Study protocol

Study Title:

Evaluating the use of eye-tracking technology in the diagnosis of neurological patients, including patients with reduced consciousness

Internal Reference No: **C-EYE_DIAGNOSIS_X001**

Ethics Ref: **11/2022 (Commission resolution of 28.03.2022)**

Primary Investigator:	Dr. habil Grzegorz Zurek, Professor of the Wroclaw University of Health and Sport …… **signature**
Research Team (at the Facility):	
Sponsor:	AssisTech Sp. z o.o.

The study was carried out within the framework of the National Centre for Research and Development competition 2/1.1.1/2020 grant application number: **POIR.01.01.01-00-2125/20.**

Confidentiality Statement

This document contains confidential information. It must not be disclosed to anyone other than the Sponsor, the Research Team, the supervising institution, and members of the Research Ethics Committee.

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1. SYNOPSIS / Study outline

Study title	**Evaluating the use of eye-tracking technology in the diagnosis of neurological patients, including patients with reduced consciousness**
Justification of Tests	Currently, the diagnostics of consciousness disorders in people who suffer severe brain damage is based on standardised behavioural assessment. However, behavioural diagnostics often fails because of the severe cognitive, sensory and motor deficits associated with impaired consciousness, or because of the heterogeneous etiology and pathophysiology associated with the condition. Diagnosing consciousness disorders is based on traditional psychological and psychiatric tests, which require verbal contact with the patient. The use of the visual communication channel in assessing the state of consciousness and diagnosing cognitive function seems perfect for patients who are unable to communicate verbally and lack the motor skills to communicate their needs to medical personnel and their caregivers. Recently published studies conducted with patients with disorders of consciousness using the eye tracking device, C-Eye, as an alternative communication tool, indicate its diagnostic potential for people with this condition.
Type of clinical trial	Observational study of a medical device after CE authorisation.
Participants of Tests	Brain-damaged neurological patients with communication barriers, diagnosed as being in unresponsive wakefulness syndrome (UWS) or minimal consciousness state (MCS), for whom sight may be the only route of communication.
Expected number of Study participants	The number of observations to be analysed in Poland and Germany combined is: **90**
Planned sample size	**90 (2 x 45)**, where 45 – sample size for each Test: (Test 1 (MCSD): Minimum Awareness Detection, Test 2 (CFA): Cognitive Function Assessment)
Follow-up duration	No further follow-up of patients is planned.
Planned Study period	Total duration: 11 months: **May 2022 - March 2023** Phase 1: Preparation for the Study: 2 months: **May - June 2022** Phase 2: Observation study: 7 months: **July 2022 - January 2023** Phase 3: Closing the Study: 2 months: **February - March 2023**
Primary objective of the Study	Evaluation of C-Eye X system application in the neurological diagnostics of patients with reduced consciousness.

Secondary objective of the Study	Comparing the results of C-Eye diagnosis with those obtained from commonly used behavioural and psychological scales in the evaluation of patients with reduced consciousness.
Exploratory aim	Demonstrating that diagnostics of the state of consciousness and cognitive function of patients with consciousness disorders performed using C-Eye X allows a more objective assessment of the condition of patients who, according to traditional methods, remain in no contact with the surrounding world.
Primary endpoint	Obtaining reliable clinical data confirming the diagnosis of the state of consciousness and cognitive function of patients with reduced consciousness, in whom the diagnostic tool developed during the project was applied.
Secondary endpoint	Evaluation of differences between the results of the state of consciousness and cognitive functions of patients with reduced consciousness obtained by behavioural methods and using C-Eye X
Device name	C-Eye X
Manufacturer	AssisTech Sp. z o.o.
Main application	Eye tracking in the diagnostics of consciousness disorders and cognitive functions of people with reduced consciousness and communication barriers.
Duration of device use to date (years)	7 years

2. BACKGROUND AND RATIONALE

The diagnostics of consciousness disorders in people who suffered severe brain damage is based on standardised behavioural assessment. However, behavioural diagnostics often fails because of the severe cognitive and motor deficits associated with impaired consciousness, or because of the heterogeneous etiology and pathophysiology associated with the condition. The need for an accurate diagnosis and prognosis goes beyond the needs of the patients themselves, as their care is associated with a significant stress burden, mainly due to the high uncertainty of the prognosis. Currently, the diagnosis of consciousness disorders and cognitive functioning is based on traditional psychological and psychiatric tests that require verbal contact with the patient. The use of the visual communication channel in diagnosis of the state of consciousness and cognitive function seems perfect for patients who are unable to communicate verbally and lack the motor skills to communicate their needs to medical personnel and their caregivers.

Studies published in recent years using the C-Eye eye-tracking device as an alternative communication tool among patients with disorders of consciousness indicate its diagnostic potential in this condition. A definite advantage of using the C-Eye system in this context is that the patient with reduced consciousness makes the decision to cooperate on their own. C-Eye is further characterised by non-invasiveness, adaptation to the neurological patient with visual and cognitive deficits, and easy and intuitive operation by the examiner-diagnostician.

The project will be implemented in a group of patients who, as a result of various causes (e.g. trauma, stroke, hypoxia), have suffered brain damage resulting in a significantly reduced state of consciousness, unable to communicate other than by eye movement (visual channel). The project will use the C-Eye X device, which is the next generation of the previously used C-Eye PRO system.

Previous publications in this area indicate that, despite significant deficits in the level of consciousness or cognitive function, such patients are able to establish communication by sight, and their memory or linguistic functions remain at a high level, allowing conscious communication using their sight.

Participation in the project poses no risk to the patient. The tasks that will be performed are not taxing on their functioning, nor do they carry the risk of impairing their health.

The team's research to date in the field covered by the project has been published in the following journals:

1) *Kujawa K., Żurek A., Gorączko A., Olejniczak R., Zurek G.: Monitoring eye movements depending on the type of visual stimulus in patients with impaired consciousness due to brain injury. Int. J. Environ. Res. Public Health 2022, 19(10), 6280; https://doi.org/10.3390/ijerph19106280*
2) *Kujawa K, Zurek G, Kwiatkowska A, Olejniczak R, Zurek A: Assessment of language functions in patients with disorders of consciousness using and alternative communication tool. Frontiers in Neurology, 20 July 2021 https://doi.org/10.3389/fneur.2021.684362*
3) *Kujawa K., Żurek A., Gorączko A., Olejniczak R., Żurek G.: Implementing new technologies to improve visual-spatial functions in patients with impaired consciousness. International Journal of Environmental Research and Public Health, 2022: vol. 19, nr 5, art. 3081. https://doi.org/10.3390/ijerph19053081*
4) *Kujawa K, Żurek A, Gorączko A, Zurek G. Application of high-tech solution for memory assessment in patients with disorders. Frontiers in Neurology, 31 March 2022 https://doi.org/10.3389/fneur.2022.841095*

3. OBJECTIVES

The aim of this Study is to perform a clinical evaluation of the authors' original battery of diagnostic tests in the C-Eye X system, addressed to patients who have suffered damage to the central nervous system (CNS) and communicate with the help of the organ of sight (a test to differentiate patients' state of consciousness and a test to assess the level of cognitive function in patients), as well as to evaluate the proposed diagnostic method (procedure) (including the type and scope of diagnostic tasks and how diagnostic observation is carried out using the C-Eye X system). The intention of the project's authors is to introduce a novel diagnostic solution that will help reduce misdiagnoses (currently believed to be up to 40% of errors) made for such patients, due to the inadequacy of current behavioural tools to work with patients after severe brain damage.

