Summary of

STATISTICAL ANALYSIS PLAN (SAP)

SAP Version: V1.0, Date: March 5, 2025

EPIBONE

Evaluation of the EPIONE robotic system for image-guided percutaneous bone procedures

A prospective study on feasibility, safety and accuracy

Sponsor:

Name	Function	Signature
Silène LAUNAY	**Clinical Project Leader**	Signed by: Silène LAUNAY Signer Name: Silène LAUNAY Signing Reason: I am the author of this document Signing Time: 12-Aug-2025 | 5:24:45 PM CEST 86E47106860140E0B10C2E181E4C06A0

Protocol version

The version of the protocol used is revision C dated October 08, 2024.

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List of abbreviations and definition of terms

ACRONYM	DEFINITION
aCRF	Annoted Case Report Form
ADE	Adverse device effect
AE	Adverse event
ANSM	Agence nationale de sécurité du médicament et des produits de santé / National Agency for the Safety of Medicines and Health Products
BMI	Body Mass Index
CIP	Clinical Investigation Plan
CRF	Case Report Form
DD	Device Deficiency
FU	Follow-up
ICH	International Council for Harmonization
mITT	Modified Intent To Treat
MSK	Musculoskeletal
PP	Per Protocol
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®

1 - Introduction

The Statistical Analysis Plan (SAP) outlines the statistical methodology to be used for analyzing the study data and specifies the requirements for statistical programming, including tables, figures, and listings. It describes exploratory variables, populations, planned data transformations and manipulations, and other analysis details not provided in the study protocol.

The analyses described are based on the clinical study protocol revision C dated 08-Oct-2024 (ID: CA-BO-CIP-0060) and will be prepared in accordance with the International Council for Harmonisation (ICH) E9 guideline.

Statistical analyses will be conducted by the ICUREsearch biostatistics unit in collaboration with the Sponsor.

The SAP will be validated and signed off before the clinical study database lock.

2 - Objectives

2.1 Primary objective

PRIMARY OBJECTIVE	PRIMARY ENDPOINT
To evaluate the feasibility of the EPIONE robotic system assistance for bone percutaneous procedures.	Successful introducer insertion with the assistance of the EPIONE device

2.1.1 Definition of the primary endpoint

The primary endpoint is the successful introducer insertion with the assistance of the EPIONE device. Any insertion of an introducer with the EPIONE device is considered successful if it has not been converted to manual insertion.

2.2 Secondary objectives

SECONDARY OBJECTIVES	SECONDARY CRITERIA
1. To evaluate the safety of the EPIONE robotic system assistance for bone percutaneous procedures	Adverse event(s): All AEs, serious and non-serious, related and not related to the device and/or the procedure(s).
2. To evaluate the accuracy of the EPIONE robotic system assistance for bone percutaneous procedures	Lateral and angular deviations

2.2.1 Definition of secondary criteria

1- <u>Secondary endpoint 1:</u>

Number and description of AEs including their severity, their imputability to the device and/or the procedure(s).

2- <u>Secondary endpoint 2:</u>

Measure of lateral and angular deviations defined as:

- Lateral deviation (d): The distance (mm) between the tip of the inserted introducer in its final position and its orthogonal projection on the first planned trajectory.

- Angular deviation (°): The 3D angle (°) between the inserted introducer in its final position and the first planned trajectory.

2.3 Hypotheses

It is assumed that the rate of procedures successfully assisted by the EPIONE device ("feasibility") is not inferior to that observed in the preclinical study (96.4%). More specifically, a rate of 97% successful insertions has been considered in the sample size calculation.

3 - Methodology of the study

This French multicentric study is an interventional (category 1[1]), pivotal, prospective, non-randomized, non-comparative, single arm study. It is being conducted on a new version of the EPIONE device without CE marking, with a view to extending its indication to CT-guided percutaneous bone procedures on MSK structures.

The patients are expected to be followed for a duration of one month (at least 3 weeks and at most 8 weeks).

The study flow chart is detailed in Appendix 1 (see Section 9.1).

3.1 Study design

3.1.1 Inclusion criteria

1. Patient ≥18 years,
2. Patient with indication of CT-guided percutaneous bone procedure under general anesthesia validated at a multidisciplinary consultation meeting,
3. Patient who has signed an informed consent form,
4. Patient covered by a social security system.

