# **Protocol title:** Augmented Reality-Assisted Neurosurgical Drain placement (ARANED)

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# Study synopsis

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| **Protocol - full title** | Augmented Reality-Assisted Neurosurgical Drain placement | |
| **Protocol acronym - short title** | ARANED | |
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| **Study sponsor** | Name: UZ Brussel<br>Address: Laarbeeklaan 101, B-1090 Brussels, Belgium | |
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| **Background** | The **Augmented Reality-Assisted Neurosurgical Drain placement** (ARANED) study is part of a larger project called **Surgical Augmented Reality Assistance** (SARA). The goal of the SARA project is to assess the added value of **augmented reality** (AR) during surgery in terms of usability, relevance and (surrogate) outcomes (measuring for accuracy, usefulness, gain in time, patient safety and physician comfort). To this end, a series of experiments is defined, complementary to each other, and involving a variety of medical specialties, focusing on cranial and spinal neurosurgery and orthopedic surgery. The use of the AR device with associated software will first be assessed with several preclinical experiments based on geometric models, anthropomorphic models and cadavers.<br>Clinical testing within the scope of the SARA project will be limited to class II pilot studies, and all procedures will take place in specific settings where the safety of the human subjects cannot be compromised. Completion of larger-scale clinical randomized trials are beyond the scope of this project.<br><br>ARANED focuses on neurosurgical drain placement. Drain placement is an often-used procedure for patients with increased intracranial pressure (**intracranial hypertension**; ICH) or with intracranial hemorrhage (**intraparenchymal hemorrhage** (IPH) or **chronic subdural hematoma** (CSDH)), with the goal to drain **cerebrospinal fluid** (CSF) or blood, respectively, as well as to measure pressure in the specific compartment the drain is positioned in. To drain CSF, a so-called **external ventricular drain** (EVD) is placed. The placement of any intracranial drain is almost always performed freehand, following inspection and planning on CT images of the patient. For EVD placement additional, literature-defined landmarks are employed, however, these are not patient-specific. As detailed below, these procedures and their accuracy have been studied extensively in literature, making them a suitable subject for clinical testing.<br><br>AR-assisted placement of EVD and intra-hematoma drains (using a **head-mounted display** (HMD) – the Microsoft HoloLens - with proprietary software) will be performed in the context of the ARANED trial. Beside geometric and clinically relevant (e.g. clinically used accuracy scale) outcome variables, surgeon experience (intuitiveness, ergonomics, quickness) will be evaluated, and used as a feedback to the technical developments behind the study. User experience can be influenced by several factors, such as the efficiency of the workflow, ergonomics (regarding both the **head-mounted display** (HMD) itself as well as the use of the device and the software), the ease of data flow, etc. Wherever possible, feedback from the clinical experiences will be used to support further technical developments. This way, exploration of advanced topics beyond pure accuracy measures becomes possible, including but not limited to:<br>• Inattentional blindness (confusion between real and virtual world),<br>• The use of historical images (i.e. updating preoperative images to better reflect the current situation)<br>• Marker-free navigational tracking<br>• Different points-of-view for multiple surgeons<br>• Telepresence<br>• … |

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| **Participants to include** | Adult patients requiring external ventricular drain (EVD) placement. The current clinical status does not prevent the patient from undergoing the standard treatment for the abovementioned condition(s). The patient or his legal representative received a detailed verbal explanation of the study treatment, after which they had the chance to ask any questions. The patient or his legal representative read the **informed consent** (IC) document after which it was signed in duplicate. |
| **Study design** | In order to assess the accuracy of AR in drain placement surgery with the clinical feasibility in mind, we will sequentially recruit 10-15 patients. Prior to enrollment of these patients, the surgeons will have a brief adjustment period in which the holographic information will not be displayed on the patient but elsewhere in the field of view of the surgeon (unregistered), to adjust to the HoloLens and the use of the AR navigation interface while still adhering to the conventional drain placement methods. For the following 10-15 patients the AR overlay will be registered to and displayed on top of the patient, showing the relevant anatomy in its supposed actual location (giving the impression of "see-through vision"). This conversion not only assures optimal patient safety, but also allows us to investigate and improve upon the concurrently developed AR user-interface.<br><br>Thus, a clinical experiment will be set up where current practice is compared to AR guidance. Minimal invasive drain placement in the CSF-space (ventricle) will be performed in standard fashion, but with the aid of a 3D model of the patient and the specific compartment to be targeted displayed in the field of view of the surgeon, either without registration to the patient (i.e. next to the patient serving as an in-room 3D visualization), or with registration to the patient (i.e. on top of the patient providing the surgeon with the impression of "see-through vision"). Results from these drain placements (accuracy being measured using clinical scales) will be compared to historical controls from literature and from our center. |
| **Primary objective/endpoint** | To demonstrate the feasibility and added value of an AR based (neuro)navigation system implemented on the HoloLens aimed towards external ventricular drain (EVD) placement in critical care settings. EVD placement accuracy will be assessed using the Kakarla scale, ranging from good (grade I) to poor (grade III) placement. We will implement a comparative analysis of the clinical outcome data to normal ranges based on historical values obtained from literature and from our center. |
| **Secondary objectives/endpoints** | • Improvement of user experience (intuitiveness, ergonomics, quickness; using the questionnaires in Appendix B)<br>• Decrease of duration of procedure compared to same procedure performed without AR (based on historical values of procedure time, recorded at our institution)<br>• Decrease of difference in outcome (accuracy scale) and of difference in duration of procedure between surgeons of different expertise levels compared to same intervention without AR (flattening of the learning curve)<br>• Improvement of clinical outcome measures with AR-assisted surgery compared to standard practice (using the scales in Appendix C)<br>• Improvement of pathology-specific clinical outcome measures:<br>  o Revision rate<br>  o Complication rate<br>  o Velocity of the decrease in ICP<br>  o Evolution of midline shift |

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| **Exploratory objectives/endpoints** | • Explore development and optimization of an efficient and ergonomic workflow in a well-structured pipeline (pipeline from imaging to display of holograms)<br>• Explore and describe necessity for continuous implementation of technical advances improving the AR experience, such as:<br>  o Correcting for inattentional blindness (confusion between real and virtual world),<br>  o Correcting for the use of historical images (i.e. updating preoperative images to better reflect the current situation),<br>  o Implementing marker-free navigational tracking,<br>  o Exploring cooperation by offering different points-of-view for multiple surgeons,<br>  o Explore assistance of these interventions by using telepresence,<br>• … |
| **Safety monitoring** | All data from every single patient will be collected in a unique **electronic Case Report Form** (eCRF) which perfectly matches the source documents (e.g. study charts at the hospital). It is the investigator's responsibility to ensure completion and to review and approve all eCRF data. Thus, accuracy and authenticity of all data entered on the eCRFs is guaranteed by the investigator. Adverse events, both related and unrelated to study treatment, will be monitored on an ongoing basis and their frequencies reported semi-annually. Clinical outcome data will be tabulated and compared to historical values from literature as well as normal ranges for the institution, based on retrospective review of historical clinical data from the institution. |
| **Statistical design & sample size** | This is a class II, single-arm, clinical pilot study investigating feasibility, safety and efficacy of a proprietary software solution for augmented reality-display, and registration and tracking of patient-specific anatomic models on the Microsoft HoloLens, with the aim to provide guidance during external ventricular drain placement. The protocol will enroll 10-15 patients over the course of one year. |
| **Investigational product** | SARA consortium-developed proprietary software solution for Microsoft HoloLens |
| **Study period** | • Recruitment Start Date (FPI): 01/01/2019<br>• Estimated recruitment End Date (LPI): 30/06/2020<br>• End of study: the first follow-up appointment of the last patient to receive study treatment, or death of the last patient in this trial (whichever comes first). |

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# 1 Introduction and background

## 1.1 Context of the project

Extensive knowledge of surgical anatomy has always been the cornerstone of successful surgical or non-surgical invasive procedures. Due to limited imaging possibilities in the early days of surgery, large incisions were often made in order to expose as much normal anatomy as possible for orientation purposes. This most often led to longer and more extensive interventions that were difficult to perform for the surgeon, had steeper learning curves, but also led to more patient discomfort and higher likelihood of complications. Limited-access procedures where no relevant anatomy is exposed for orientation, such as cranial drain placement, relied on (and currently still do) predefined external anatomical landmarks, most often without adaptation to the patient's specific situation.

The advent of 3D imaging modalities has vastly improved pre-operative planning. Surgeons have become very adept at interpreting these slice-based imaging modalities, which are typically presented in an axial, coronal and sagittal fashion. Based on these, the physician produces a mental image of the 3D anatomy. Alternatively, a 3D reconstruction is displayed on a screen during the intervention. For orientation, the surgeon uses his knowledge of anatomy but also occasionally glances at the screen. The problem is that the images are uncorrelated to the actual patient and that the surgeon continually has to mentally align the anatomy from the imaging modalities with the patient before him. This puts an unnecessary cognitive load on the surgeon, for one, and secondly, often extensive surgical exploration looking for anatomical landmarks still has to be performed for orientation during the surgical intervention.