3.1.Primary Objective

Evaluation of the application of the C-Eye X system (proprietary diagnostic tests – MCSD and CFA and eye tracking technology) in the neurological diagnosis of patients with reduced consciousness.

3.2. Secondary Objectives

Comparing the results of C-Eye diagnosis with those obtained from commonly used behavioural and psychological scales in the evaluation of patients with reduced consciousness.

3.3.Exploratory objective

Demonstrating that diagnostics of the state of consciousness and cognitive function of patients with consciousness disorders performed using C-Eye X allows a more objective assessment of the condition of patients who, according to traditional methods, remain in no contact with the surrounding world.

4. STUDY DESIGN

The Study will be conducted as an open-label Study..

After meeting the inclusion criteria, the patient will begin participation, which will last up to 15 days (one test) or up to 30 days (two tests) per patient. Patients can be added at different stages of the project; there is no requirement that all patients start participating at one time. Depending on the patient's state of consciousness (as determined by the Test 1 diagnosis or based on a previous CRS-R diagnosis prior to inclusion in the Study), they will complete a test to assess state of

consciousness (MCSD group) and/or a test to assess state of cognitive function (CFA group), in the case of a diagnosis higher than UWS. The decision to include a patient in one group or the other will be made by the investigator. Assuming that (for various reasons, dependent or independent of the patient/facility/investigator) not every patient will participate in the entire project (due to dropping out), the results obtained in 90 observations (45 per test) will be included in the analysis. This means that it is permitted to replace a patient excluded from the Study (during the course of the Study) with another patient. The permissible number of patients so replaced may not be greater than 10% of the total expected number of observations (i.e. for both groups combined: MCSD and CFA). The final decision to replace a patient excluded from the Study with another patient is made by the Primary Investigator. At the same time, it is assumed that the dropout rate allowed in the Study is 10% (i.e., the minimum number of patients who will participate in the entire Study is 81, total for both groups: MCSD and CFA).

The number of visits per patient will depend on the test and will be (see Appendix A for a detailed visit):

- **7 visits** (first initial visit – screening, next five screening visits, the final
  - seventh one – Closing Visit) for Test 1 – Minimally Conscious State Detection Test (MCSD Test)
- **5 visits** (first initial visit – screening, next three screening visits, the last
  - fifth one – closing visit) for Test 2 – Cognitive Functions Assessment Test (CFA Test)

4.1.Primary and Secondary Endpoints

Primary endpoint: Obtaining reliable clinical data confirming the diagnosis of the state of consciousness and cognitive function of patients with reduced consciousness in whom the diagnostic tool developed during the project was applied.

Secondary endpoint: Evaluation of differences between the results of the state of consciousness and cognitive functions of patients with reduced consciousness obtained by behavioural methods and using C-Eye X.

The total score a patient can obtain per trial for performing tasks in the MCSD test (using the C-Eye X) is 11. It consists of the results obtained in the subscales of attention, language function, visuospatial function, autopsychic orientation, memory and abstract thinking. On the other hand, the total number of points a patient can obtain in a single trial for performing tasks in the CFA test (using the C-Eye X) is 24, and consists of scores obtained in the subscales of auditory sensitivity,

visual function, auditory-visual integration, command execution, autopsychic orientation and pressure localisation test.

The total score that a patient can obtain in the MOCA test is 30 in a single measurement, consisting of the points obtained in each subscale, i.e. visual-spatial function, naming, attention, language, verbal fluency, abstracting, deferred recall and orientation.

The total score a patient can obtain on the CRS-R test is 23. It consists of the scores obtained in each subscale, i.e. visual, auditory, motor, oromotor/verbal, communication and arousal functions.

The percentages of the MCSD and CFA test scores will be compared with the relative scores (also reported in %) obtained by the patient in the CRS-R test and the MOCA test. This will allow us to capture potential discrepancies between the results of the two tests, and will also be an indication to change the way we diagnose patients towards using the communication channel that is possible in their case (vision).

4.2.Study Participants

4.2.1. Overall Description of Study Participants

Participants will include people recovering from severe brain injury who meet the project's inclusion criteria. Thus, they will be neurological patients after brain damage with communication barriers, diagnosed as being in unresponsive wakefulness syndrome (UWS) or minimal consciousness state (MCS), for whom sight is the only route of communication.

4.2.2. Inclusion Criteria of study participants

Criteria for patient inclusion in the Study:

1. Completed 18 years of age.
2. Consent of the legal guardian to participate in the Study and access to medical records.
3. Medical diagnosis indicating damage to the central nervous system.
4. Having and sharing a description of imaging tests (alternatively MR or CT) and (alternatively) ophthalmoscopy, ophthalmology, auditory tests.
5. Presentation of a list of medications used by the patient that may affect the results obtained in tests of cognitive function.

6. Acceptance by a physician (e.g. neurologist, neurosurgeon, internist) to participate in a clinical trial, taken after reviewing the Study protocol, including there is a need to take into account:
   a. the ability to communicate only by sight (no verbal, sign or other communication),
   b. the absence of dementia and aphasic disorders before the event that led to CNS damage and the patient's current condition,
   c. preserved at least one functioning eyeball (possibility of cooperation with an eye tracker).

4.2.3. Exclusion Criteria

Criteria for excluding a patient from the Study:

1. Visual defect (refractive defect) diagnosed before the incident, requiring work with glasses with lenses of more than ±3 diopters.
2. Inclusion of drug treatment during the Study (observation), which can affect the patient's cognitive functioning (both in terms of cognitive enhancement and impairment/dementia).

5. COURSE OF STUDY

It will take 7 months to conduct the clinical evaluation; the assumed period of implementation of the Study is July 2022 - January 2023. The following work will be carried out:

- Recruitment of patients (acquisition of target group): 45 observations (in total from all the facilities included in the Study) for the diagnosis of state of consciousness – Test No. 1 (MCSD), and 45 observations (in total from all the facilities included in the Study) for the diagnosis of cognitive functions – Test No. 2 (CFA); The majority of the group among whom the recruitment will be carried out will include patients residing in facilities in Poland, about 15 –20% will be patients from facilities in Germany.
- Conducting studies in an established group of patients at independent facilities in Poland and Germany. A detailed description of the activities undertaken during each visit and their sequence is presented in Appendix A.
- Depending on the patient's state of consciousness, they will participate in Stage 1 and/or Stage 2. The Study will consist of:

Stage 1: performing MCSD Test (5 x within 14 days). After this series of testing is completed, a possible test will be conducted:
Stage 2: performing examination using the CFA Test (3 x in 14 days).