3.1.2 Non-inclusion criteria

1. Patient with contraindication to general anaesthesia,
2. Patient undergoing a procedure without appropriate breathing control,
3. Patient scheduled for CT-guided percutaneous procedures on head and neck, including skull and cervical vertebrae,
4. Patient with medical, psychosocial, or emotional conditions unable to fully understand the study protocol, give an uninfluenced informed consent, or meet the study requirements during its whole duration.
5. Pregnant or breast-feeding women,
6. Patient under legal protection (tutorship, guardianship, …),
7. Patient already participating in another interventional clinical study.

3.2 Population

The study population consists of individuals who benefited from the assistance of the EPIONE robot during CT-guided percutaneous bone procedures, namely patients with musculoskeletal disorders.

[1] https://ansm.sante.fr/uploads/2022/02/04/20220204-modalites-pratiques.pdf

3.2.1 Sample size

The sample size calculation was performed based on a one-sample non-inferiority test design. The preclinical study showed that 96% of insertions assisted with the EPIONE device were successful. Assuming 97% feasibility with EPIONE system, with a clinically acceptable margin of 0.08, the sample size necessary to achieve 90% power and maintain the type I error rate at 5% for this non-inferiority margin was calculated to be approximately 67 insertions.

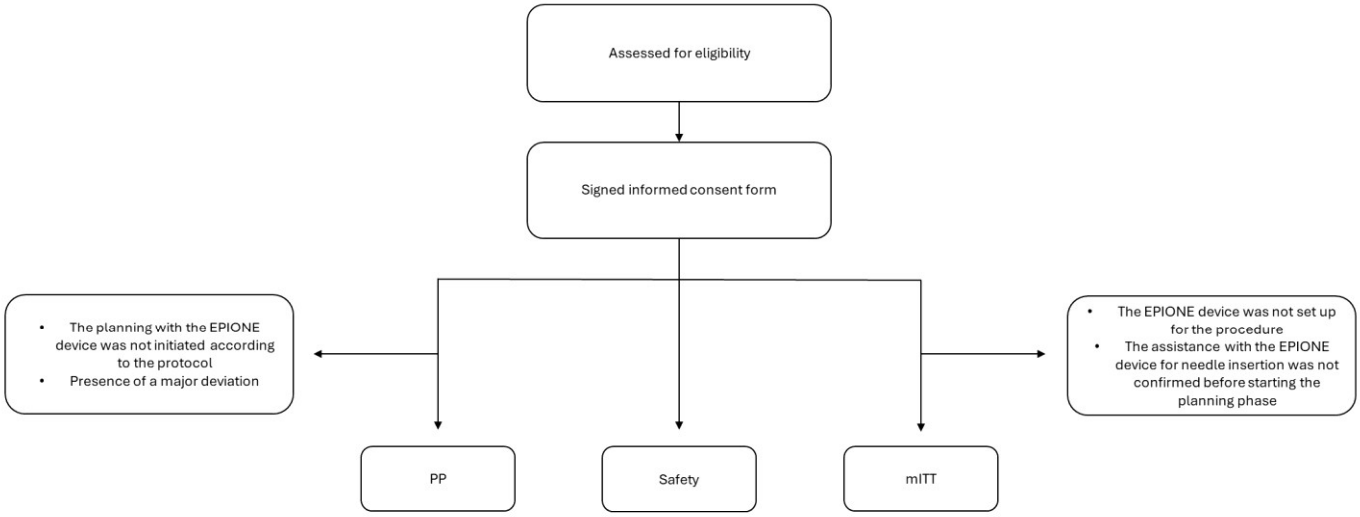
The sample size was calculated using the Cohen's arcsine transformation, which is a preferred method when dealing with proportions close to the boundaries (0 or 1) as it helps to stabilize the variance and normalize the data.

Considering the practice of the centers, i.e. an average of 2 introducer insertions per patient (different locations of MSK disorders possible, different treatments possible during the same procedure), it is planned to include a minimum of 34 patients in the study.

3.2.2 Analysis population

The analysis populations will be precisely defined and validated during the data review meeting.

