STUDY PROTOCOL

DIAGNOSTIC ACCURACY OF ROBOTIC CRANIAL BIOPSIES USING CIRQ® ACTIVE CRANIAL AND AUTOMATIC IMAGE REFERENCING

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1 INVESTIGATIONAL DEVICE DESCRIPTION

Intended Purpose	Cirq® Robotic Alignment Module is intended to enable motorized positioning by transferring motions to the Cirq® Robotic Disposable Kinematic Unit. It is an accessory to compatible Brainlab image guided surgery applications.
Intended Use and Indications for Use	Cirq® Robotic Alignment Module is intended to enable motorized positioning by transferring motions to the Cirq® Robotic Disposable Kinematic Unit. It is an accessory to compatible Brainlab image guided surgery applications and it is indicated for spine and cranial procedures.

2 OBJECTIVES

The aim of this study was to show that the diagnostic reliability of brain biopsies with the Cirq® Arm System including Cirq® Robotic Alignment Module Cranial reaches at least a clinically acceptable value of 90%. The results of the study were planned to be analyzed and published at the hospital and used to provide evidence for the clinical safety and performance of the Cirq® Arm System or further benefits will be derived, if the data obtained allow this.

In addition, the following clinical factors shall be investigated:

- Comparison between the planned and the received trajectory will be determined by comparing the actual trajectory identified in the intraoperative Loop-X® image data set with the trajectory planned in the pre-operative image data set and quantitatively measuring the deviations
- The spectrum of indications (type of lesion and location of the lesion)
- Comparison of procedure duration
- Limitations of the technique (type of positioning of the patient, access requirements and technical accessibility)
- System stability and accuracy as a function of trajectory length
- Comparison with frame-based stereotactic biopsy and its diagnostic reliability from the literature

3 ENDPOINTS

Primary Endpoint

The primary endpoint is the determination of the diagnostic yield (the percentage of diagnostically significant biopsies) on the biopsy material after biopsy removal using Cirq® Robotic Alignment Module Cranial.

Secondary Endpoints

- Determine the accuracy of the procedure by determining the exact location of the cranial entry point compared to the planned trajectory
- Determine the accuracy of the procedure by determining the exact location of the needle tip compared to the planned trajectory.
- Determine the accuracy of the procedure by determining the trajectory's angular deviation compared to the planned trajectory.
- Determine the procedural time.
- Calculate the diagnostic rate as a function of the trajectory length.
- Calculate the needle tip deviation as a function of the trajectory length.
- Calculate the angular deviation as a function of the trajectory length.
- Collect any technical difficulty in during the robot-guided biopsy.

4 DESIGN

The patient comes to the neurosurgical clinic with an intracranial lesion and can potentially be included in the study if MRI imaging shows a lesion for which a stereotactic biopsy is validated by the neurosurgical team, and the patient meets the inclusion criteria.

This is followed by the collection of the neurological status to record the preoperative status. Pre-operative imaging should be an MRI (= magnetic resonance imaging) of the head with contrast agent (as long as there are no contraindications to this). Diagnostics are carried out according to the usual protocols (including a 3D thin-film MPR data set including T2 FLAIR and 3D T1 weighted with and without Gadolinium acquisitions. No additional diagnostic imaging procedures are necessary. The imaging diagnostics should not be older than 4 weeks and should have been recorded under the current symptoms of the patient. The location of the lesion, its characterization, the volume, depth, or length of the planned trajectory are to be documented. Also, the usual preliminary planning for the optimal and lowest-risk definition of the trajectory should be carried out (for example, in the sense of segmenting risk structures such as eloquent cortex areas, vessels, fiber pathways with the corresponding risk profile of the patient or the procedure). After usual anesthesiologic preparation, the planned operation is then carried out.

In the operating room, the duration of the procedure is documented in the form of the incision-suture time. The usual procedure of surgical preparation takes place with patient positioning, clamping in the head clamp and registration of the patient. The registration should be carried out as usual using Loop-X® and the Brainlab Automatic Image Registration software. The surgeon shall pay attention to the sterile concept and note the user-friendliness during setup and dismantling. In particular, the accessibility of the trajectory with the system should be documented here, in particular whether a reassembly was necessary or ergonomic problems occurred. Details of this will be documented in the case report form after the procedure. The operation is performed according to routine clinical procedures.

Screenshots should be taken and stored at certain times of the operation: after setting the trajectory, after drilling, after setting the anchor and after inserting the biopsy needle.

Postoperatively, the neurological status shall again assessed and the usual postoperative control imaging with MRI performed. Complications and adverse events shall be documented and, if necessary, reported to the authorities after the usual vigilance process (in the case of serious undesirable events). Finally, the diagnosis is documented after receiving the histopathological (and/or molecular genetic) assessment. A further follow-up examination in the context of the study is not necessary.

The data shall be documented in case report forms and stored locally at the hospital after transfer. The evaluation of the image data for the determination of the trajectory in the postoperative data and the trajectory deviation shall be carried out with the support of Brainlab. The analysis and evaluation of the remaining data shall be performed by the hospital. Finally, a manuscript shall be submitted for publication in a peer-reviewed journal if possible.