The execution of MCSD will be preceded by a CRS-R test, while the execution of CFA will be preceded by a CRS-R and a MOCA test.
Stage 2 can be conducted after a diagnosis above UWS is obtained in Stage 1, or bypassing Stage 1 if said diagnosis was obtained earlier, prior to inclusion in the Study, based on the CRS-R test.

6. SITE SELECTION:

1. Settled situation with local NHF (applies to Polish facilities) and/or have the right to undertake clinical trials.
2. The presence and secondment for the purpose of this Study of at least two persons – therapists (one of the specialties: physiotherapist, speech therapist, psychologist, educator, occupational therapist), with at least one year of experience in working with C- Eye, ready to work with the patient using C-Eye in the framework of the ongoing Study (in case one of them is unable to perform the work). The names of the therapists selected to work with C-Eye X in the clinical trial (investigators) must be known at the stage of signing the tripartite agreement (Centre - Sponsor - CRO).
3. Investigator Certification:
    - the investigator has to obtain a Certificate of Training Completion for: 'Working with C-Eye X within the framework of a clinical trial', confirming the ability to operate and work with the C-Eye X system; training organised by the Sponsor (after prior arrangement of the date and other organisational matters between the facility and AssisTech Sp. z.o.o.);
    - having or obtaining a GCP Certificate by the investigator.
4. Hours of operation with C-Eye (ensuring the availability of the investigator) are 9:00 a.m. - 6:00 p.m., conducting the Study depending on the patient's activity/reactivity status.
5. Declaration of inclusion in the Study (using C-Eye), according to the following guidelines:

- about 10 observations per Test, per facility in Poland,
- about 5 observations per Test, per facility in Germany,

whereby the determination of the details of cooperation, including financial issues, is carried out on the basis of the concluded tripartite agreement (Centre - Sponsor - CRO), defining the principles of cooperation.

6. The rules for the therapist (investigator) to work with the patient are governed by the facility's internal regulations, but if the patient feels safer in the presence of a family member, the family member may be present with the patient during the examination, under the rules set by the Contractor.

7. STUDY PROCEDURES

The launch of the Study for a patient takes place after the patient meets the inclusion criteria. The decision on eligibility for the Study is made by the physician after reviewing the screening protocol, conducted in accordance with the patient evaluation form provided by the Sponsor. All physicians responsible for including patients in the Study at facilities in Poland and Germany will qualify patients according to the same screening procedure.

Qualified patients (or their legal guardian) must give informed consent to participate in the Study. Demographic and health data will be collected from project participants, which will then be entered by the investigator into an Electronic Case Report Form (eCRF).

After collecting this data, the patient will perform Test 1 (MCSD). The allowable time for a patient to perform Test 1 five times is 15 days (the first day of testing is the day of collection of informed consent, medical history, physical examination and eligibility criteria – Appendix A), with intervals of at least one day between test repetitions. Each time, on the day the patient will perform Test 1, it will be preceded by a CRS-R test. The schedule of appointments for patients qualified for Test 1 is shown in Table 1, Appendix A. Thus, after performing the presented procedure five times, the patient's state of consciousness will be described in two scales, which will be subject to further analysis performed under the direction of the Principal Investigator.

Observation for Test 1 can be considered successful when data are collected in the patient within the assumed time of 15 days according to the procedure described above. A patient's observation that fails to meet even one of the stated criteria (demographic and health data, CRS-R five times, and Test 1 five times) will not be considered fully completed.

If the diagnosis of the patient's state of consciousness obtained in Test 1 is higher than the UWS (so their condition will be at least MCS-) they will be qualified to perform Test 2. Patients who did not perform Test 1, but who had a score of at least MCS- in a previous CRS-R diagnosis prior to inclusion, may also be included in Test 2.

After completing a series of 5 measurements in Test 1 (MCSD), the pucomeatient's qualifying physician examines the patient at the final visit, according to the patient evaluation form provided by the Sponsor.

The procedure in Test 2 (CFA), for a patient qualified by a previous CRS-R diagnosis, begins with the collection of data on informed consent, medical history, physical examination and inclusion criteria – Appendix A. These will be collected on the first day after the patient enters the trial and entered by the investigator into the eCRF. Patients qualifying on the basis of Test 1 results will be able to proceed immediately to cognitive status assessment.

During the following 14 days, the patient will perform Test 2 three times at intervals of at least one day, which will be preceded each time by a MOCA and CRS-R test (Table 2, Appendix A). Thus, after the procedure outlined, the patient's level of cognitive function will be described using two scales (behavioural: CRS-R and MOCA and electronic - C-Eye X) which, in combination with the results of CRS-R, will be the subject of further analysis performed under the direction of the Principal Investigator.

After completing a series of 3 measurements in Test 2 (CFA), the patient's qualifying physician examines the patient at the final visit, according to the patient evaluation form provided by the Sponsor.

The occurrence of any adverse reaction must be reported in accordance with the rules set forth later in the protocol, reported using the Adverse Event Report Form, attached as Appendix 2 to this protocol.

8. INFORMED CONSENT

Informed consent to participate in the Study must be given by either the patient or the person legally responsible for the Study participant. The participant and/or the person responsible for the Study participant will be informed about the title of the Study, its objectives and goals, the ethics committee's approval issued, the conduct of the Study, and the possibility of withdrawing from participation in the Study at any stage.

Other information regarding the project and participation in the Study will be provided upon patient request.

Protection of personal data is ensured in accordance with Article 13 (1) and (2) of the General Data Protection Regulation of 27 April, 2016. (Hereinafter referred to as GDPR (Polish: RODO)).

The Patient Informed Consent Form for participation in the Study is attached as Appendix 1 to this protocol.

9. SCOPE OF DATA COLLECTION

For the purpose of broader analyses, the results obtained will be supplemented with the following patient demographics:

- sex,
- body height,
- body mass,
- date of birth,
- education,
- professional activity/occupation (before the event),
- smoking,
- handedness,
- information about the condition of the eye (possible visual defect and its type).

The patient health data collected will be as follows:

- nature of brain damage and etiology,
- date of injury occurrence,
- a clinical description of the brain damage created by the imaging study,
- the presence of chronic diseases before the injury,
- administered medications,
- having hearing and vision correcting devices before injury (including during ongoing examinations, all diagnostic sessions).

10. RANDOMISATION AND CODEBREAKING (if applicable)

Not applicable

11. SUBSEQUENT ASSESSMENTS

Follow-up tests are not provided for in the Study.

12. DEFINITION AND END OF STUDY

Termination of the patient's participation in the project occurs when the doctor examines the patient at the final visit, i.e. immediately after the last (fifth) measurement in Test 1– MCSD and/or the last (third) measurement in Test 2 – CFA.

