with the treating physicians).

After the hyperacute stroke phase, patients will receive information of the clinical study by the shadow researcher, and those patients who will sign the informed consent will be definitively included in the study. Where admitted by the Ethics Committee and local laws, a next-of-kin or legal representative may receive and sign the informed consent if the patient is not able to receive the information because of his/her clinical condition. However, if the condition of the patient improves later-on, a re-consent will be required.

Only data from those patients with signed informed consent will be included in the eCRF.

The local clinical stroke expert from the study board will monitor the recruitment, by periodical review of the screening log and meetings with the shadow researcher to identify un-expected loses of inclusion and problems with inform consent. The CRO will globally monitor the recruitment evolution of the study.

In case of slow/insufficient recruitment, the following mitigation strategies are planned:

- Revision of the inclusion/exclusion criteria
- Positive incentives for recruitment
- Evaluation of additional clinical sites

3.2.1 Clinical sites

Three high volume comprehensive stroke centers will contribute to the recruitment:

- Universitätsklinikum Heidelberg in Germany

- Hadassah Medical Organization in Tel-Aviv, Israel
- Fundació Hospital Universitari Vall d'Hebron – Institut de Recerca (VHIR) in Barcelona, Spain

The 3 centers have been selected because of their high-volume stroke admission and demonstrated experience conducting acute and subacute clinical trials. Research structures are already stablished in the 3 sites, and the respective clinical leaders have experience on coordination of national and international clinical trials.

Punctual collaborations between the three clinical sites have occurred previously, and one of the global Consortium objectives is the development of an established trial network.

The 3 sites have been also selected to obtain a sample of stroke patients from different countries and continents, avoiding biases of too homogeneous samples.

3.2.2 Recruitment competitiveness

All three clinical sites will compromise a minimum recruitment of patients through the clinical study. Additional recruitment will be incentivized by positive prizes like higher relevant contribution in publications, communications in congress, public diffusion,… Bundle payments will be provided every 10 extra-patients recruited in each center.

The CRO will monitor the individual sites recruitment performance. If underperformance occur, interviews with the local study board will be performed to try to identify bottlenecks in the recruitment local process.

3.2.3 Evidence supporting the ability of the individual clinical sites to recruit the required number of study participants within the planned timeline

A description of each clinical site is provided below:

Fundació Hospital Universitari Vall d'Hebron – Institut de Recerca (VHIR) in Barcelona, Spain

VHIR represents the largest academic hospital in Catalonia and one of the most important centers in Spain. The Stroke Unit at HVH is a reference centre for a catchment area of 1.4 millions and attends more than 1600 stroke patients every year. The VHIR is a well-known and internationally recognized Comprehensive Stroke Centre, with European Stroke Organization certification.

The local principal investigator has an extensive experience applying Information and Communication Technologies to achieve a higher level of care and best access to proven therapies in acute stroke patients in the region of Catalunya. The VHIR Comprehensive Stroke Unit consists in a multidisciplinary team of Stroke Neurologist, Neurointerventionalist, Neursurgeons, Rehab physicians, Occupational Therapists, Stroke nurses, social workers, and Technicians working together with the aim of a continued improvement in stroke care for our patients. The VHIR Stroke Center has a large experience in clinical research and stroke trials in acute ischemic and hemorrhagic stroke. The scientific contribution of the VHIR Stroke Center is remarkable with 250 publications in the last 5 years, some of them in high impact factor journals such as NEJM, JAMA, LANCET. The principal investigator and several members of the Stroke Unit of the Vall d'Hebron Hospital are part of the Catalan Stroke Network, a collaborative clinical research network that has borne fruit in numerous publications in international journals of high impact.