**Augmented reality** (AR) may increase the accuracy [1] and safety [2] of the surgery, allow for more minimally invasive surgical approaches and reduce the duration and cost of interventions. AR may also prove beneficial for surgeons in training [3], as it provides realistic 3D visualizations of normal and pathological anatomy which can be manipulated and inspected from all angles.

The **Augmented Reality-Assisted Neurosurgical Drain placement** (ARANED) study is part of a larger project called **Surgical Augmented Reality Assistance** (SARA). SARA took shape as a project by the interaction between a group of people with relevant expertise and interested in the potential of this novel technology, as well as clinicians (the end-users) expressing a clear clinical need. The project aims to investigate the feasibility of using AR for pre-operative planning, per-operative visualization and navigational support, and assess its impact on surgical training. Clinical validation of the technical solutions is a crucial step in assessing the real-world accuracy and usefulness of the augmented reality holographic information provided to the surgeons.

## 1.2 State of the art: navigation in surgery

### 1.2.1 Neuronavigation

Current neuronavigation uses optical or electromagnetic tracking technology to establish and maintain correspondence between preoperative imaging and the patient with high accuracy [4–6]. A tracked reference frame is fixed to the patient's anatomy, and registered to the preoperative imaging. From then on, imaging can be easily viewed in the corresponding plane by placing a tracked pointer on the patient anatomy. The advent of neuronavigation has facilitated minimally invasive surgery, relying on imaging instead of direct sight. Various "(neuro)navigation systems" have been commercialized [7]. They are not often used for routine interventions due to a number of inherent limitations:

- Bulkiness of devices – An additional computer system, external tracking camera and multiple screens are needed, taking up space in the operating theatre
- Setting up the system and patient registration are time-consuming and error-prone

- The need to mentally transpose the 2D or 3D images on an external screen to the actual patient puts a significant cognitive load on the surgeon (*Figure 1*). Moreover, a pointer device is held inside the patient's anatomy (for example against the brain tissue) while the surgeon looks elsewhere (at the screen). This interrupts workflow, but can also be dangerous.
- The control over what imaging data is displayed on the screen is too limited for the surgeon, who cannot touch the screen directly due to sterility constraints.
- The outside-in tracking by an external tracking device (**infrared** (IR) camera) often creates a 'line of sight' problem. When the line of sight is blocked, the workflow breaks.
- Navigation mostly makes use of 'historical images': the imaging information is not updated as surgery progresses, even though anatomy alters during surgery.

Although it is possible to present the anatomical images in a virtual world, it is still constrained by a screen (*Figure 1*), only linking the virtual world and the patient by means of a tracked pointer. AR aims at blending this virtual world with the actual world in a more ergonomic way, addressing many of the limitations of current neuronavigation. AR using a **head-mounted display** (HMD) is not yet applied in (neuro)surgical practice but is receiving increased attention lately.

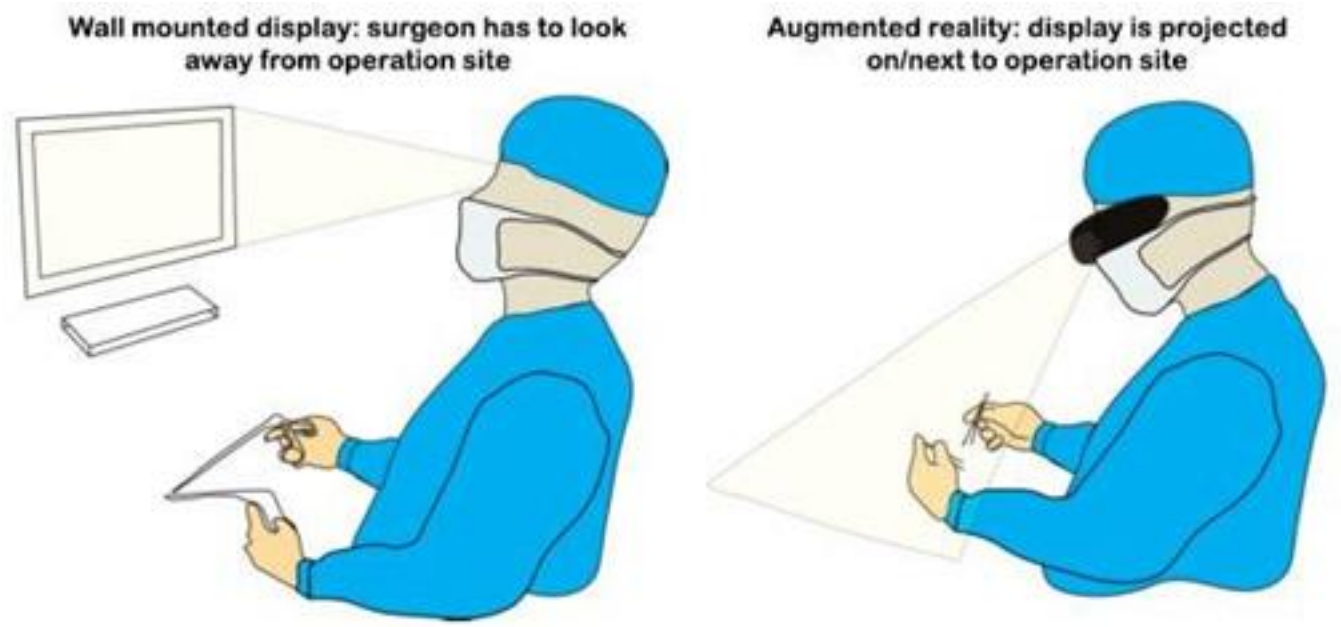



*Figure 1. Current situation: the surgeon looks at an external display (left). With AR, the image could be projected directly on a relevant surface (right) (adapted from [8])*

### 1.2.2 AR navigation

Neurosurgery was one of the first and is currently the most popular surgical specialty where AR is used [9]. In most cases presented in literature until now, the augmented data is presented into the surgical microscope, as an overlay on top of the magnified view of the surgical site [10–15]. AR microscopic surgery is until now the only AR application in surgery which has been commercialized. Such AR systems don't require a pointer device, as it is the focal point of the microscope that is navigated. As the operating microscope is used for many neurosurgical interventions, the surgeon is also very familiar with its use which adds to ergonomics. However, AR microscopic surgery suffers from many similar issues as neuronavigation as described earlier and the microscope itself is not practical for all phases of surgery or for procedures that would otherwise not require a surgical microscope.

Besides AR on the surgical microscope, hand-held cameras have also been used. In this case, the captured images together with the AR overlays are displayed on a screen in the OR [16–19]. Such systems can be more conveniently used in all steps of the surgery, from skin incision to tumor resection. However, the positioning of these cameras is not straightforward, and they still require the surgeon to look away from the surgical field to a screen.

To overcome this problem, several research groups explored the use of mobile devices such as smartphones and tablets, that immediately display the AR overlays while looking at the patient [20–24]. This, however, forces the surgeon to put down his/her instruments in order to pick up the device. Secondly, even though in a more practical fashion, the information is still observed on a screen. Others have proposed AR systems where a projector is used to display the virtual elements on top of the real world [1]. Whereas such systems allow to maintain direct vision of the patient and operating field, allow for intuitive visualization and potentially resolve the eye-hand coordination problem, they suffer from a major parallax error which increases with the depth of the anatomical structures.

The only approach that does not suffer from any of these limitations, is the use of smartglasses and other HMDs which either project an AR enhanced camera view [25] on the glasses (potentially with unacceptable lag for use during surgery) or come with transparent "see-through" glasses. The great advantage of using such HMDs, next to ergonomics, is that the surgeon's head can be tracked to adapt the point of view. This still requires an external tracking camera in most instances, however, as most smartglasses do not possess accelerometers or an inside-out tracking mechanism.

Most available literature on the use of smartglasses or similar HMDs in surgery remains experimental in nature – not clinical – or proposes systems not truly augmenting the perceived world [26–28]. Only one recent clinical report has examined the clinical application of smart glasses for surgical navigation [29] (using a customized version of the Epson Moverio to allow for external tracking).