13. DISCONTINUATION / WITHDRAWAL OF PARTICIPANT FROM STUDY

Each Study participant and/or Study supervisor has the right to discontinue (withdraw consent) at any time during the Study.

14. SOURCE DATA

The source documents used in the Study will consist of hospital records, including:

- medical history, previous and current medications taken,
- clinical observation sheets,
- diagnostic Imaging.

All documents will be kept at the medical facility implementing the Study with patients under conditions of confidentiality in accordance with data protection rules. In all documents related to the Study, in addition to the signed consent, a code – a unique patient identifier – will be used with respect to the Study participant, ensuring proper identification of the Study results collected and stored; in no case will data about the Study participant be described with their name.

15. DESCRIPTION OF MEDICAL DEVICE

C-Eye X is an integrated device consisting of a touchscreen computer, an eye tracker (a special infrared camera that tracks eye movements) and pre-installed software (run in 'kiosk' mode) that

includes a diagnostic module in the variant under clinical evaluation in this Study (and in it 2 proprietary diagnostic tests: Minimal Consciousness Detection (MCSD) and Cognitive Function Examination (CFA).

People with neurological dysfunctions and developmental disorders working with C-Eye X perform tasks based on multimedia content. The patient marks the content displayed on the device's screen (i.e. graphics, photos, texts) with their eyes by focusing on it. The patient's

Fig. 1 C-Eye X set used during the study

choice or selection of a particular item/object displayed on the screen is based on holding the eye in one place for a long time. The user interface of the C-Eye X system was created with the following design considerations in mind:

ease and intuitiveness of use of the system by the user - investigator, diagnostician,

no unnecessary buttons, functionalities, hindering the operation of the equipment, as well as the reliability of the diagnosis,

elements (different types of content, responses) with which, by definition, the patient interacts (through activation with the eyes) are maximally large, clear highly contrasting (in relation to the background on which they are presented), unambiguous so that a patient in a state of reduced consciousness struggling with cognitive and visual deficits can select them, mark them with the eyes.

Key assumptions about the C-Eye X system:

1. The visual fixation point (cursor) in diagnostic tests is a small grey dot with a white outline. The cursor was chosen so as not to attract the attention of the subject. It is not possible to change the cursor settings in Diagnosis.

2. Only the answers in tasks or actions performed (such as tracking) can be marked by the patient's eyes Other buttons on the screens are locked to operation by sight (e.g. commands, back button, etc.) – they can only be clicked by touch (this is done by the examiner, diagnostician).

3. The limit for taking measurements is enabled – a maximum of one measurement per day.

4. Marking the answers 'by sight' in the tasks is possible after the reading of the instruction by the lecturer has ended.

5. The time to mark items 'by sight' is constant for most tasks at 1.2 s (e.g. time to mark answers in questions about name, year of birth). In tasks where actions on the screen happen

automatically (e.g. tracking, reflex inhibition, etc.), other mechanisms are used to determine the results.

6. If no answer is given for 1 min, the task boards will automatically change to the next one. The process can be stopped by pressing pause. Screens containing instructions for the test taker require clicking the yellow ‘next’ arrow or entering the test result to move to the next board. They do not automatically change to the next.

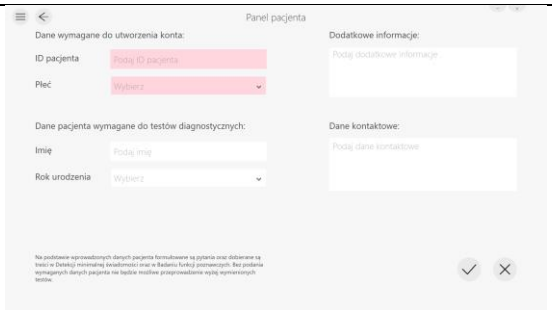
7. The test taker has the option to pause tasks in both tests (button  in the middle, at the bottom of the screen) – pause allows one to temporarily stop the test (during the pause one cannot mark the content of tasks). One can continue the test by selecting the button again. If one chooses to pause and exit the test, the results will not be saved. Detail commands/sounds are read again, after the task is restarted – if a pause was selected during their playback.

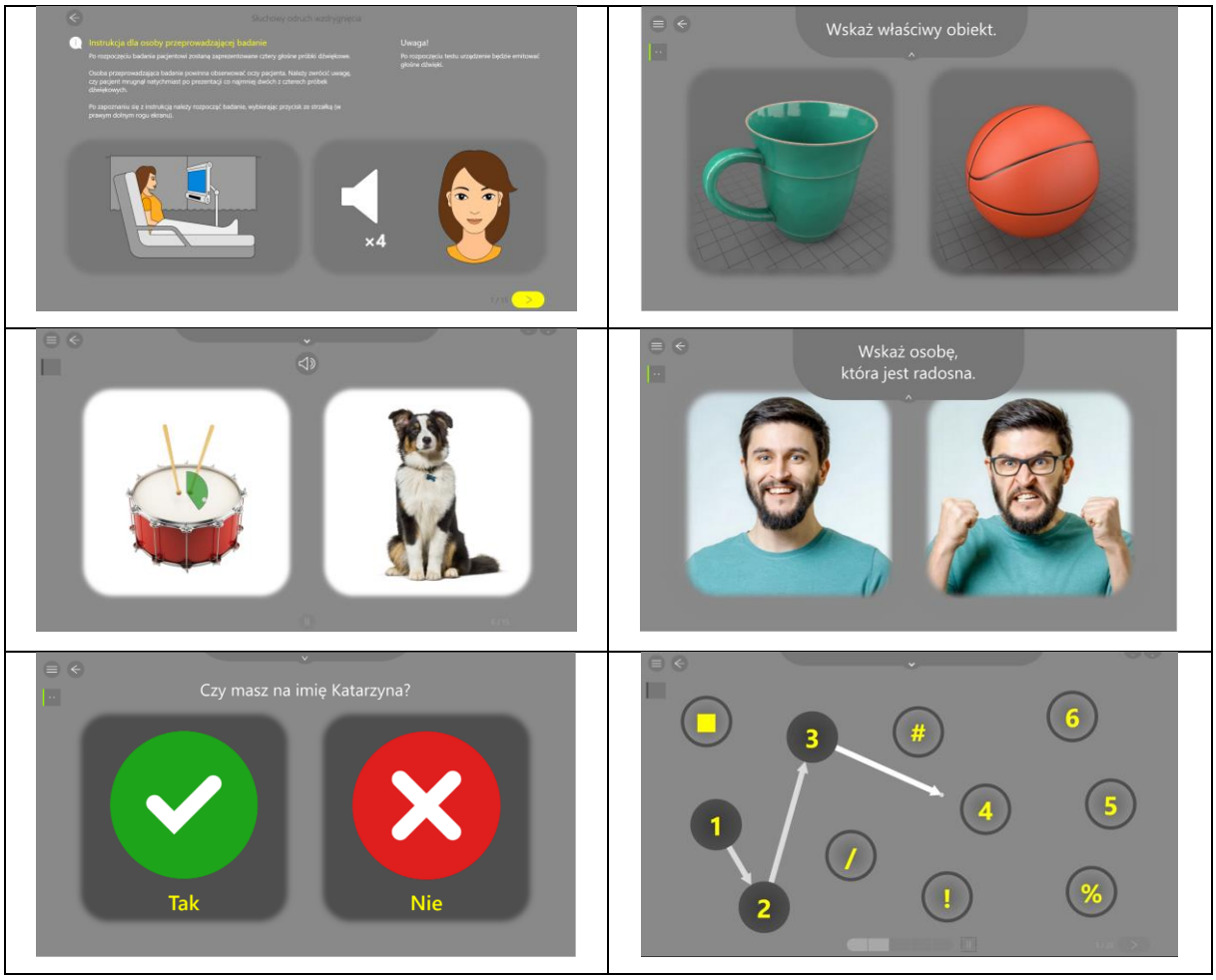
8. It is not possible to cancel the selection or change the answer given.