Consort Flow Chart



3.2.2.1 mITT population

All selected patients who have confirmed their signed informed consent and for whom:

- the EPIONE device has been set up for the procedure,
- the assistance with the EPIONE device for needle insertion was confirmed before starting the planning phase.

3.2.2.2 PP Population

All patients for who the planning with the EPIONE device has been initiated according to the protocol without any major deviations.

3.2.2.3 Safety Population

All patients who have confirmed their signed informed consent.

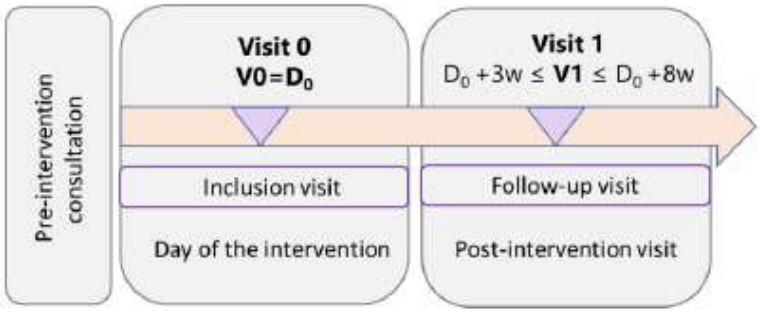
3.3 Visits

The study is composed of the following visits:

- Visit 0: Inclusion visit (day of the intervention),
- Visit 1: Follow-up visit (visit post-intervention).

The study flow chart is detailed in Appendix 1 (see section 9.1).

3.3.1 Study outline



4 - Subject Evaluations

4.1 Demography

The following demographic data were collected:

- Age
- Sex
- Weight (Kg)
- Height (Kg)

4.2 Patient History

Relevant data relating to the patient's history were collected:

- Oncology
- “High-energy” traumatic fractures
- “Low-energy” traumatic fractures

4.3 Concomitant treatment (V0)

Relevant data relating to the patient's concomitant treatment at baseline were collected.

4.4 Type of MSK disorders

- Bone tumors: benign or malignant / bone metastases
- Weakened / fractured bone
- Type of medical procedure(s) performed

4.5 End of Study, Premature Termination, and Withdrawal/Discontinuation from the Study

4.5.1 End of Study

A patient will have definitively completed the study when he or she has completed all study visits, with the end-of-study visit corresponding to visit 1.

4.5.2 Early termination

A patient will have stopped the study early in the event:

- decided by the patient
- decided by the sponsor:

  The date and reason for this early termination of study participation will be entered on the appropriate page of the case report form (CRF). Patients are withdrawn from the study the date of this decision.
- decided by the investigator:
  - Patient health or safety event that, on the investigator's advice to not allow the patient to participate to study visits,
  - Failure to comply with the clinical investigation procedure,
  - Pregnancy,
  - In the event of an ADE, judged by the investigator to be severe and which could jeopardize the health of the patients, the investigator may stop the study in agreement with the sponsor.
- decided by the competent authority:
  - Inability of the investigator(s) to enroll patients according to the planned schedule
  - Lack of signed consent
  - Major violations of the protocol/ lack of investigating center compliance
  - Incomplete or erroneous data
  - Safety concern
- due to patient lost to follow-up:
  - A patient will be considered lost to FU if a member of the research team has not heard from the patient after 3 attempts to contact him/her.

4.5.3 Withdrawal/Discontinuation from the Study

Patients are always free to withdraw from the study without giving any justification. When a patient withdraws consent, he/she will be asked for the possibility of using the data already collected. If he/she objects to this, the data will be archived and will be excluded from the study analysis. No further justification will be requested.

5 - Statistical considerations

5.1 Descriptive statistics

Each collected parameter will be described for the entire study population.

- **Qualitative variables** will be described using the count and percentage of each variable, as well as the number of missing data points. Patients with missing data will not be included in the percentage calculations. The handling of missing data will depend on the variable being analyzed (see Section 5.5.2).

- **Quantitative variables** will be described by the number of observed values, mean, standard deviation, median, extreme values (minimum and maximum), and the number of missing data points. Data management (missing, outlier, incomplete data) will be handled based on the variable being analyzed (see Section 5.5).