### 1.2.3 HoloLens in surgery

The HoloLens, developed by Microsoft Corporation, is the first device of its kind. It combines an HMD with an integrated full-powered, untethered computer and a multitude of sensors that can register the real world around it, and also track the position of the device itself (and thus of the wearer's head) using accelerometers, gyroscopes and an inside-out tracking system. So far, only four reports on the use of the Microsoft HoloLens in surgery have been published in medical scientific literature. The first consists of a report on a phantom study in the field of vascular surgery, but does not assess any clinical validation [30]. The second and third, by Incekara et al. [31] and Li et al. [32], are both a first attempt in validating the use of an HMD (the Microsoft HoloLens) in a clinical neurosurgical setting. These prospective studies provide an estimate of the feasibility and accuracy of HMDs in tumor incision planning and **external ventricular drain** (EVD) placement, respectively, but have some shortcomings: the authors only used generic open-source software for 3D model creation and visualization and thus did not have a customized user interface for hologram manipulation nor a method for automated registration. They also attest to insufficient accuracy. This is due to the fact that they did not develop a customized application to optimize accuracy of placement and stability of the hologram relative to the physical world but rather made use of the HoloLens' built-in SLAM (Simultaneous Localization And Mapping) algorithm.

The fourth publication is by our own research group. This work came about as the result of ongoing collaboration between UZ Brussels and VUB-ETRO. An application for AR based neuronavigation with the HoloLens was developed in the context of a master thesis by Ir. T. Frantz. This application, which is Unity-based, provides the technology necessary for each of the components in the SARA project, ranging from 3D model generation over user interface, automated segmentation and registration to validation.

As shown in *Figure 2*, our system has previously been used in the OR for testing purposes and proof-of-concept demonstration.

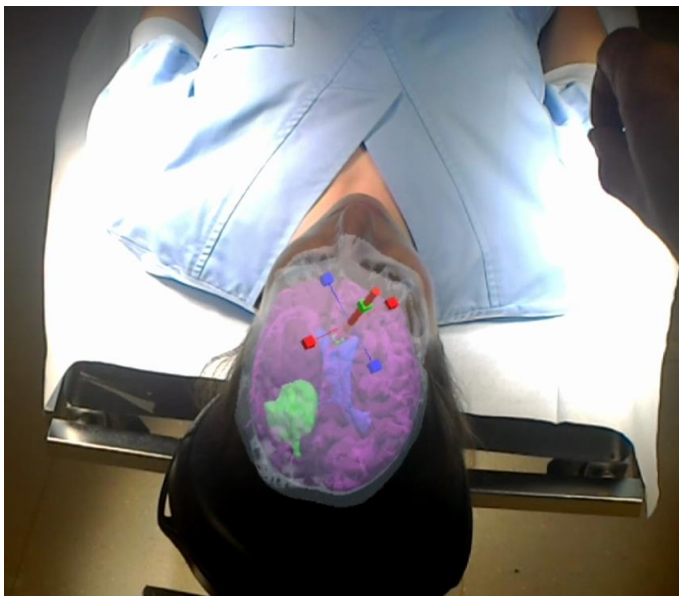


*Figure 2. Holographic semi-transparent overlay of patient anatomy in current interface*

In the experimental setup using phantom models, Frantz et al. [33] showed a mean perceived drift between the virtual object and physical object of no more than 1.41 ± 1.08 mm when using an optimized version of the Vuforia tracking software development kit (*Table 1-1*).

| Condition | $^{-}90°$ | $^{-}45°$ | $0°$ | $^{+}45°$ | $^{+}90°$ | Mean | $\sigma$ | SEM |
|---|---|---|---|---|---|---|---|---|
| Control [mm] | 6,27 | 3,59 | 0,62 | 4,60 | 6,90 | 4.39 | 3.34 | 1.29 |
| Vuforia [mm] | 0,83 | 1,46 | 1,24 | 0,08 | 3,42 | 1.41 | 1.08 | 0.67 |
| Δ | -87% | -59% | 0%* | -98% | -50% | -68% | -68% | -48% |

* Shown to be insignificant.
$\sigma$: Standard deviation.
*SEM:* Standard error of the mean.

*Table 1-1. Change in mean perceived drift for each measurement angle (from Frantz et al)*

It was also demonstrated that a test person is able to pinpoint a predefined point on the physical object (only visible on the virtual object) within 5mm in 93% of cases, comparing favorably to literature (*Table 1-2*). This is also clinically highly relevant when a cranial burr hole needs to be made, for example. It was thus demonstrated that our system is as precise as current neuronavigation methods and can be used for initial clinical testing.

| Study | <2mm | 2-5mm | 5-10mm | >10mm |
|---|---|---|---|---|
| Rae et al. | 50% | 0% | 50% | 0% |
| Frantz et al. | | | | |
| Matched* | 87% | 13% | 0% | 0% |
| Control | 19% | 34% | 40% | 7% |
| Vuforia | 53% | 40% | 7% | 0% |

* Results matched to reflect measurements taken from a starting position, without introducing movement.

*Table 1-2. Comparison of published surface localization results (from Frantz et al)*

## 1.3 State of the art: drain placement

Drain placement is an often-used procedure for patients with increased intracranial pressure (**intracranial hypertension**; ICH) or with intracranial hemorrhage (**intraparenchymal hemorrhage** (IPH) or **chronic subdural hematoma** (CSDH)), with the goal to drain **cerebrospinal fluid** (CSF) or blood, respectively, as well as to measure pressure in the specific compartment it is positioned in. To drain CSF, an EVD is placed. In current practice, the minimally invasive placement of any intracranial drain is most often performed freehand, after inspection of and planning on CT images of the patient. For EVD placement additional, literature-defined landmarks are employed. These landmarks are not patient-specific, and literature even dictates to follow them even in the presence of anatomy-altering pathology [34]. As detailed below, these procedures and their accuracy have been studied extensively in literature, making them a suitable subject for clinical testing. Since all of these procedures are currently always performed in a "blind" fashion (i.e. without visual feedback, relying on either anatomical landmarks and standard angles in the case of EVD placement or on the uncorrelated CT-images and measurements made on these in the case of hematoma drainage), they provide the ideal context for demonstrating the added value of an AR-based visualization system for neuronavigation.

For EVD placement, an accuracy scale for drain placement in the CSF spaces has been described in literature [35,36], given below in *Table 2-1*. To promote conformity within our clinical assessment and to be able to lump patients together for statistical analysis, we will subdivide this accuracy scale into three tiers (right column).

| ***Grade*** | ***Description*** | ***Assessment*** |
|---|---|---|
| *1* | *Appropriately placed catheter in the ipsilateral frontal horn including tip of the 3rd ventricle* | *Good placement* |
| *2* | *Suboptimal placement in the contralateral frontal horn, corpus callosum or interhemispheric fissure* | *Suboptimal placement* |
| *3* | *Placement in other brain parenchyma or other fluid filled spaces* | *Poor placement* |

*Table 2-1. Accuracy scale for EVD placement in the CSF spaces as described by Kakarla et al. [35]*

Accuracy rates according to this scale have been reported in literature to be between 77 and 79% for good placement, between 10 and 14% for suboptimal placement and between 7 and 13% for poor placement using the freehand technique [35,36]. Multiple passes were reported in 5,4% of the EVD placements [36]. Similar studies have been performed when using guides or image guidance [35,36]. In literature, the overall complication rate (covering drain-related infections, post-placement hemorrhage and malplacement of the ventricular drain) ranges from 14,2 to 16,1% [36,37]. Hemorrhage has been reported to range from 1,8 to 33% [35,37,38], and reported infection rates range from 5,4% to 10,2% [36,37]. Kakarla et al. reported a mortality rate of 0,6% [35].

For intra-hematoma drain placement for IPH, a scale defined for the MISTIE trial [39] is used (*Table 2-2*):

| ***Assessment*** | ***Description*** |
|---|---|
| *Good placement* | *Placed along the entire longitudinal axis of the hematoma with the fenestrated segment in the epicenter of the clot, circumferentially surrounded by the hematoma* |
| *Suboptimal placement* | *Over- or undershooting the target position or in eccentric location, yet fully engaging the IPH and suitable for dosing* |
| *Poor placement* | *Not engaging the IPH (i.e. catheter perforations not in contact with the clot), not allowing safe/effective dosing, hence requiring replacement* |

*Table 2-2. Accuracy scale for drain placement in an IPH*

Literature reports that for IPH drainage using catheters, 58% of drains is in good position, 28% is suboptimally placed (but sufficient for drainage and intra-hematoma administration of specific drugs), and 14% is poorly placed (requiring repositioning) [40]. The overall complication rate goes up to 33,3% [41,42] and Barrett et al. also reported a mortality rate of 13,3% [42].