9. Selecting the back arrow and confirming that you want to abort the test exits the test, without saving the results of the completed tasks. It is not possible to return and complete an aborted test.

10. In questions about the patient’s name and year of birth, the first part of the question is read with a voiceover and the second part is read by a synthesiser. The voice of the synthesiser depends on the voices available on the device – male voices are selected first, then female voices (in the absence of male voices).

Sample screens – charts from the C-Eye X diagnostic module, presented as part of the clinical trials conducted:





It is the responsibility of researchers working with C-Eye to read the investigator's brochure that comes with the C-Eye X system. In addition, during the investigator training organised by the Sponsor, all investigators will be instructed on how to operate the C-Eye X in the context of conducting diagnostic tests (subject to clinical evaluation), as well as maintenance and safe operation of the device.

16. SAFETY REPORTING AND DEFINITIONS

16.1. Adverse Event (AE)

Any medical event that causes adverse effects in a clinical trial participant, even if there is no causal relationship with the products used in the clinical trial.

16.1.1. Adverse Device Effect (ADE)

An adverse event related to the use of an investigational medical device. This includes any adverse events resulting from inadequacies or inaccuracies in the instructions for use,

deployment, implantation, installation, handling or malfunction of the investigational medical device, as well as events resulting from use error or intentional misuse.

16.1.2. Serious Adverse Event (SAE)

A serious adverse event that results in a subject's death, life-threatening at the time of the event, the need for hospitalisation or prolongation of hospitalisation as a result of the event, permanent or significant impairment of health, or any other effect of the medicinal product that the physician, to the best of their knowledge, considers to be serious. A severe adverse event is also an event other than one that causes death, hospitalisation or severe life-threatening conditions, but which may pose an immediate threat to the Study participant or may require intervention to prevent one of the previously mentioned outcomes.

Planned hospitalisation for a pre-existing condition or a procedure required by a risk management plan, without serious deterioration of health, is not considered a serious adverse event.

16.1.3. Serious Adverse Device Effects (SADE)

- Adverse operation of the device that caused any consequences in the nature of a severe adverse event, i.e.:
- caused deaths,
- led to serious deterioration of health, by:
  - life-threatening illness or injury, or
  - o permanent impairment of body structure or function, or
  - for required inpatient hospitalisation or extension of existing hospitalisation, or
  - the need for medical or surgical intervention to prevent a life-threatening illness or injury or permanent damage to a body structure or function.

This includes defects in the device that may have led to a serious adverse event if:

- appropriate action has not been taken, or
- no intervention was made, or
- had the circumstances been less fortunate.

16.1.4. Unanticipated Adverse Device Effect (UADE)

Means any adverse effect on health or safety caused by or related to the device, if this effect or hazard was not previously recognised in terms of its nature, severity or degree of occurrence in the test plan, as well as any other unforeseen problem related to the device that relates to the rights, safety or well-being of the participants.

An event is considered anticipated if an effect that by its nature, incidence, severity or outcome has been previously identified in a risk analysis report.

16.1.5. Serious Unanticipated Adverse Device Effect (SUADE)

A device-related serious adverse effect that, due to its nature, incidence, severity or consequences, is not identified in the current version of the risk analysis report.

16.2. Reporting of AE

The occurrence of any adverse events will be reported within 24 hours simultaneously at two levels:

1) to the person representing the facility where the research is being conducted (the details of this person, along with their email, phone number and fax address, will be included in the contract with the facility)

and

2) to Ms Krystyna Barytska - an employee of AssisTech Sp. z o.o (email: krystyna.barytska@assistech.eu, mobile: +48 537 446 406 address: AssisTech Sp. z o.o. ul. Trzy Lipy 3, 80-172 Gdańsk, Poland).

The form for reporting an adverse event is attached as Appendix 2 to this protocol..

16.3. Annual Reports

Investigators will be required to submit Study reports to AssisTech Sp. z o.o. and the Principal Investigator upon completion of the Study.

17. STATISTICS

Statistical analysis in the project will be carried out by biostatistics specialists participating on behalf of an external CRO working with the Sponsor on this Study.

17.1. Description of Statistical Methods

Nominal and ordinal scale data will be presented as counts (N) and percentages (%) in each of the categories analysed, with the denominator used to determine the percentages given.

The range of summaries for interval scale variables, in each of the categories analysed, will include: mean with standard deviation, median and lower and upper quartile, maximum and minimum value, as well as the number of people for whom estimates of basic statistics were made.

If graphical presentation of the data is necessary, box-plots (median, quartiles, range of outliers or minimum/maximum values) and/or graphs of averages with 95% confidence intervals will be used.

The distribution of the variables will be evaluated based on the quantile-quantile (Q-Q) plot and the results of the Shapiro-Wilk test. Homogeneity of variance will be assessed using Levene's test.

For the CRS-R and MOCA tests, and the C-Eye X MCSD and CFA tests, the results will be presented as:

1) the sum of scores for all subscales of the test,
2) the point value obtained in each subscale,
3) the percentage of the total score for all subscales of the test related to the maximum value possible for the test (23 points for the CRS- R test, 30 points for the MOCA test, 11 points for the MCSD test, 24 points for the CFA test),
4) the percentage value in each subscale related to the maximum value possible in the subscale.

In each subsequent visit following visit 1, the relative percentage increases in total and subscale scores will be shown for visit 1. In addition, from all consecutive visits, the sum total of the test and subscale scores for each test will be determined; the data will be presented as raw values (points) and percentages related to the sum total of the maximum possible value for the test/subscale.

Analysis of the results of each test over time (in 3 or 5 consecutive visits) will be carried out using analysis of variance with repeated measures and contrast analysis (for raw or transformed data) or Friedman analysis of variance – depending on the type of data distribution, for both raw data and transformed percentages.