Universitätsklinikum Heidelberg (UKH)

UKHD is the largest single university hospital in Germany and one of the leading university hospitals in Europe. UKHD has more over 2,000 hospital beds and more than 110,000 in-patients and 1.000,000 out-patients are treated per year. The Department of Neurology (consisting of the Department of

General Neurology and Department of Neuroradiology) has extensive experience in the planning and conduction of randomized multicenter stroke trials, resulting in over 500 publications on ischemic stroke from the UKDH over the last 5 years. Imaging in acute stroke and stroke treatment has been a major research focus of the Department of Neuroradiology at UKHD for decades, and 55 publications on acute stroke imaging and treatment have resulted from this work within the last 5 years. More recently PD Dr. Vollmuth and Prof Bendszus, the principal investigator at the UKHD, have started several collaborations to investigate the use AI systems for neuroradiological tasks such as screening, diagnosis, and prognostication. Prof. Martin Bendszus and his research team at UKHD have considerable experience in thrombectomy for stroke, patient recruitment and coordination of clinical trials, e.g. the previous THRILL trial of thrombectomy in stroke with contraindications against intravenous thrombolysis (Bendszus et al., 2015) and he is the coordinating investigator of TENSION, an investigator-initiated, prospective, open label, blinded endpoint (PROBE), multinational, European, two-arm, randomized, controlled, post-market study to compare the safety and effectiveness of endovascular thrombectomy as compared to best medical care alone in the treatment of acute ischemic stroke (AIS) in patients with extended stroke lesions defined by an ASPECT score of 3-5 in an extended time window (up to 12 hours, or unknown time of symptom onset).

Stroke Unit at Hadassah-Hebrew University Medical Center (HMC-SU)

HMC-SU is a tertiary comprehensive referral academic center for stroke in Israel. The catchment area contains about 1.2 million inhabitants in Jerusalem and the periphery and the HMC-SU treats around 1200 stoke patients yearly. The HMC-SU provides state of the art stroke therapy including endovascular thrombectomy on a regular basis and has a long-term track of implementing innovative treatments in stroke. The HMC-SU consists of a multi-disciplinary team led by an experienced stroke neurologist (RRL) and junior faculty stroke experts as well as stroke fellows and also includes highly experienced interventional neurosurgeon (JEC) and neuro-radiologist (JMG). The team also includes physical, occupational and speech therapists as well as social workers and stroke nurses and research coordinators. We also collaborate on a regular basis with hematology, neurosurgery, cardiology, vascular surgery and diagnostic radiology on campus. The HMC-SU team is highly experienced in conducting clinical research and has a long term track record of scientific publications on the topic.

The PI and part of the HMC-SU team are part of a multicenter Israeli Stroke Registry as well as the EndoVascular treatment And ThRombolysis in Ischemic Stroke Patients (EVATRISP) prospective EU based registry and the Cerebral Venous Thrombosis European registry. These collaborations resulted in several publications in leading scientific journals over the last few years.

3.3 Additional supply availability

The 3 clinical sites will receive by mail a tablet with internet access for the data recollection of screening and recruitment of patients during the acute stroke phase. The end-of-user software for the data inclusion required for the AI models will be installed in the tablet. A database for screening-log of all acute stroke patients admitted to the clinical site will also be installed.

The shadow investigator accompanying the treating physicians in the acute stroke patient's reception will use the tablet for patient screening and data inclusion.

3.4 Data Management Plan

A **Data Management Plan** (DMP) will be at the core of the research data management. It will provide an analysis of the elements of the VALIDATE data management policy about all the data that will be generated within the project. The DMP will cover the complete data life cycle. The DMP will be delivered simultaneously to the Study Initiation Package, and will be regularly updated (months 18 and 30). A description of all data that will be generated or collected will be provided, as well as information on the purpose of the data collection, their relation to the objectives of the project, the types and

formats of the data, data re-use, data origin, their expected size and 'data utility', i.e. to whom it could be useful. It will also provide details on data interoperability and practical data management procedures, e.g., guidelines for documenting activities.

According to the open science principles, all data generated within the project will be made publicly available, following the rule of Open Science practices in Horizon Europe regulated under the Article 17 of the HE General MGA v1.0. VALIDATE will implement its open science approach according to the "as open as possible, as closed as necessary" principle, maximizing openness in research while protecting intellectual property and commercialisation efforts. Open science will play an integral role within the proposed methodology and will increase the chances of the project delivering on its objectives.