5.2 Statistical tests

All tests other than the non-inferiority test of the primary endpoint will be two-sided with a global alpha risk level of 5%. A p-value less than 0.05 will be considered statistically significant. All confidence intervals will be two-sided and presented with a 95% confidence level.

The non-inferiority test of the primary criterion will be one-sided with a global alpha risk level of 5%. A p-value less than 0.05 will be considered statistically significant. Confidence interval will be one-sided and presented with a 95% confidence level.

5.3 Duration

The duration (in days) will be calculated as the difference between the start date and the end date + 1. (For example, the duration of a medication (in days) = end date of the medication - start date of the medication + 1).

5.4 Data management

5.4.1 Treatment of missing data

No methodology for dealing with missing data has been implemented in this study.

Any subject with missing data for the primary endpoint will be considered censored for the primary analysis. The same process will be applied to the secondary endpoints.

If there is a significant number of missing values for a subject (or if data has been confirmed as being incorrect), a decision will be made in consultation with the Sponsor regarding the handling of this data.

5.4.2 Treatment of outlier data

In the case of outlier values, the secondary endpoint (lateral and angular deviations) should be assessed through statistical analysis using the actual values, as well as at least one other analysis after the outliers have been removed or their effect reduced.
An outlier search will be performed, and the actions to be taken will be determined in consultation with the Sponsor.

5.4.3 Treatment of incomplete and missing dates

No management of incomplete/missing dates will be performed for any pre-study events (all medical events or patient history that occurred before the start of the study, for example a previous fracture). Incomplete/missing dates will be labeled as such in all listings. However, for calculations, sorting, or assignments based on dates, the actions to be taken will be defined in consultation with the Sponsor.

6 - Statistical methods

6.1 Analysis methods

The statistical analyses will be based on the data from the different sites that participated in the study. The ICUREsearch statistics team will perform all statistical analyses.

Descriptive statistics for qualitative and quantitative variables and individual data listings will be generated.

6.1.1 Main analysis

The objective of this study is to evaluate the feasibility of the EPIONE robotic assistance for bone percutaneous procedures. The primary endpoint of this study is the successful insertion of the introducer with the assistance of the EPIONE device. Non-inferiority of the success rate of the EPIONE device, compared to the pre-clinical study (feasibility observed during pre-clinical tests), will be concluded if the lower bound of the one-sided 95% confidence interval for the observed proportion of successful EPIONE device uses is greater than or equal to 0.88 (0.96 minus a non-inferiority margin of 0.08).

A non-inferiority test for proportions will be conducted. The variable of interest is the success rate (proportion) of the introducer insertion with the assistance of the EPIONE device. The non-inferiority test will compare the success rate observed in the study with the reference value of 0.88.

The success rate will first be calculated, followed by the computation of a one-sided 95% confidence interval for this proportion. Non-inferiority will be concluded if the lower bound of the 95% confidence interval for the success rate is greater than or equal to 0.88.

Null hypothesis (H0): The success rate is less than 0.88.

Alternative hypothesis (H1): The success rate is greater than or equal to 0.88 (non-inferiority).

The frequency and percentage of successful introducer insertions with EPIONE device assistance will be reported.

This analysis will be conducted on the mITT population.

6.1.2 Secondary analyses

6.1.2.1 Secondary endpoint n°1

The objective of this analysis is to evaluate the safety of the EPIONE robotic assistance for bone percutaneous procedures.

The number of adverse events (AEs) will be described overall, by intensity, severity, and relationship with the device on a descriptive table. The frequency and percentage of AEs, ADEs, SAEs, SADEs, minor and major complications along with the 95% confidence interval, will be presented.

This analysis will be conducted on the safety population.

6.1.2.2 Secondary endpoint n°2

The objective of this analysis is to evaluate the accuracy of the EPIONE robotic assistance for bone percutaneous procedures.
A descriptive table displaying the mean lateral and angular deviations, based on expert review, will be provided.

This analysis will be conducted on the mITT and PP populations.

7 - Computer systems, software and program validation

7.1 System

The analyses will be conducted by a biostatistician from ICUREsearch. All analyses will be performed using Microsoft® Windows 11®.