For patients enrolled in Test 1, the percentages of total scores for all subscales of the test relative to the maximum value possible in the test will be used to compare the scores during the

follow-up period (in 5 consecutive visits) obtained by the MCSD C-Eye X test with those of the CRS-R test. The analysis will be conducted using one-way analysis of variance (the type of test will be a factor) with repeated measures and contrast analysis. If the assumptions of normality of distribution are not met, an appropriate nonparametric method or logarithmic transformation or aligned rank transformation will be used. The relative percentage increases in total scores at the last visit relative to the Visit 1 and the summed (from all measurements over time) total scores relative to the summed maximum possible on a given test (%) will be compared using Student's t-test or Mann-Whitney U-test, depending on the type of data distribution.

For patients enrolled in Test 2, the percentages of total scores for all subscales of the test related to the maximum value possible in the test will be used to compare the results during the follow-up period (in 3 consecutive visits) obtained with the CFA C-Eye X test with the results of the CRS-R and MOCA tests. The analysis will be conducted using one-way analysis of variance (the type of test will be a factor) with repeated measures and contrast analysis. If the assumptions of normality of distribution are not met, an appropriate nonparametric method or logarithmic transformation or aligned rank transformation will be used. Relative percentage increases in total scores at the most recent visit relative to the Visit 1 and the summed (from all measurements over time) total scores relative to the summed maximum possible on a given test (%) will be compared using one-factor analysis of variance (the type of test will be a factor) with Tukey's post-hoc test or Kruskal-Wallis one-factor analysis of variance, with multiple comparisons tests of mean ranks for all samples, depending on the type of data distribution.

Passing-Bablok orthogonal regression will be used to evaluate the consistency of test scores (summed percentages of total scores for all subscales of the test related to the maximum possible value for the test) of the MCSD and CFA C-Eye X with the CRS-R and MOCA tests. In addition, Pearson's linear correlation coefficient or Spearman's rank coefficient will be determined depending on the distribution of the data. If the assumptions of normality of distribution are not met, an appropriate nonparametric method or logarithmic transformation will be used.

The selection of appropriate methods will be discussed further in the Statistical Analysis Plan.

17.2. The Number of Participants

Due to the lack of rationale, it is not possible to statistically estimate the sample size. The number of participants (90 in 2 groups of 45) was chosen due to logistical feasibility and the Study's budget.

17.3. The Level of Statistical Significance

A statistical significance level of $p < 0.05$ will be used. All tests will be two-sided.

17.4. Procedure for Accounting for Missing, Unused, and Spurious Data

Completion (imputation) of data deficiencies is not expected. For each variable analysed, the number and percentage of missing data in each category will be provided.

17.5. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Not applicable

17.6. Inclusion in Analysis

The results of all patients who participate in the Minimal Consciousness Detection Test (Test 1 – MCSD) and the Cognitive Function Examination Test (Test 2 – CFA) will be included in the analysis.

18. ACCESS TO SOURCE DATA/DOCUMENTS

Authorised representatives of the Sponsor, the facilities where the Study will be conducted, as well as the monitoring bodies, will have direct access to the collected data.

19. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The Study will be conducted in accordance with the currently approved study protocol, the approval of the Ethics Committee of the Academy of Physical Education in Wroclaw (approval number 11/2022) and the Helsinki Declaration, as well as the regulations and standard operating procedures of Poland and Germany.

The Study will conduct regular monitoring of the procedures and manner of data collection, as well as its compliance with the assumptions and source documents.

Monitors will verify this and how the study is conducted and that data is generated, documented and reported in accordance with applicable legal requirements.

20. ETHICS

Prior to the Study, approval was obtained from the Senate Committee on Research Ethics at the Academy of Physical Education in Wroclaw (approval no. 11/2022; date: 28.03.2022).

20.1. Approvals

The Study has received appropriate ethics committee approvals and is conducted in accordance with the Declaration of Helsinki.

20.2. Participant Confidentiality

The Study team will ensure that the anonymity of the Subjects is maintained. Patients will be identified by code – the participant's identification number on the Clinical Observation Card (CRF) and in the C-Eye X system.

All documents will be securely stored and accessible only to authorised representatives of the Sponsor, the facilities where the study will be conducted, as well as monitoring authorities.

The Study software environment, which is the responsibility of the external CRO, will be installed on a server infrastructure that provides security in accordance with ISO 27001.

21. DATA HANDLING AND RECORD KEEPING

The data collected will be sent electronically directly to a medical data collection platform that ensures information security in accordance with ISO 27001. Supervision of the security of the collected data will be performed by a CRO selected by the Sponsor that specialises in conducting such projects.

22. FINANCING AND INSURANCE

The research is co-financed under the National Research and Development Centre's competition 2/1.1.1/2020 grant application number: POIR.01.01.01-00-2125/20.

Insurance for patients included in the Study is provided by the Sponsor.

23. PUBLICATION POLICY

Publication of the results obtained in the Study will be carried out in accordance with the principles of good ethics in scientific research and the relevant requirements of scientific journals.

APPENDIX A: SCHEDULE OF PROCEDURES

Test 1: Minimally Conscious State Detection Test (MCSD Test)

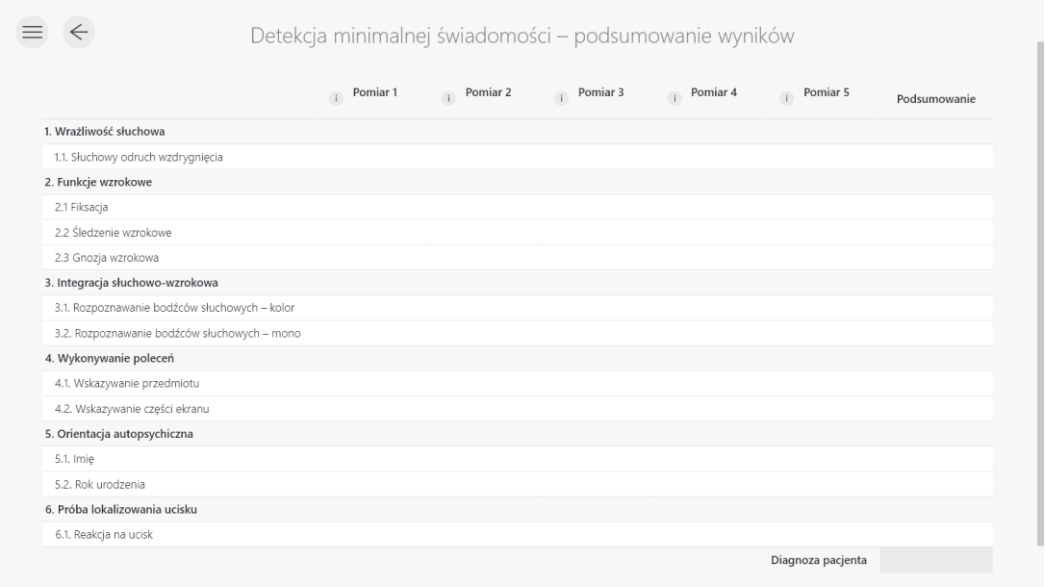
Procedures	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Final Visit
Informed consent, Medical history, Physical examination, Eligibility criteria	**x**						
CRS-R		**x**	**x**	**x**	**x**	**x**	
C-Eye X		**x**	**x**	**x**	**x**	**x**	
Completion of data in eCRF + uploading results from C-Eye X to online repository (after the visit)	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Physical examination, Compliance with protocol, Adverse event							**x**