For twist-drill drainage of CSDH, [43] no specific scale has been described so far. For consistency with the abovementioned scales, we suggest the following classification (*Table 2-3*):

| ***Assessment*** | ***Description*** |
|---|---|
| *Good placement* | *Drain positioned in the hematoma in the subdural space* |
| *Suboptimal placement* | *Placement in the subdural space but not in the hematoma* |
| *Poor placement* | *Incorrect placement of the drain: subcutaneous placement, epidural placement or intraparenchymal placement of the drain* |

*Table 2-3. Accuracy scale for drain placement in a CSDH*

No data on the accuracy of twist-drill drain placement is currently available in literature, but the overall complication rate has been reported to range from 3 to 26,9%, recurrence rate from 10 to 33% and mortality rate from 2,9 to 11,4% [43,44]. Sindou et al. also reported insufficient evacuations in 3,3 to 5,7% of the cases [43], and Weigel et al. reported a cure rate (full autonomy after surgery) in up to 88,2% of the patients [44].

In this study we aim to demonstrate that AR-assistance in EVD placement surgery increases the accuracy and clinical results, flattens the learning curve for these procedures and increases surgeon comfort by making the procedure more visual in nature. For accuracy testing, the clinically validated accuracy scales will be used to compare outcomes to historical values from literature, but also historical values from retrospective review of drain placement procedures performed previously at UZ Brussel.

# 2 Study Design

In order to assess the accuracy of AR in EVD placement surgery with the clinical feasibility in mind, we will sequentially recruit 10-15 patients. Adequate accuracy of registered-hologram drain placement has been demonstrated in our phantom trials, that will be continued concurrently with the clinical trial in order to optimize any technical issues, the user interface and the user experience, and to demonstrate learning-curve effect in a safe manner. Thanks to Li et al [32], the preliminary work to demonstrate the efficacy and safety of the use of the HoloLens for clinical drain placement has already been done. Prior to enrollment of these patients, the surgeons will have a brief adjustment period in which the holographic information will not be displayed on the patient but elsewhere in the field of view of the surgeon (unregistered), to adjust to the HoloLens and the use of the AR navigation interface while still adhering to the conventional drain placement methods. For the following 10-15 patients the AR overlay will be registered to and displayed on top of the patient, showing the relevant anatomy in its supposed actual location (giving the impression of “see-through vision”). This conversion not only assures optimal patient safety, but also allows us to investigate and improve upon the concurrently developed AR user-interface.

Thus, a clinical experiment will be set up where current practice is compared to AR guidance. Minimal invasive drain placement in the CSF-space (ventricle) will be performed in standard fashion, but with the aid of a 3D model of the patient and the specific compartment to be targeted displayed in the field of view of the surgeon, either without registration to the patient (i.e. next to the patient serving as an in-room 3D visualization), or with registration to the patient (i.e. on top of the patient providing the surgeon with the impression of “see-through vision”). Results from these drain placements (accuracy being measured using clinical scales) will be compared to historical controls from literature and from our center.

In order to optimize image processing from a technical point of view (optimization of segmentation procedure), but also for the mentioned concurrent phantom trials we will also (aside from the imaging data from the prospectively included patients) use imaging (CT and MRI) data, obtained retrospectively and fully anonymized, from 20 randomly selected patients.

# 3 Patient selection criteria

Patients must meet all of the following recruitment criteria to be eligible for enrolment into the trial:

1. Diagnosis of any intracranial pathology requiring external ventricular drain placement.
2. Age ≥18 years.
3. The patient or his/her legal representative must be able to understand the planned study treatment after receiving a detailed verbal explanation, after which they had the chance to ask any remaining questions.
4. No contraindication for evaluation by CT.
5. Baseline CT is performed maximum 1 week before initiation of treatment (usually even performed at the moment of diagnosis, immediately prior to the intervention).
6. Current clinical status does not prevent the patient from undergoing the standard treatment for the abovementioned condition(s); standard inclusion and exclusion criteria for surgery in general will be applied.
7. Willingness and ability to comply with scheduled visits, treatment plans and other study procedures.
8. The patient or his/her legal representative signed and dated the **informed consent** (IC) document indicating that the patient (or legal representative) has been informed of all the pertinent aspects of the trial.

# 4 Treatment plan

## 4.1 HoloLens application

### 4.1.1 Pre-operative phase

The patient will be screened for eligibility as mentioned above. Further screening assessments will include anamnesis, documentation of the medical history, clinical examination (including vital parameters) and baseline CT-imaging of the brain. If the patient is deemed eligible for inclusion, information on the trial will be provided to the patient. If the patient agrees to participate in the trial, a signed IC document will be obtained.

Upon inclusion, standard procedures for clinical management of patients requiring drain placement will apply. Baseline imaging of the brain is performed pre-operatively, as is common practice for these procedures. The obtained imaging material (as anonymized DICOM images) will be prepared for transfer to HoloLens (segmentation, 3D modelling and subsampling) using proprietary software developed by the SARA-consortium. Planning of the intervention itself will be performed either on a planning station (a computer equipped with the beforementioned software) or on the HoloLens itself, using the 3D models as guidance (see Part 10 for ethical considerations). This concludes all preparations required for the intra-operative application of the HoloLens.

### 4.1.2 Operative phase

The procedure itself will take place in a standardized fashion, performed by surgeons (in this case neurosurgeons or neurosurgeons in training) of different expertise levels (but always with adequate expertise and clearance to perform this procedure, as is current clinical practice). Surgical technique for the procedure is described below. The main difference is the use of the HoloLens as an AR device for visual aid during the procedure, which will not alter the operational workflow. The HoloLens will only be used immediately before and during the planned surgical procedures.

***Surgical technique***

The patient is installed on the operating table in the supine position. Patients will be sedated. The entry point is decided by the surgeon (usually at Kocher's point), based on the pathology at hand, pre-existing anatomical knowledge and knowledge of anatomical landmarks, but also surgical planning information based on the preoperative CT scan, as well as the augmented reality-displayed surgical trajectory. The entry point is then marked on the skin (after local shaving if necessary) and the patient undergoes standard surgical prepping (disinfection) and draping. A stab incision is made at the entry point, after which the hand drill is placed against the skull and a drill trajectory is made in the skull, following the predefined trajectory that the drain should follow. This trajectory is based, again, on the pathology at hand, pre-existing anatomical knowledge and knowledge of anatomical landmarks and trajectories, surgical planning information based on the preoperative CT scan, and, importantly, the augmented reality-displayed surgical trajectory. The drain is then placed through the drill hole and advanced until the predefined depth (decided upon based on the surgical planning). After placement, flow of CSF or blood (depending on the pathology) through the drain is checked, after which it is secured to the skin with suture thread and connected to a drainage system.

***Analysis***

The following measures pertaining to the surgical experience will be recorded during and after the surgical procedures:

- Duration of the surgical procedure (in minutes)
- Number of passes of the drain before correct placement
- Surgeon's estimate of success of placement (using the graded scale detailed below)
- Surgeon experience (detailed questionnaire available in Appendix B)

### 4.1.3 Post-operative phase & follow-up

Within 24h after surgery the patient will undergo a CT-scan to assess the position of the newly-placed drain. The primary endpoint, accuracy of drain placement evaluated on the immediate postoperative CT and graded according to clinical relevance, will be evaluated using the abovementioned Kakarla scale (*Table 2-1*).

In the further post-operative period, the patient's status will be monitored as it would be for every patient undergoing standard treatment for the abovementioned pathologies: in the immediate post-operative phase the patient is monitored in the Intensive Care Unit (ICU). In the following days the patient may undergo additional imaging of the brain if deemed necessary, and his/her clinical status will be continuously monitored, as is common practice. Based on the clinical evolution, the drain may or may not be removed, and the patient may or may not be transferred to the neurosurgical ward.

As soon as the patient is deemed adequately fit, he/she will be discharged from the hospital and a first follow-up appointment will be planned after 6 weeks. At this appointment the patient's clinical status and cranial imaging status will be assessed one final time, after which the patient has completed his/her participation in the trial.

## 4.2 Clinical evaluation, imaging & follow-up

Patients will be clinically monitored in accordance with standard of care for patients requiring EVD placement. We do not intend to do extensive research concerning the pathology, but rather want to get a notion of the possible difference in outcome related to the use of the HoloLens. The evaluations mentioned in this chapter will therefore be limited to the regular standard of care and only data obtained until the first follow-up appointment will be used for the trial. The schedule and types of assessments are presented in *Table 4*. The schedule is flexible as long as changes do not, in the opinion of the investigator, expose the patient to undue risk or induce bias in the evaluation of the endpoints. Data from the specified assessments will be collected in the **electronic Case Report Form** (eCRF).

| Protocol related procedures and assessments | Screening | Surgery | Post-operative period | Hospital discharge | Follow-up |
|---|---|---|---|---|---|
| | ≤ Day 0 | Day 0 | Weekly | | |
| Signed IC | X | | | | |
| Prior medical history | X | | | | |
| Physical examination | X | X | X | X | X |
| Clinical follow-up scales | X | X | X | X | X |
| Adverse events monitoring | X ↦ | | | X | X |
| Concomitant therapy | X ↦ | | | X | X |
| *Other assessments* | | | | | |
| CT-scan | X | X within 24h following surgery | (X) when deemed necessary for clinical reasons | | X |
| *Study treatment* | | | | | |
| Surgery using HoloLens | | X | | | |
| Survival status | | | | | X |

*Table 4. Protocol related procedures and assessments. The bold line indicates the end of the patient's participation in the trial.*

Assessments outlined in *Table 4* include the following components:

- Prior medical history – diagnosis, prior and/or current treatments, history of other diseases (active or resolved), concomitant illnesses, and demographics.