SIMPLIFIED STUDY WORKFLOW

i. Perform preoperative imaging (MRI).
ii. Plan the trajectory preoperatively.
iii. Register the patient intraoperatively with AIR (Automatic Image Registration) and Loop-X®.
iv. Navigate to the preplanned trajectory and drill hole with Cirq®.
v. Open the Dura.
vi. Insert a biopsy needle and perform the biopsy.
vii. Take a screenshot to show the actual position of the tip while in place for accuracy measurements.
viii. Perform postoperative MRI (directly after surgery) or intraoperative Loop-X® with tip in place and outline where the tip was.
ix. Determine accuracy of tip by measuring the target point and entry point error.
x. Determine diagnostic yield on the biopsy material

5 DIAGNOSTIC INFORMATION

Preoperative Diagnostic
All procedures that are NOT part of the routine clinical procedure are marked in cursive.

MRI Imaging:

- MRI head standard sequences (MP-RAGE +- KM, DWI, PWI, FLAIR, T2, T2 SPACE or 3D FLAIR) shall be performed as part of the standard clinical routine.
- The volume of the lesion shall be measured in cm^3 based on the contrast agent uptake or in the case of lesions that do not uptake contrast agent, based on the FLAIR or T2 changes or DWI changes (e.g., abscesses).

Clinical Data:

- Main localization (brain area) shall be documented: frontal, temporal, parietal, occipital, corpus collosum, insula, basal ganglia, cerebellum, cellular peduncle.
- Side of the brain: right/left
- *Location in an eloquent area*: yes/no; if yes, which function is the most affected (motor, language, sight, memory)
- *Preoperative lesion volume in cm^3* (measured using Elements®, Brainlab AG, Munich, Germany)
- Preoperative Karnofsky performance score (KPS) and clinical status

Intraoperative Diagnostic
- Imaging:
    - Loop-X® shall be used intraoperatively to register the patient position
    - Loop-X® shall be used intraoperatively to take images *while the biopsy needle is in place to determine the position of the biopsy needle*
- Procedure time: The following will be measured:
    - From first incision – final suture
    - *Time to set up the system*
    - *Time to do the Automatic Image Registration with Loop-X®*
    - *Time to do the perioperative Loop-X® control scan*
    - *Duration of the biopsy procedure from the time the first coordinate on the system is set to the biopsy needle removal*

- **Intraoperative survey information**
    - Query on system setup, Accessibility of the trajectory, usability of the system
    - Adjustment of the trajectory:
        - *Screenshot after orienting the trajectory*
        - *Screenshot after setting the anchor bolts*
        - *Screenshot after placing the biopsy needle*
        - *Queries on usability, system feedback*

An extension of the operating time is not expected

Postoperative Documentation

- *Biopsy taken as planned (i.e., surgery successful): yes/no*
- *Queries on the benefit of the robotic system*
- *Errors during the robotic biopsy: yes/no and comment field*
- *Karnofsky performance score and clinical status at discharge*
- *Any complications shall be documented*
- *Any new neurological deficits: yes/no and if applicable grading of the deficits according to the Landriel-Ibanez classification (Landriel Ibañez et al. 2011)*
- *Postoperative MRI 48h after the procedure according to the clinical routine*
- *Final histological diagnosis*
- *Information on whether a second surgical intervention is necessary because the pathological report was not diagnostic.*

6 SUBJECT POPULATION

The study participants include adult patients with intracranial lesions that require a stereotactic biopsy for pathological diagnosis.

Inclusion criteria

Subjects must meet all the following inclusion criteria to participate in this clinical investigation:

1. Subject has been diagnosed with an intracranial lesion with the indication for a diagnostic stereotactic biopsy validated by the neurosurgical staff
2. Subject has given consent to participate in the study.
3. Subject is at least 18 years old.
4. Patient affiliated to French national healthcare

Exclusion criteria

Subjects will be excluded from participating in this clinical investigation if one or more of the following exclusion criteria are met:

1. Subject is < 18 years of age.
2. Subject has contraindications on narcosis, operation, MRI scan, and/or Gadolinium contract agent
3. Pregnancy
4. Patient unable to consent

Sample size

50 consecutive patients who are planned to undergo a brain biopsy will be included. This prospective observational study is intended to show that the biopsy removal with the Brainlab products leads to a clinically acceptable diagnostic yield of 90% or higher. Marcus et al. 2018 calculated pooled diagnostic reliability for robotically controlled biopsy sampling in a systematic review of 94.9% (280/295). Therefore, it is expected that a clinically acceptable diagnostic reliability of at least 90% will be achieved in 45 out of 50 patients.

Follow-Up

The follow-up ended at the end of the hospital index stay. No patients were lost to follow-up.

7 REFERENCES

Landriel Ibañez, Federico Alfonso; Hem, Santiago; Ajler, Pablo; Vecchi, Eduardo; Ciraolo, Carlos; Baccanelli, Matteo et al. (2011): A new classification of complications in neurosurgery. In *World neurosurgery* 75 (5-6), 709-15; discussion 604-11. DOI: 10.1016/j.wneu.2010.11.010.

Marcus, Hani J.; Vakharia, Vejay N.; Ourselin, Sebastien; Duncan, John; Tisdall, Martin; Aquilina, Kristian (2018): Robot-assisted stereotactic brain biopsy: systematic review and bibliometric analysis. In *Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery*. DOI: 10.1007/s00381-018-3821-y.