Test 2: Cognitive Function Assessment Test (CFA Test)

Procedures	Screening	Visit 1	Visit 2	Visit 3	Final Visit
Informed consent, Medical history, Physical examination, Eligibility criteria, etc.	**x**				
CRS-R		**x**	**x**	**x**	
MOCA test		**x**	**x**	**x**	
C-Eye X		**x**	**x**	**x**	
Completion of data in eCRF + uploading results from C- Eye X to online repository (after visit)	**x**	**x**	**x**	**x**	**x**
Physical examination, Compliance with protocol, Adverse event					**x**

APPENDIX B: C-Eye X TEST RESULTS TABLES

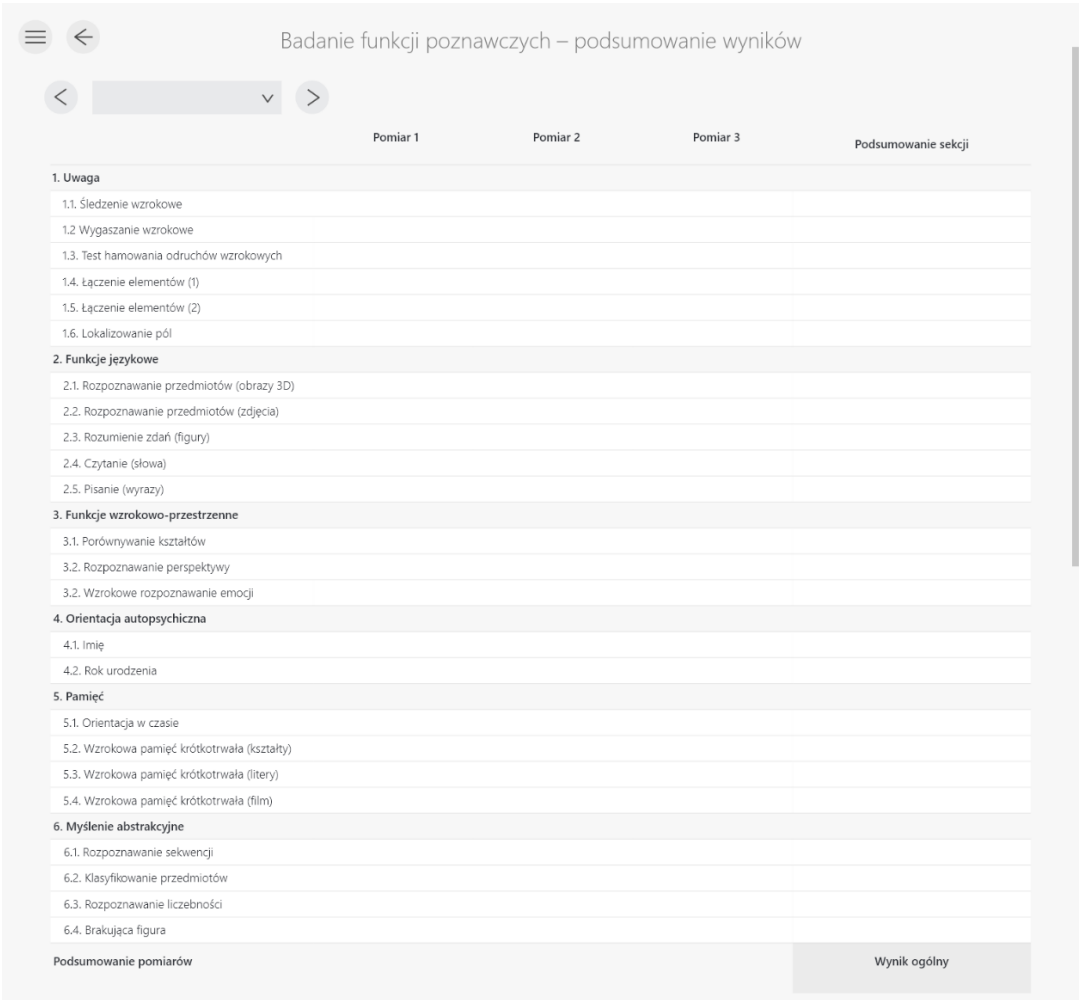
Test 1: Minimally Conscious State Detection Test (MCSD Test)



Detekcja minimalnej świadomości – podsumowanie wyników

	Pomiar 1	Pomiar 2	Pomiar 3	Pomiar 4	Pomiar 5	Podsumowanie
1. Wrażliwość słuchowa						
1.1. Słuchowy odruch wzdrygnięcia						
2. Funkcje wzrokowe						
2.1 Fiksacja						
2.2 Śledzenie wzrokowe						
2.3 Gnozja wzrokowa						
3. Integracja słuchowo-wzrokowa						
3.1. Rozpoznawanie bodźców słuchowych – kolor						
3.2. Rozpoznawanie bodźców słuchowych – mono						
4. Wykonywanie poleceń						
4.1. Wskazywanie przedmiotu						
4.2. Wskazywanie części ekranu						
5. Orientacja autopsychiczna						
5.1. Imię						
5.2. Rok urodzenia						
6. Próba lokalizowania ucisku						
6.1. Reakcja na ucisk						
					Diagnoza pacjenta	

Test 2: Cognitive Function Assessment Test (CFA Test)



Badanie funkcji poznawczych – podsumowanie wyników

	Pomiar 1	Pomiar 2	Pomiar 3	Podsumowanie sekcji
1. Uwaga				
1.1. Śledzenie wzrokowe				
1.2 Wygaszanie wzrokowe				
1.3. Test hamowania odruchów wzrokowych				
1.4. Łączenie elementów (1)				
1.5. Łączenie elementów (2)				
1.6. Lokalizowanie pól				
2. Funkcje językowe				
2.1. Rozpoznawanie przedmiotów (obrazy 3D)				
2.2. Rozpoznawanie przedmiotów (zdjęcia)				
2.3. Rozumienie zdań (figury)				
2.4. Czytanie (słowa)				
2.5. Pisanie (wyrazy)				
3. Funkcje wzrokowo-przestrzenne				
3.1. Porównywanie kształtów				
3.2. Rozpoznawanie perspektywy				
3.2. Wzrokowe rozpoznawanie emocji				
4. Orientacja autopsychiczna				
4.1. Imię				
4.2. Rok urodzenia				
5. Pamięć				
5.1. Orientacja w czasie				
5.2. Wzrokowa pamięć krótkotrwała (kształty)				
5.3. Wzrokowa pamięć krótkotrwała (litery)				
5.4. Wzrokowa pamięć krótkotrwała (film)				
6. Myślenie abstrakcyjne				
6.1. Rozpoznawanie sekwencji				
6.2. Klasyfikowanie przedmiotów				
6.3. Rozpoznawanie liczebności				
6.4. Brakująca figura				
Podsumowanie pomiarów				Wynik ogólny

Appendix 1

INFORMED CONSENT OF THE PATIENT TO PARTICIPATE IN THE STUDY (ICF form)

Name of the participant	
Name of the legal guardian/legal representative of the aforementioned participant:	
Address of residence:	
Phone number:	

Study title: **Evaluating the use of eye-tracking technology in the diagnosis of neurological patients, including patients with reduced consciousness.**

Aim of the Study: **Evaluation of C-Eye X system application in the neurological diagnostics of patients with reduced consciousness.**

Demonstrating that diagnostics of the state of consciousness and cognitive function of patients with consciousness disorders performed using C-Eye X allows a more objective assessment of the condition of patients who, according to traditional methods, remain in no contact with the surrounding world.