- Physical examination – examination of major body systems (especially neurological evaluation), body weight and height (at screen only), vital parameters (i.e. temperature, blood pressure, and heart rate) and clinical follow-up scores (GCS, mRS, NIHSS, MGS; Appendix C).
- Adverse Events – Adverse events that are recorded in this trial are medical or surgical complications. Nature of the complication, date of appearance, relationship to the surgical procedure/trial intervention, offered treatment and outcome will be recorded. Patients will be followed for adverse events during the study until at least the first follow-up appointment, or until all serious adverse events have resolved or are determined to be "chronic" or "stable", whichever is later. Serious adverse events should be monitored and reported from the time that the patient is included in the study (cfr. Part 8).
- Concomitant therapy – concomitant medications and treatments will be recorded from the time that the patient is included, during the study, and up until the first follow-up appointment.
- CT-scan – CT imaging of the brain:
    - Signs of increased intracranial pressure of any cause (e.g. trauma, anoxia, …), requiring placement of an EVD (e.g. GCS ≤ 8)
    - Hematoma volume and evolution, evolution of midline shift
- Survival status – information on the patient's post-operative survival will be collected for all patients until the first follow-up appointment.

## 4.3 Concomitant therapy

The use of the HoloLens does not interfere with the patients' (medicinal) therapy. Medical treatment will therefore be continued or adjusted based on the requirements for the planned surgical procedure. This includes the standard post-operative care and follow-up.

All concomitant medications and blood products, as well as interventions (e.g. analgesic use or paracentesis) received by patients until the end of study inclusion will be recorded on the eCRF.

## 4.4 Life Style Guidelines

The use of the HoloLens does not interfere with the patients' life style. Lifestyle adjustments will therefore only be adjusted if necessary based on the requirements for the planned surgical procedure. This includes the standard period of post-operative care and follow-up.

# 5 Statistical design

This is a class II, single-arm, clinical pilot study investigating feasibility, safety and efficacy of a proprietary software solution for augmented reality-display, and registration and tracking of patient-specific anatomic models on the Microsoft HoloLens (further referenced to in this paragraph as “the experimental treatment”) in patients requiring EVD placement.

A patient is considered evaluable if he has signed informed consent and has undergone the HoloLens-assisted surgical intervention. Primary endpoint is accuracy according to the abovementioned Kakarla scale and can be evaluated within 24 hours after surgery. Patients will be encouraged to complete follow-up (which does not differ from standard follow-up for these pathologies) in order to evaluate the secondary endpoints (clinical outcome, cfr below) but will remain evaluable in the context of the trial even if planned follow-up has not been completed.

## 5.1 Objective & endpoints

We wish to demonstrate the feasibility and added value of an AR based (neuro)navigation system implemented on the HoloLens for guidance during EVD placement. EVD placement accuracy will be assessed using the Kakarla scale, ranging from good (grade I) to poor (grade III) placement. These clinical outcome data will be compared to normal ranges based on historical values obtained from literature and from our institution.

Secondary endpoints:

- Improvement of user experience (intuitiveness, ergonomics, quickness; using the questionnaires in Appendix B).
- Decrease of duration of procedure compared to same procedure performed without AR (based on historical values of procedure time, recorded at our institution)
- Decrease of difference in outcome (accuracy scale) and of difference in duration of procedure between surgeons of different expertise levels compared to same intervention without AR (flattening of the learning curve)
- Improvement of clinical outcome measures with AR-assisted surgery compared to standard practice (using the scales in Appendix C)
- Improvement of pathology-specific clinical outcome measures:
    - Revision rate
    - Complication rate
    - Velocity of the decrease in ICP
    - Evolution of midline shift

Exploratory endpoints:

- Explore development and optimization of an efficient and ergonomic workflow in a well-structured pipeline (pipeline from imaging to display of holograms)
- Explore and describe necessity for continuous implementation of technical advances improving the AR experience, such as:
    - Correcting for inattentional blindness (confusion between real and virtual world),
    - Correcting for the use of historical images (i.e. updating preoperative images to better reflect the current situation),
    - Implementing marker-free navigational tracking,
    - Exploring cooperation by offering different points-of-view for multiple surgeons,
    - Explore assistance of these interventions by using telepresence,
    - …

## 5.2 Sample size calculation

When aiming to objectively demonstrate an accuracy improvement of EVD placement obtained through AR guidance in comparison to the freehand technique, we’d aim for 95% correct placement

as is the case for guidance using conventional neuronavigation systems. Testing against the null hypothesis EVD placement accuracy of 70-80% with current freehand techniques, thus would be the alternating hypothesis accuracy of 95% using AR guidance. Given a significance level (i.e. the probability of rejecting $H_0$ when it is true) of 5% (alpha=0,05) and power (i.e. 1-beta, the probability of confirming the added value) of 80% (beta=0,20), minimally 67 patients would be needed.

However, given the purpose of the current study being the evaluation of the system's feasibility for intraoperative use in a critical care setting, this number will be limited to 10-15 patients, as is common practice for such studies. Following positive results, this trial may be followed by such a larger, randomized controlled trial. Dropout is expected to be unlikely, since the surgery is planned unrelated to the study and will not be cancelled under normal circumstances.

## 5.3 Accrual

Patients will be enrolled in a consecutive fashion over the course of one year. Patient inclusion can only take place in case one of the mentioned medical investigators is present to ensure correct adherence to study protocol. We will account for all of the patients registered in the study. The number of patients who were not evaluable, who died or withdrew before treatment began will be specified. The number of patients lost to follow-up will be given.

## 5.4 Statistical analysis

Dichotomized comparisons will be used to compare drain placement accuracy performed with versus without surgical AR assistance. Results obtained from the Kakarla scale after surgery with the AR guidance will be tabulated and compared to historical values obtained from literature and from our institution. These historical values are based on previous research in drain placement (without the use of AR guidance), and will be matched with the cases of the current study.

To achieve these dichotomized comparisons, we will use cut-offs within the accuracy scale to define different benchmarks of good versus bad drain placement. The cut-off can be placed at either side of the 'suboptimal placement'-category (cfr. Part 1), depending on the degree of accuracy we wish to pursue: a comparison with the cut-off above this category will analyze the improvement of perfect placement, whereas the cut-off below this category will analyze acceptable drain placement in general. Given the eventual alternating hypothesis of increased placement accuracy related to the use of AR guidance, along with the small expected sample size, these comparisons will be performed through one-sided Fisher's exact tests.

# 6 Patient registration procedure

Prior to undergoing any study-specific procedure, patients must read the patient information brochure and sign the current **Institutional Review Board** (IRB)-approved IC form (see Part 10.3 for the procedure during emergency situations). Screening procedures can then take place as listed in Part 4. Subjects meeting the eligibility criteria for study participation will start experimental treatment as soon as is estimated possible by the investigator.

## Patient withdrawal

A patient may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. Unless the subject specifically withdraws his consent for use of the obtained data, the patient will remain evaluable within the trial if he has undergone the AR-assisted surgical procedure since the primary endpoint and some secondary endpoints are based on results that are obtained immediately after the surgical intervention.

If a subject does not return for the scheduled follow-up visit, every effort should however be made to contact the subject and to document subject outcome, if possible. If the subject withdraws consent, no further evaluations should be performed and no attempts should be made to collect additional data, and the data obtained until that point will not be used in the final analysis.

A patient may be withdrawn from the trial in case the surgical intervention cannot be performed for any reason (for example sudden unexpected adverse event preceding the surgery and precluding it), or in case of withdrawal of patient consent

# 7 Forms and procedures for collecting data

## 7.1 Case Report Forms / Electronic Data Record

As used in this protocol, the term eCRF should be understood to refer to an electronic data record (Excel and Microsoft Access file). This eCRF will be completed for each included subject. The completed original eCRF is the sole property of the study sponsor (UZ Brussel) and will not be made available in any form to third parties, appropriate regulatory authorities, without written permission of the UZ Brussel.

It is the investigator's responsibility to ensure completion and to review and approve all eCRF data. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all data entered on the eCRFs.

Subject source documents are the physician's subject records maintained at the trial site. In most cases, the source documents will be the hospital's or the physician's chart or a study chart. The source documents must match the information collected on the eCRF.

## 7.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g. eCRFs and hospital records), all original signed IC forms, copies of all eCRFs, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to local regulations during a period of 20 years.