To facilitate the development of the DMP according to international standards, we will use the Horizon Europe programme-recommended Data Stewardship Wizard tool. Further, VALIDATE will follow the **FAIR** principles as outlined in the proposal. Data standards such as DICOM, LOINC, ICD-10, etc. will be adhered to and we will put special focus on interoperability

3.5 Reporting obligations to regulatory bodies and ethics committees

VHIR has finalized the study protocol. The building of an electronic case record file (eCRF) and its maintenance will also be developed by VHIR. VHIR will develop a database for managing, analyzing and reporting all data acquired in the clinical trial, monitor progress of patient recruitment at all sites and intervene proactively in case of delays. Registering of the clinical study in clinicaltrials.gob is in process at the moment. Two submissions for evaluation from the VHIR CEIm have been already submitted. The study is at the moment being in process for an independent Data protection evaluation.

An ethics committee evaluation for the pre-clinical retrospective phase of the study has obtained approval in Hadassah-Hebrew University Medical Center (HMC-SU). A similar submission has been performed in the Universitätsklinikum Heidelberg, and is pending of evaluation.

Each site is responsible for the training of local researchers and enrolment of patient independently.

All three clinical sites will closely interact with the lead of the consortium and will provide data and support dissemination, transfer, scientific data pooling and sharing.

3.6 Sponsor responsibilities

Monitoring will be performed by a trained person appointed by the Sponsor to ensure compliance with the Clinical Investigation Protocol, applicable national regulations and international standards, patient safety and data validity. The Sponsor may designate one or more individuals to monitor the progress of the clinical study. The Sponsor is ultimately responsible for the conduct of the study.

Each clinical site is responsible for the appropriate deidentification of subject data; NORA is responsible for the anonymization of the data for open access. The investigational site should provide access to the source data of the subjects if necessary, during the study.

All regulatory documents (e.g. MEC/IRB approval, contracts, etc.) will be reviewed for each actively participating center.

The monitoring schedule is based on the following considerations: enrollment rate, study compliance at the center, magnitude of data corrections required, study stage (e.g. start-up or follow-up), complexity of the investigation, IRB/MEC request, audit/inspection.

The monitor activities include:

• Check that the study is conducted, recorded and reported in compliance with the Clinical

Investigation Protocol, the good clinical practice, and applicable regulations. Acts to oversee the progress of the study.

• Check signed and dated informed consent of the subjects and check that this timing of signing is in line with the protocol and IRB/MEC approval. Ensure that essential documents (e.g. contract, MEC/IRB approval) are maintained in the Site Regulatory File.

• Ensure recording of deviations from protocol and store in Site Regulatory File or eCRF.

• Ensure that the principal investigator is informed and knowledgeable of all relevant document updates concerning the clinical study (e.g. Clinical Investigation Protocol and Investigator Brochure). Ensure that amendments to the protocol and/or Investigators Brochure are provided to the MEC/IRB and/or Competent Authority by the principal investigator.

The monitor will review critical clinical data that effect study endpoints. Data collection for reasons other than to support the protocol-defined objectives will not be monitored.

3.7 Major milestones

We expect the following milestones:

- Regulatory and ethics submission package: 6 months (already sent for evaluation)
- Receipt of regulatory and ethics approval: 2 months
- Initiation of clinical sites (APIs for AI models and NORA integration in the electronical medical record of each center, staff trainings..): 12 months
- Completion of patients' recruitment: 18 months
- Final follow-up outcomes recollection: 3 months
- Analysis of study results: 2 months
- Diffusion in international congress, press release, public diffusion through SAFE: 4 months