Approval was obtained from the Senate Committee on Research Ethics at the Academy of Physical Education in Wroclaw (approval no. 11/2022; date: 28.03.2022).

I hereby declare that I have been informed in detail about the conduct of the Study and the participation in the Study of the participant(s), of whom I am the legal guardian/legal representative. I understand what the Study is about and what my consent is needed for.

I give my informed consent to participate in the Study.

Please turn over!

I the undersigned:

- I agree to participate in the research project and am aware that I may withdraw from the Study at any time without giving reasons. By signing the consent to participate in the Study, I do not waive any due rights. I have received a copy of this form bearing my signature and date,
- I agree that in order to monitor the correctness of the execution of the Study, representatives of the Sponsor of the Study (AssisTech), the CRO of the contracted Study monitoring company (2KMM), as well as domestic, foreign or international institutions overseeing the Study, may inspect the personal data and medical records of the Subject (whom I represent), provided they are related to the study.

I declare that:

- I have been informed that I can ask questions about the experiment being conducted and the investigator will give me answers according to their best knowledge,
- I am not a person deprived of liberty, I do not have an official or other relationship with the investigator,
- I consent to the processing by AssisTech Sp. z o.o. (the Study Sponsor), based in Gdansk, Poland, and 2KMM (the company monitoring the Study on contract), based in Katowice, Poland:
    - my personal information,
    - personal data and medical data (data on health and results obtained from the Study) of the Subject, of whom I am the legal guardian / legal representative,

  in order to inform me of the Subject's eligibility for the Study and to collect and process statistical data collected during the diagnostic observations.

I agree to receive information with the use of means of remote communication in the form of telephone contact or SMS (text message) in accordance with the requirements of the General Data Protection Regulation (GDPR) of 27 April, 2016.

In addition, I declare that I have been informed that I can withdraw the consent I have given at any time, and that withdrawal of consent does not affect the legality of the processing carried out on the basis of consent before its withdrawal. I know that giving consent is voluntary but necessary to participate in the Study.

By signing this document, I also confirm that I have read the attached Information Clause regarding the processing of my personal data.

.....	…….....
investigator's signature	signature of legal guardian/legal representative

Location and date ……..

PARTICIPANT'S STATEMENT - CONSENT TO PERSONAL DATA PROCESSING

Name of the participant	
Name of the legal guardian/legal representative of the aforementioned participant:	
Address of residence:	
Phone number:	

Subject of the Study: **Evaluating the use of eye-tracking technology in the diagnosis of neurological patients, including patients with reduced consciousness.**

In accordance with Article 13(1) and (2) of the General Data Protection Regulation of 27 April, 2016 (hereinafter referred to as GDPR/Polish: RODO), I would like to inform you that:

1. Your personal data controller is AssisTech Sp. z o.o., based in Gdansk, St. Trzy Lipy 3

2. The contact person for data protection issues at AssisTech Sp. z o.o. is the Data Protection Officer: Izabela Maksim: izabela.maksim@assistech.eu, mobile 537 446 406

3. Your personal data will be processed for:

- implementing a new diagnostic method to improve the neurological diagnosis of patients with decreased consciousness using an eye tracking technique,
- protecting the health of patients by informing them of the opportunity to participate in a clinical trial (resulting from research work),
- assessing eligibility for the Study and invitation to participate in the Study,
- reporting on the effects of the Study,

using remote communication in the form of telephone contact or SMS (text message), based on Article 6(1)(a) of the General Data Protection Regulation of 27 April, 2016.

4. The recipients of your personal data will be authorised employees of the data controller and entities that – within the framework of contracts binding them with the controller – carry out the purpose of processing expressed in item 3.

5. Your personal data will not be transferred to third countries and international organisations.

6. Your personal data will be kept for the period necessary due to the business needs of the data controller, but no longer than 20 years.

7. You have the right to access the content of your data and the right to rectify, erase, restrict processing, the right to data portability, the right to object, the right to withdraw consent at any time without affecting the legality of the processing carried out on the basis of consent before its withdrawal.

8. You have the right to lodge a complaint with a supervisory authority if you consider that the processing of personal data concerning you violates the provisions of the GDPR/RODO.

9. Your provision of personal data is voluntary, and the consequence of failure to provide personal data will be the inability to fulfil the purposes indicated in item 3.

10. Your personal data will not be processed through profiling.

I hereby declare that I consent to the processing of personal data of the participant and myself to the extent necessary for the implementation of the research project in which I participate.

.....	…….....
investigator's signature	signature of legal guardian/legal representative

location and date ……..

Appendix 2

ADVERSE EVENT REPORT FORM

Fill out the form and email it to krystyna.barytska@assistech.eu or call +48 537 446 406

Patient information

Patient ID:		Date of birth (DD-MM-YYYY): ____ - ____ - _____
Body height (cm):	Body mass (kg):	Sex: □ M □ F

Information about the adverse event

Report type: ☐ Primary report ☐ Follow-up report	
Date of obtaining information about the event (DD-MM-YYYY) ____ - ____ - _____	
Date the event occurred (DD-MM-YYYY):____ - ____ - _____	Date the event ceased (DD-MM-YYYY): ____ - ____ - _____ ☐ The event is still ongoing
Description of adverse event:	

Event classification

☐ **Severe adverse event**

- ☐ Death, date (DD-MM-YYYY): ____ - ____ - _____
- ☐ Threat to life
- ☐ Permanent or significant disability or impairment
- ☐ Hospitalisation/extension of it date from: ____ - ____ - _____ □ continues
- ☐ Other medically relevant

☐ **Non-serious adverse event**

Linking an adverse event to C-Eye X: □ definitely related □ high probability of relation □ likely related □ doubtful relation □ unrelated	Justification for linking the event to C-Eye X:

Event outcome:	
□ recovery	□ recovery with permanent consequences
□ under treatment	□ no successful treatment
□ fatal	□ unknown

Additional information (laboratory tests, medical history, etc.):

Information on the reporting person

First name:	Surname:
Email address:	Phone numer:
Signature:	Date of the report (DD-MM-YYYY): ____ - ____ - _____