## 7.3 Study Monitoring

This study will be initiated as a single center study. During the conduct of this study at a single site (UZ Brussel), the sponsor will monitor for the completeness and accuracy of the eCRF content.

## 7.4 GDPR-compliancy

In accordance with the recent installment of the **General Data Protection Regulation** (GDPR) on the 25th of May 2018, following measures will be taken:

- All personal data of the participating patients will be processed by the PI of this study or anyone working directly under his supervision.
- To ensure protection of all personal data during processing, a **Data Protection Officer** (DPO) (dpo@vub.be) will be appointed.
- The gathered data will only be used to investigate the endpoints mentioned in this protocol under *5.1 Objective & endpoints*. As mentioned before, a patient may withdraw his consent for the use of any previously obtained data at any time. This withdrawal requires no justification from the patient, nor will it have any influence on the quality of the provided care.
- The only investigators with access to personal data are investigators with a medical background (physicians) and physicians caring for the patient. All other involved parties and investigators will only be able to view anonymized data (see Part 10).
- There will be no transfer of personal data to any other countries.
- All personal data will be retained as explained above in Part 7.2.

# 8 Reporting adverse events

## 8.1 Safety Monitoring

Adverse events will be monitored on an ongoing basis and their frequencies reported semi-annually. The worst event for each patient will be described. Both events related and unrelated to treatment will be captured. Clinical outcome data will be tabulated and compared to normal ranges for the institution, based on historical values obtained at the institution.

### 8.1.1 Adverse events

All observed or volunteered adverse events regardless of suspected causal relationship to the investigational product(s) or intervention will be reported as described in the following sections. For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event (cfr. below) requiring immediate notification to the study sponsor / IRB / **Internal Ethics Committee** (IEC). For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

As the use of the HoloLens has no direct impact on the workflow of the standard surgical procedure, we do not expect it to cause any adverse events whatsoever. We expect general surgery-related complications as they would happen in the standard of care for the abovementioned pathologies, but none of these complications are directly linked to the use of the device.

#### 8.1.1.1 Definition of an adverse event

An adverse event is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the application of the study treatment regardless of the causal relationship. Examples of adverse events include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- …

A serious adverse event is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. Worsening of signs and symptoms should be reported as adverse events in the appropriate section of the eCRF. Disease progression should not be reported as adverse event.

*Abnormal Test Findings*

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to discontinuation from the trial, significant additional therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

*Serious Adverse Events*

A serious adverse event is any untoward medical occurrence that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is an important medical event. Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. An example of such events is intensive treatment in an emergency room or at home for convulsions that do not result in hospitalization.

Progression of the pathology during the study (including signs and symptoms of progression) should not be reported as an adverse event unless the outcome is fatal during the trial or within the safety reporting period. Hospitalizations due to signs and symptoms of disease progression should not be reported as serious adverse events. If the pathology has a fatal outcome during the trial or within the safety reporting period, then the event leading to death must be recorded as a serious adverse event.

#### 8.1.1.2 Hospitalization

Adverse events reported from clinical trials associated with hospitalization or prolongation of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/ICU (e.g. from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g. caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions.

For same-day surgeries (outpatient/ambulatory procedures), hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g. for work-up of persistent pre-treatment lab abnormality, for single treatment-responsive seizure in a patient with known epilepsy);
- Social admission (e.g. patient has no place to sleep);

- Administrative admission (e.g. for yearly physical exam);
- Protocol-specified admission during a clinical trial (e.g. for a procedure required by the trial protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g. for elective cosmetic surgery);
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products;
- Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

### 8.1.2 Severity Assessment

Complications will be classified as medical (infection, electrolyte disturbance, etc.) or surgical. The investigator will use the following definitions of severity as defined by the Clavien-Dindo classification [45] to describe the maximum intensity of the adverse event (*Table 5*). The grade reported in the adverse event eCRF must be consistent with the description of the Clavien-Dindo grade included in the narrative section of the serious adverse event report.

**Table 5**. Classification of Postoperative Complications (Clavien-Dindo)

| Grade | Definition |
|---|---|
| Grade I | Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. |
| | Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside. |
| Grade II | Requiring pharmacological treatment with drugs other than such allowed for grade I complications. |
| | Blood transfusions and total parenteral nutrition are also included. |
| Grade III | Requiring surgical, endoscopic or radiological intervention |
| Grade IIIa | Intervention not under general anesthesia |
| Grade IIIb | Intervention under general anesthesia |
| Grade IV | Life-threatening complication (including CNS complications)* requiring IC/ICU-management |
| Grade IVa | single organ dysfunction (including dialysis) |
| Grade IVb | multiorgan dysfunction |
| Grade V | Death of a patient |
| Suffix “d” | If the patient suffers from a complication at the time of discharge, the suffix “d” (for “disability”) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication. |

*Brain hemorrhage, ischemic stroke, subarachnoid hemorrhage, but excluding transient ischemic attacks.

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit

*Table 5. Classification of Postoperative Complications (Clavien-Dindo)*

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

### 8.1.3 Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records. In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

### 8.1.4 Withdrawal due to adverse events

Withdrawal due to adverse events should be distinguished from withdrawal due to insufficient treatment results, according to the definition of adverse event noted earlier, and recorded on the appropriate adverse event eCRF page. When a patient withdraws due to a serious adverse event, the serious adverse event must be reported in accordance with the reporting requirements defined below.

## 8.2 Reporting period

Serious adverse events require immediate notification beginning from the time that the patient is included in the study, through and including the first follow-up appointment. Any serious adverse event occurring any time after the reporting period must be promptly reported if a causal relationship to the investigational product is suspected. Adverse events (serious and non-serious) should be recorded on the eCRF from the time the patient is included in the study until the first follow-up appointment. Death must be reported if it occurs during the serious adverse event reporting period, irrespective of any intervening treatment.

### 8.2.1 Reporting Requirements

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient. In addition, each trial patient will be questioned about adverse events.

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate. Adverse event reporting to regulatory authorities will be carried out in accordance with applicable Belgian regulations.

All adverse events will be reported on the adverse event page(s) of the eCRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the eCRFs as well as on the form for collection of serious adverse event information.

# 9 Quality assurance

## 9.1 Intellectual quality assurance

The quality of all presented data will be thoroughly monitored and reviewed by both the principal investigator and sponsor. In addition, several focus groups, involving both academic peers (neurosurgeons, orthopedic surgeons, anesthetists, …) and industrial partners (Microsoft, Materialise, …), as well as an independent data monitoring committee will be employed to review all provided results, thusly ensuring a high level of quality.

## 9.2 Technical quality assurance

Post-hoc video analysis of the intra-operative footage obtained from the HoloLens' RGB camera and, if applicable, external cameras that implement a spectator view of the augmented situation, will be performed in order to assess proper functionality of the system as well as to detect whether the measured results correspond with the user's perceived performance. These results provide further feedback information for the HoloLens software, supplementary to the comparative and user experience analyses.
Additionally, this intra-operative footage will be applied for the development of a mixed reality interface, thus improving on the augmented reality interface we currently use. Through machine learning the computer will be able to recognize certain operative steps and instruments used by the surgeon, after which it can interact with the situation at hand. This will enhance the synergy between the surgeon and the software, making an even greater improvement of accuracy possible.

# 10 Ethical considerations

## 10.1 Patient protection

The study will be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subject (Appendix D), adopted by the General Assembly of the World Medical Association (1996). In addition, the trial will be performed in accordance with the protocol, International Organization for Standardization **Good Clinical Practice** (GCP) guidelines [46], and applicable local regulatory requirements and laws.

## 10.2 Subject identification & anonymization

Upon inclusion in the trial, patients will be issued a study code. eCRFs for specific patients will only use the code as will the study database, which is password protected. The only investigators with access to specific patient data are investigators with a medical background (physicians) and physicians caring for the patient. All other involved parties and investigators will only be able to view anonymized data.

The obtained imaging information (in DICOM format) will be also anonymized and coded as it will be used for further manipulation into holograms. Video information will be anonymized if it is to be viewed by anyone other than the trial investigators with a medical background (physicians) or physicians caring for the patient.

In order to optimize image processing from a technical point of view (optimization of segmentation procedure), but also for phantom trials (concurrently performed and used for evaluation and optimization of the procedures in this trial in a non-invasive fashion) we will use imaging (CT and MRI) data, obtained retrospectively and fully anonymized, from 20 randomly selected patients.

## 10.3 Informed consent

The IC form must be agreed to by the IRB/IEC and must comply with the International Organization for Standardization GCP, local regulatory requirements, and legal requirements. The IC form used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB/IEC before use.

The investigator must ensure that each trial subject, or his/her legally acceptable representative, is fully informed about the nature and objectives of the trial and possible risks associated with participation. The investigator will try to obtain written IC from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain a copy of each subject's signed consent form.