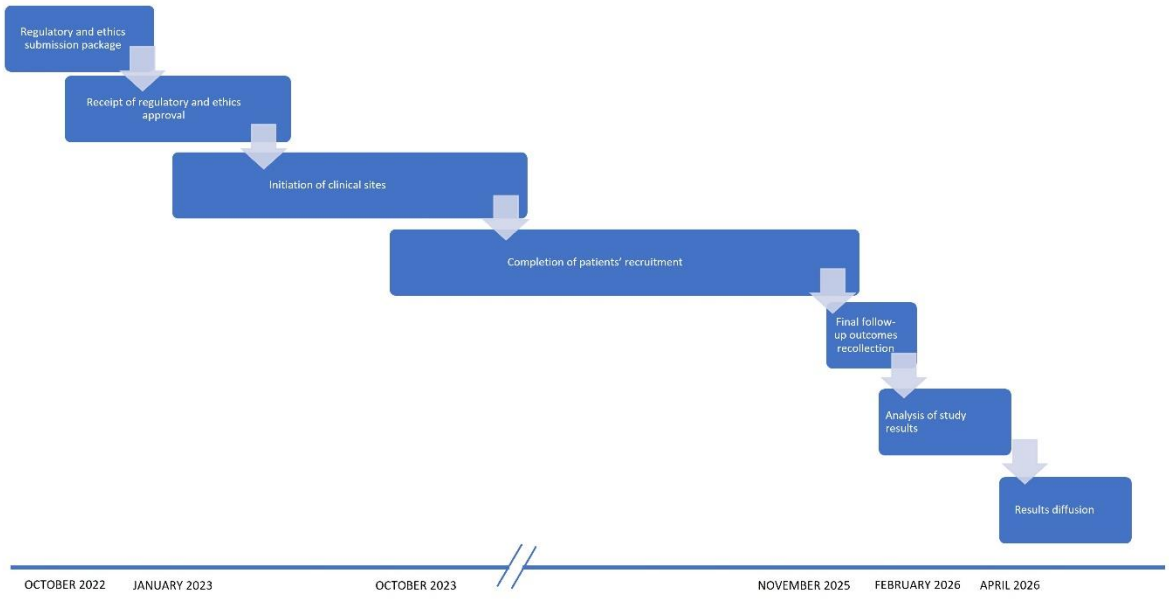
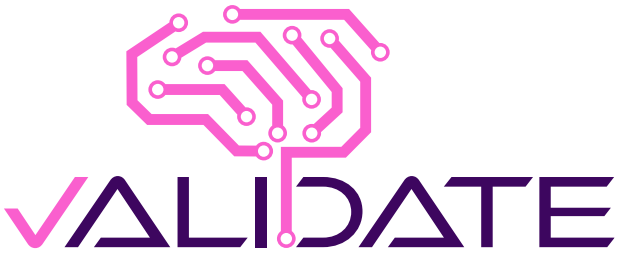


Figure 2 Estimated study process workflow

4 Patient information form



Study title	**Validation of a Trustworthy AI-based Clinical Decision Support System for Improving Patient Outcome in Acute Stroke Treatment**
Code	VALIDATE
Sponsor	VALIDATE Consortium
Coordinating investigator	Dietmar Frey, Charité Universitätsmedizin Berlin
Local principal investigator	Marta Rubiera
Center	Hospital Universitari Vall d'Hebron - VHIR
Service	Stroke Unit
Version	2, Date (08/17/2022)

Introduction

We are writing to inform you about a research study in which you are being invited to participate. The study has been approved by an Ethics Committee.

Our intention is that you receive correct and sufficient information so that you can decide whether to accept to participate in this study. To do this, read this information form carefully and we will clarify any doubts that may arise. In addition, you can consult with the people you consider appropriate.

Voluntary participation and right to withdraw consent

You need to know that your participation in this study is voluntary and that you can decide not to participate or change your decision and withdraw your consent at any time, without altering your relationship with your doctor or causing any harm to your treatment.

Artificial intelligence (AI)-powered prognostic tools and clinical decision support systems can predict the outcome of certain diseases based on a multitude of patient data at high speed, facilitating decisions by healthcare professionals.

In acute ischemic stroke, the overall treatment effect and population-wide outcome benefit of treatments such as IV thrombolysis and mechanical thrombectomy are well established. However, in individual patients it is difficult to predict the prognosis in the acute phase of stroke: some patients are candidates for these treatments but may have poor clinical outcomes (no functional improvement or even worsening).

There are multiple individual factors, and combined with each other, that in a single patient make it difficult to predict the outcome after stroke treatment. Classically this prognosis is defined by the results reported by the doctor in an evaluation at 3 months; however, in recent years, value-based medicine emphasizes the importance of self-reported health outcomes, and our plan is to collect self-reported outcomes as well.