In emergency situations, however, the study treatment must be started as soon as possible after the patient is admitted to the hospital. In these situations, the patient is usually unable to decide for him-/herself whether or not to take part in the study. Waiting until the legal representative arrives to inform him/her of the study and obtain his/her consent for the participation of the patient he/she represents would mean the normal urgent care has to be provided and the investigational treatment can no longer be offered under these conditions. Since a patient’s participation will most likely benefit the progress of his/her clinical situation under these specific conditions, we will therefore implement the investigational treatment both without the consent of the patient and without the consent of the legal representative, in accordance with the provisions of Chapter VI of the Law of May 2004 related to experiments on humans.

The consent of the legal representative will be obtained as soon as possible and the patient’s consent will be asked once the improvement in his/her clinical situation allows him/her to be informed correctly of the objectives and procedures of the study and to agree to them. If the patient (or legal representative) does not give his/her consent, the previously obtained data cannot be used for further analysis. All decisions and informed consent procedures during this emergency situation will be well documented, dated (date & time) and signed by the investigator in charge.

# 11 Trial sponsorship and financing

The sponsor of this study is C4N-NEUR and BEFY-ORTHO of UZ Brussel, Laarbeeklaan 101, 1090 Brussel, Belgium. A grant from both Imec-icon and VLAIO was obtained for the duration of the study.

# 12 Trial insurance

The sponsor of this study, UZ Brussel will offer insurance coverage for all the study participants in accordance with the Belgian law.

# 13 Intellectual property and publication policy

All data resulting from this study are the intellectual property of the study sponsor (UZ Brussel, represented by the principal investigator). No data from this study can be used for any purpose without the written consent of the study sponsor. The study sponsor stays the owner of the author's rights of all reports (partial or final) made up by the investigators in the context of this study.

The industrial partners recognize the right of the investigators to use data resulting from this study for educational purposes, for communications at congresses and for scientific publications. The sponsor of this study and the industrial partners will exchange ideas prior to each publication or public announcement and discuss results. The role of the industrial partners will stay advisory at any moment. The investigators commit themselves to restrain from any form of publication, announcement or press-release concerning results emerging from this study, without previous consultation with the industrial partners.

We aim to present results at major international conferences (EANS annual meeting, CNS annual meeting, AANS annual meeting, WFNS annual meeting) and publish the mature results in an international neurosurgery journal (preferably the Journal of Neurosurgery, World Neurosurgery, Operative Neurosurgery, Neurosurgery or the International Journal of Computer Assisted Radiology and Surgery). The article will be submitted at the latest two years after completion of the trial.

First author for all publications emerging from this protocol will be the first co-investigator of this trial listed in the beginning of the protocol. The principal investigator will be senior author for publication. Any other authors and order of the author string will be determined by the principal investigator and based on the significance of the contributions of each co-author (contribution of each author will be specifically mentioned).

# Appendix A: List of abbreviations

| | |
|---|---|
| AR | Augmented Reality |
| eCRF | Electronic Case Report Form |
| CSDH | Chronic Subdural Hematoma |
| CSF | Cerebrospinal Fluid |
| CT | Computed Tomography |
| DPO | Data Protection Officer |
| EVD | External Ventricular Drain |
| FPI | First Patient In |
| GCP | Good Clinical Practice |
| GDPR | General Data Protection Regulation |
| HMD | Head-Mounted Display |
| IC | Informed Consent |
| ICH | Intracranial Hypertension |
| ICU | Intensive Care Unit |
| IEC | Internal Ethics Committee |
| IPH | Intraparenchymal Hemorrhage |
| IR | Infrared |
| IRB | Institutional Review Board |
| LPI | Last Patient In |
| OR | Operating Room |
| SARA | Surgical Augmented Reality Assistance |

# Appendix B: User experience questionnaires

*1. Utaut-model: measuring the likelihood of technology-acceptance (Venkatesh et al. [47])*

The following items are answered on a 5-point Likert scale ranging from strongly disagree to strongly agree.

| Strongly disagree | | | | Strongly agree |
|---|---|---|---|---|
| | | | | |
| 1 | 2 | 3 | 4 | 5 |

Performance expectancy
- I would find the system useful in my job.
- Using the system enables me to accomplish tasks more quickly.
- Using the system increases my productivity.
- If I use the system, I will increase my chances of getting a raise.

Effort expectancy
- My interaction with the system would be clear and understandable.
- It would be easy for me to become skillful at using the system.
- I would find the system easy to use.
- Learning to operate the system is easy for me.

Social influence
- People who influence my behavior think that I should use the system.
- People who are important to me think that I should use the system.
- The senior management of this business has been helpful in the use of the system.
- In general, the organization has supported the use of the system.

Facilitating conditions
- I have the resources necessary to use the system.
- I have the knowledge necessary to use the system.
- The system is not compatible with other systems I use.
- A specific person (or group) is available for assistance with system difficulties

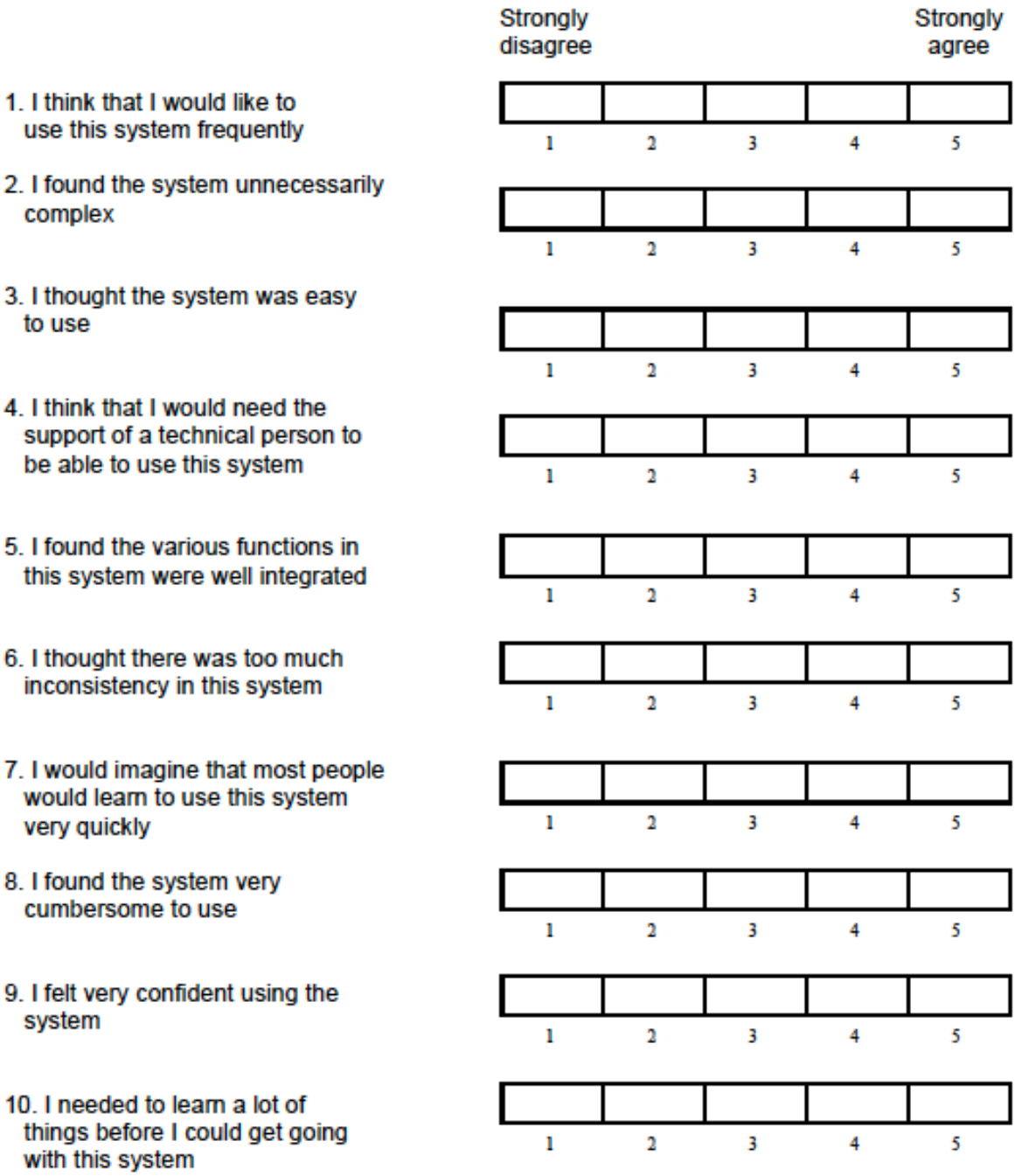
Behavioral intention (adapted from [47])
- I intend to use the system as soon as it becomes available in the hospital.
- I predict I would use the system as soon as it becomes available in the hospital.
- I plan to use the system as soon as it becomes available in the hospital.