Objective

Our aim in this study is to validate an AI-based prognostic tool to provide accurate real-time outcome prediction in patients with acute ischemic stroke.

Benefits

You/your family member will not directly benefit from your participation in this study. However, if our hypothesis is confirmed, we will have a safer, faster, more precise and evidence-based recommendation for individualized treatment, with better results for patients in the future.

Study procedures

During the time of inclusion in the study, all patients who are admitted to the emergency room with an acute ischemic stroke will be evaluated. All patients will receive the usual treatment for acute stroke in accordance with the stroke neurologists in charge. A “shadow” clinical investigator, without interaction with treating physicians, will collect the data required by the AI model in vivo. These data

will be obtained by filling in clinical data through an App on a hospital mobile/tablet, and by a connection with your electronic medical record.

Since this is data needs to be collected during your urgent treatment in the emergency room, we ask for your consent to the use of this data. If you do not want to participate in the study, the data already collected will be deleted prior to being transferred to the NORA database and no additional data will be collected from your electronic medical record. Even if you do not participate in the study, you will receive all the diagnostic procedures, treatments and regular follow-up that you require for your ischemic stroke.

On the other hand, if you agree to participate, we will assist you downloading the NORA app on your mobile device, tablet or computer and follow the monitoring plan for 3 months. This application has been clinically validated in stroke patients, improves communication between professionals and patients, and improves medication monitoring and control of vascular risk factors to prevent new episodes. Stroke patients have actively participated in the development of NORA, its use is simple and intuitive, and there is no age limitation for its use. After your admission, you will be provided with all the information and training necessary for its use. In addition, through NORA we will provide you with audiovisual information (videos) explaining the VALIDATE study and during your admission you or your relatives will be able to ask all the questions you consider pertinent.

Through NORA we will send you some forms to measure your opinion about your health results (PROMs) after suffering a stroke. In addition, we will make a telephone or video call visit for a neurologist to evaluate your health results (CROMs). We will compare the data from CROMs and PROMs with the result that our AI tool has predicted to check its reliability.

Your participation in the study will not entail the performance of any additional complementary tests (analysis, X-ray, additional face-to-face visit) to those that would normally be performed if you would not participate in the study.

Your identification data will be securely recorded in the NORA database on the hospital's servers and will be used to carry out your clinical follow-up and contact you for the study surveys (PROMS and CROMS). Additionally, for the study, we request your consent for the subsequent use of this data, which will follow a process of "anonymization" (your identification number will be modified through a secure procedure in the NORA app so that you/your family member cannot be associated with the data we collect). This anonymization procedure will be carried out before the transfer of data to the VALIDATE Consortium, so that you cannot be identified in the database that will be made public.

If informed consent has been provided by a family member, and subsequently your clinical condition allows you to understand this information form, during your admission we will ask you to reconfirm your consent to participate in the study. If for any reason you decided to change your mind and not continue in the study, you can leave the program at any time. In that case you will receive the conventional follow-up.

Data Protection

Both the sponsor and the center will ensure that the confidentiality of your personal data collected during the study is maintained, in compliance with both national data protection laws and European data protection laws (see Appendix 1).

Contact in case of doubt

If you need more information about this study, you can contact the Principal Investigator, Dr. Marta Rubiera in the Stroke Unit, Tel. 934896000, ext. 4997.

5 Informed consent

Validation of a Trustworthy AI-based Clinical Decision Support System for Improving Patient Outcome in Acute Stroke Treatment

I _____(name and surname)
Have read the information form that has been provided to me.
Have been able to ask questions about the study.
Have spoken with: _____(researcher name and surname)
I understand that my participation is voluntary.
I understand that I can withdraw from the study:
1. Whenever I wish
2. Without having to give explanations
3. Without influence on my medical care

I freely give my consent to participate in the study
I agree that the doctors responsible for this study contact me in the future in case it is deemed appropriate to add new data to those collected: Yes__ No__

Patient signature: Date: ____/____/____	Investigador signature: Date: ____/____/____
Signature of family member/representative: Date: ____/____/____	

I wish to be informed of the information derived from the research that may be relevant to my health or that of my relatives: Yes__ No__
Telephone or e-mail contact: _____
_____