Gender
- Female
- Male

Age: I am ____ years old

Experience
- Neurosurgical resident, year ___
- Certified neurosurgeon, since _____

2. *System usability scale (Brooke [48])*



*3. Socio-demographic details*

| | |
|---|---|
| **Gender:** | Male / female |
| **Year of birth:** | |
| **Profession:** | |

| | | |
|---|---|---|
| **Please indicate your dominant hand.** | O Right<br>O Left<br>O No preference | |
| **Are you currently wearing glasses/contact lenses?** | O No<br>O Yes, I wear glasses.<br>O Yes, I wear contact lenses. | |
| **Do you wear glasses/contact lenses during surgery?** | O No<br>O Yes, I wear glasses.<br>O Yes, I wear contact lenses. | |
| **Have you previously participated in a similar study?** | O Yes<br>O No | |
| **Surgical experience** | | |
| **How much surgical experience do you possess?** | O Little / I'm still in training<br>O Intermediate<br>O Extensive | |
| **Please indicate the estimated amount of surgeries you have performed (semi-) independently.** | O < 25<br>O 25 – 50<br>O 50 – 100 | O 100 – 500<br>O 500 – 1000<br>O > 1000 |
| **How many surgeries do you perform on a weekly basis?** | O …… surgeries per week | |

*4. Subjective measures related to comfort (adapted from Tanagho et al. [49])*

Do you experience one of the following discomforts? To what extent (x = somewhat; xx = quite a lot; xxx = extensively)?

| | **Yes** | **No** |
|---|---|---|
| **Eye strain** | | |
| **Headache** | | |
| **Dizziness** | | |
| **Disorientation** | | |
| **Physical discomfort** | | |
| **Poor visualization** | | |

5. *Cognitive workload: NASA-TLX (Task Load Index; Hart et al. [50])*

## NASA Task Load Index

*Hart and Staveland's NASA Task Load Index (TLX) method assesses work load on five 7-point scales. Increments of high, medium and low estimates for each point result in 21 gradations on the scales.*

| Name | Task | Date |
|---|---|---|
| | | |

Mental Demand — How mentally demanding was the task?

Very Low — Very High

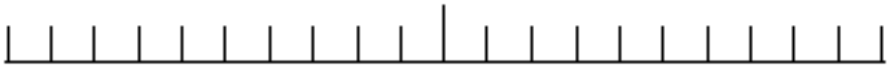
Physical Demand — How physically demanding was the task?

Very Low — Very High

Temporal Demand — How hurried or rushed was the pace of the task?

Very Low — Very High

Performance — How successful were you in accomplishing what you were asked to do?



Perfect — Failure

Effort — How hard did you have to work to accomplish your level of performance?

Very Low — Very High

Frustration — How insecure, discouraged, irritated, stressed, and annoyed wereyou?

Very Low — Very High

*6. Various subjective measures (created by Imec-SMIT or adapted from [47] and [51])*

The following items are answered on a 5-point Likert scale ranging from strongly disagree to strongly agree.

| Strongly disagree | | | | Strongly agree |
|---|---|---|---|---|
| | | | | |
| 1 | 2 | 3 | 4 | 5 |

- I feel comfortable working with this system.
- I can use the system in an intuitive way.
- I was able to finish the task efficiently (adapted from Kumcu et al. [51]).
- I felt in control over the system (adapted from Kumcu et al. [51]).
- I believe this system might have a negative influence on the safety of the patient during surgery (adapted from Kumcu et al. [51]).
- The system allows me to work accurately.
- I could complete a certain task using this system without anybody present to provide me with step-by-step guidance on what I need to do (adapted from Venkatesh et al. [47]).

If you have any additional remarks or feedback, please leave them in the box below. In case more writing space is needed, please use the backside of this document (from Kumcu et al. [51]).

# Appendix C: Clinical follow-up scales

*1. Intracranial hypertension & intraparenchymal hemorrhage*

**Glasgow Coma Scale**

| Behavior | Response | Score |
|---|---|---|
| Eye opening response | Spontaneously | 4 |
| | To speech | 3 |
| | To pain | 2 |
| | No response | 1 |
| Best verbal response | Oriented to time, place, and person | 5 |
| | Confused | 4 |
| | Inappropriate words | 3 |
| | Incomprehensible sounds | 2 |
| | No response | 1 |
| Best motor response | Obeys commands | 6 |
| | Moves to localized pain | 5 |
| | Flexion withdrawal from pain | 4 |
| | Abnormal flexion (decorticate) | 3 |
| | Abnormal extension (decerebrate) | 2 |
| | No response | 1 |
| Total score: | *Best response* | 15 |
| | *Comatose patient* | 8 or less |
| | *Totally unresponsive* | 3 |

**Modified Rankin Scale**

| Description | Score |
|---|---|
| No symptoms at all | 0 |
| No significant disability despite symptoms; able to carry out all usual duties and activities | 1 |
| Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance | 2 |
| Moderate disability; requiring some help, but able to walk without assistance | 3 |
| Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance | 4 |
| Severe disability; bedridden, incontinent and requiring constant nursing care and attention | 5 |
| Dead | 6 |

*2. Intraparenchymal hemorrhage*

**National Institutes of Health Stroke Scale**

| Instructions | Scale definition | Score |
|---|---|---|
| 1a. Level of Consciousness (LOC) | Alert; keenly responsive | 0 |
| | Arousable by minor stimulation | 1 |
| | Obtunded | 2 |
| | Unresponsive or reflex response | 3 |
| 1b. LOC Questions (Month & Age) | Answers both questions correctly | 0 |
| | Answers one question correctly | 1 |
| | Answers neither question correctly | 2 |
| 1c. LOC Commands (Open/close eye & Grip/release non-paretic hand) | Performs both tasks correctly | 0 |
| | Performs one task correctly | 1 |
| | Performs neither task correctly | 2 |
| 2. Best Gaze (Horizontal eye movements) | Normal | 0 |
| | Partial gaze palsy | 1 |
| | Total gaze paresis | 2 |
| 3. Visual | No visual loss | 0 |
| | Partial hemianopia | 1 |
| | Complete hemianopia | 2 |
| | Bilateral hemianopia | 3 |
| 4. Facial Palsy | Normal | 0 |
| | Minor paralysis | 1 |
| | Partial paralysis | 2 |
| | Complete paralysis | 3 |
| 5. Motor Arm (score both sides separately) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement. | 4 |
| | Amputation or joint fusion | N/A |
| 6. Motor Leg (score both sides separately) | No drift | 0 |
| | Drift | 1 |
| | Some effort against gravity | 2 |
| | No effort against gravity | 3 |
| | No movement. | 4 |
| | Amputation or joint fusion | N/A |
| 7. Limb Ataxia | Absent | 0 |
| | Present in one limb | 1 |
| | Present in two limbs | 2 |
| | Amputation or joint fusion | N/A |

| | | |
|---|---|---|
| 8. Sensory | Normal | 0 |
| | Mild-to-moderate sensory loss | 1 |
| | Severe to total sensory loss | 2 |
| 9. Best Language | No aphasia; normal. | 0 |
| | Mild-to-moderate aphasia | 1 |
| | Severe aphasia | 2 |
| | Mute, global aphasia | 3 |
| 10. Dysarthria | Normal | 0 |
| | Mild-to-moderate dysarthria | 1 |
| | Severe dysarthria | 2 |
| | Intubated or other physical barrier | N/A |
| 11. Extinction and Inattention | No abnormality | 0 |
| | One of the sensory modalities | 1 |
| | Profound hemi-inattention | 2 |
| Total score: | *No stroke* | 0 |
| | *Minor stroke* | 1 – 4 |
| | *Moderate stroke* | 5 – 15 |
| | *Moderate to severe stroke* | 16 – 20 |
| | *Severe stroke* | 21 – 42 |

### *3. Chronic subdural hematoma*

| **Markwalder Grading Scale** | |
|---|---|
| **Description** | **Score** |
| Patient neurologically normal | 0 |
| Patient alert and oriented; mild symptoms such as headache; absent or mild neurological deficit, such as reflex asymmetry | 1 |
| Patient drowsy or disoriented with variable neurological deficit, such as hemiparesis | 2 |
| Patient stuporous but responding appropriately to noxious stimuli; severe focal signs such as hemiplegia | 3 |
| Patient comatose with absent motor responses to painful stimuli; decerebrate or decorticate posturing | 4 |

# Appendix D: Declaration of Helsinki

At the time this protocol was issued, the full document was available on the World Health Organization website at http://www.who.int/bulletin/archives/79%284%29373.pdf

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