Patient signature: Date: ____/____/____	Investigator signature: Date: ____/____/____

Signature of family member/representative: Date: ____/____/____	

I accept the future use of my anonymized data in unrelated research: Yes__ No__

Patient signature: Date: ____/____/____	Investigador signature: Date: ____/____/____
Signature of family member/representative: Date: ____/____/____	

SECTION FOR THE REFUSAL OR REVOCATION OF INFORMED CONSENT (SIGNATURE OF THE PATIENT AND/OR FAMILY MEMBER/REPRESENTATIVE)

I, ...or familiy

member/representative (*if applicable)* ..... of the patient (patient's

name) ..... deny/revoke the consent to participate in the study,

signed above.

This revocation of the informed consent means that from the date on which it is signed, no more medical data can be collected and that the data already collected for the study is not used, and that my electronical medical record is not accessed for purposes of data collection for this study.

Date of the refusal/revocation: ____/____/____

Signature:

Appendix 1: Protection of personal data related to the patient information sheet document and informed consent of the study

Study title	**Validation of a Trustworthy AI-based Clinical Decision Support System for Improving Patient Outcome in Acute Stroke Treatment**
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Local principal investigator	Marta Rubiera
Center	Hospital Universitari Vall d'Hebron - VHIR
Service	Stroke Unit
Version	2, Date (08/17/2022)

Who is responsible for data processing?

The VALIDATE-Consortium, which is the Sponsor of this study, is based in Berlin. Both the Center and the Sponsor are responsible for the processing of your data. The Center is responsible for all the data that appears in the history and that can identify you and the Promoter of those that are collected in this study in an anonymous way. The role of the data controller is to ensure that your information is used correctly. The Sponsor and the Center will comply with data protection regulations:

-Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016 regarding the protection of natural persons with regard to the processing of personal data and the free circulation of these data

- Organic Law 3/2018 of December 5, on the Protection of Personal Data and guarantee of digital rights.

Which data will be collected and used?

The Sponsor will not collect more data than is necessary to carry out this study (related to their pathology, the tests carried out and the treatment received).

What will this data be used for?

The Sponsor will use this data to answer the study question(s) and related research, which are explained in the information form provided to you.

The Sponsor and the researcher could re-use this data for other research projects; those future projects may be focused on any other topic and may be irrelevant to the objectives of this preliminary study. Confidentiality will be respected at all times and compliance with current legislation will be guaranteed. Your information will only be used in research that has received a favorable report from a Research Ethics Committee, and in a way that does not contradict the preferences expressed by you in the signed consent. In those countries where the law does not require approval by a Ethics Committee, the favorable report of the data protection delegate or an expert in the terms established in the applicable regulations will be required.

We will give you access to the data we are collecting and to a completely open database.

What about confidentiality?

At all times, the confidentiality of your data will be maintained. During your participation in the study you will be identified by a code, and neither the investigator nor the Hospital will transfer to the Sponsor any information that can directly identify you. The list that relates the identification code with the data that identifies you (name, surname, medical record number, ...) will be deleted through a secure anonymization procedure before data transfer, so you cannot be identified with your data once transferred out of the Health Center.

The data we share with the general public will not contain your name, just a code number that does not identify you; people will not know your name or that the data is yours. In addition, we will not share any other information that we believe could identify you.

If you change your mind and withdraw your consent to participate in this study (you can call Dr. Marta Rubiera at 932744997) we will not collect any additional data about you. We will delete your data if

you withdraw before we deposit it in the database. However, data or research results that have already been shared with other researchers or the general public cannot be destroyed or withdrawn.

By agreeing to participate, you will be making a free and generous donation to research that could help others. It is possible that some of the research conducted using your information could ultimately lead to the development of new methods for studying the brain, new diagnostic tests, new drugs, or other commercial products. If this occurs, there is no plan to provide you with any part of the benefits of these products and you will have no ownership rights in these products.

To the best of our knowledge, the data we post openly does not generally contain information that can directly identify you. The generated Database will not contain your name, only a code, so that the public will not know your name or that the data is yours. In addition, the data will not include information that we think would help people close to you guess what the data is about you, such as facial features or the day you participated. If we write a scientific article about the study or share the data with others, we will do so in such a way that you cannot be directly identified. However, if a security breach (cyber attack) occurs, this could lead to someone associating you with your data. This risk is very low because your data is stored in a secure database, and stroke is a very common disease, so identification from the data we store in the database would be practically impossible.

All the information that we request is necessary to be able to participate in this study and it is mandatory that you provide it, to guarantee its correct development. In the NORA app we will keep the private part of your data (name, contact information, etc.) in a safe place to carry out your personalized clinical follow-up. The Center and the Promoter are obliged to keep the data collected for the study, according to the legal deadlines established in the regulations: the Promoter, for at least the time necessary to carry out the study, and the Center, for the time necessary to provide an adequate attendance. After this period, we will destroy your information to protect your privacy. Access to your personally identified information will be restricted to the principal investigator of the study/collaborators, health authorities and the Research Ethics Committee, when required to check the data, study procedures, and compliance with good clinical practice standards; but always

maintaining their confidentiality. Your identity may be revealed in exceptional cases, such as situations of medical emergency for your health or legal requirement. The treatment, communication and transfer of personal data of all participants will comply with the provisions of the applicable regulations.

Letting us use and share your data is voluntary. However, you must be willing to share your data in this way to participate in this study.

If you are not willing, you will not be able to participate in the study. By signing below, you are agreeing to provide your data for future research. In this way you accept that the data may be shared with other researchers from other institutions around the world. The details, results, and implications of these studies are unknown.

What rights do I have?

With respect to your data, you have the following rights:

You can ask at any time what data is being saved (right of access), who is using it and for what purpose; you can request a copy of your personal data for your own use. You can request to receive a copy of the personal data provided by you to transmit it to other people (portability). You can correct the personal data provided by you (right of rectification) and limit the use of data that is incorrect (right of rectification and deletion). You can object to the use of your personal data or restrict it (right to object). In relation to the rights over your personal data, we remind you that there are some limitations in order to guarantee the validity of the research and comply with the legal duties of the Promoter and the authorization requirements of medicines: the data collected up to that moment cannot be Delete even if you stop participating in the study or even if you withdraw your consent to data processing. Likewise, you will have the right to withdraw consent on data processing, which will determine your cessation of participation in the study. For the same reason, if you withdraw from the study, we will keep the information about you that has already been collected so far, but we will not continue to collect information, and if it has not been transferred to the database, we will not use it for study purposes. study. To protect your rights, we will use as little information as possible.

Likewise, we inform you of your right to file a claim with the Data Protection Agency in the event of any action by the Promoter or the Center that you consider violates your data protection rights. If you wish, you can contact the data protection delegate of your Hospital for the study, or contact the principal investigator of the Sponsor (next section).

Who do I contact?

Principal investigator of the study: Marta Rubiera. Telephone 932746000, extension: 4997

Center DPO contact details: dpd@ticsalutsocial.ca

Contact details of the Promoter by postal mail: Dietmar Frey. VALIDATE consortium. Charité Lab for Artificial Intelligence in Medicine. Charité Universitätsmedizin Berlin. Chariteplatz 1, 10117, Berlin, Germany

Will my data be shared and transferred?

The Promoter may transfer or share your data with other researchers inside or outside the European Economic Area. In any case, the recipients of the data will not have access to any code that allows their data to be related to you.

The laws in some of these countries may not be as strict as those in your country. Therefore, your data may be exposed to a slightly higher risk of loss of confidentiality. In that case, the Promoter will ensure that data transfers respect your rights and confidentiality. All data recipients will sign/accept a Data Transfer Agreement or equivalent terms of use agreement agreeing, among other things, not to attempt to re-identify research participants. Likewise, the Promoter will guarantee that the necessary protections are established to maintain the confidentiality of your data and guarantee the protection of your privacy and will not allow your data to be crossed with other databases that could allow your identification.

How will the results be communicated?

The Promoter will publish the results of the study, preferably in scientific journals, congresses, and through public dissemination through the organization SAFE (Stroke Alliance for Europe). The anonymity of the study participants will be always maintained.