7.2 Software

The analyses will be performed using SAS® software version 9.4. ICUREsearch reserves the right to use R® (CRAN) software for graphical representations.

7.3 Program validation

The biostatistician will be responsible for reviewing each program and the associated SAS® output. The SAS® "Log" will be saved and examined for logical errors, syntax issues, and fatal errors.
The raw results of the statistical analysis will be directly generated by the SAS software in the form of TLF (Tables, Listings, and Figures) in pdf format.
The results will be checked for typographical errors, spelling mistakes, and implausible values. The consistency of the results will be reviewed with the principal investigator.

8 - Conventions

8.1 Data formats and rules

8.2 Report

All sections of tables, figures, and listings are detailed in Section 9.4. They will be prepared using SAS® software (SAS Institute Inc., Cary, NC, USA) as PDF files (one PDF file per main section).
The footers will be presented as follows: "ICUREsearch SAS – CONFIDENTIAL."
List of page and table configuration requirements:

- Font type = Calibri
- Font size = 8 pt (minimum)
- Paper size = A4 (21 cm x 29.7 cm)
- Page orientation: portrait or landscape as needed
- Graphics: PNG or JPG format

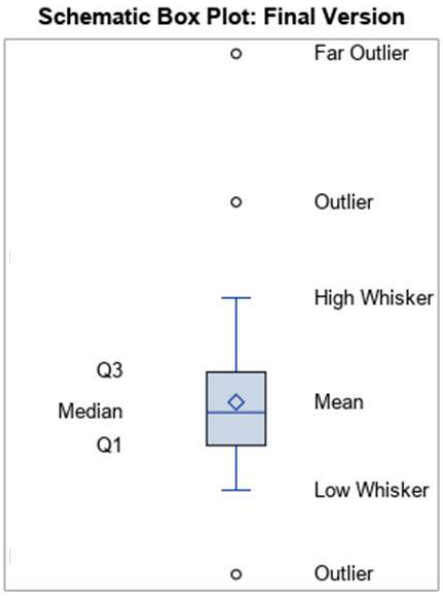
The statistics will be presented as follows:

Parameter	Statisics / Category	Value
Gender	N	XX
	n | Missing	XX|XX
	Male, n (%)	XX (XX.X)
	Female, n (%)	XX (XX.X)
Height (cm)	N	XX
	n | Missing	XX|XX
	Mean (std)	XX (XX.X)
	Median [IQR]	XX [XX ; XX]
	Min ; Max	XX ; XX

Parameter	Statisics / Category	All	Cluster 1	Cluster 2	Pvalue
	N		XX	XX	X.XXXX
	n | Missing		XX|XX	XX|XX	
XXXX	Mean (std)		XX (XX)	XX (XX)	
	Median [IQR]		XX [XX ; XX]	XX [XX ; XX]	
	Min ; Max		XX ; XX	XX ; XX	
XXXX	N		XX	XX	X.XXXX

Parameter	Statisics / Category	All	Cluster 1	Cluster 2	Pvalue
	n | Missing		XX|XX	XX|XX	
	Mean (std)		XX (XX)	XX (XX)	
	Median [IQR]		XX [XX ; XX]	XX [XX ; XX]	
	Min ; Max		XX ; XX	XX ; XX	

The boxplots will be presented as follows:



An individual is considered an outlier when their value is less than 1.5 times the interquartile range (IQR) below Q1 and more than 1.5 times the IQR above Q3. An individual is considered a far outlier when their value is less than 3 times the IQR below Q1 and more than 3 times the IQR above Q3.
Example: We want to represent the boxplot of the individuals' heights in our population. The first quartile (Q1) is 160 cm, the median is 170 cm, and the third quartile (Q3) is 180 cm. The interquartile range is Q3 – Q1 = 180 – 160 = 20.
1.5 * 20 = 30, Q3 + 30 = 180 + 30 = 210 cm, Q1 – 30 = 160 – 30 = 130 cm.
So, if an individual is shorter than 130 cm or taller than 210 cm, they will be considered an outlier.
3 * 20 = 60, Q3 + 60 = 180 + 60 = 240 cm, Q1 – 60 = 160 – 60 = 100 cm.
Therefore, an individual will be considered a far outlier if they are shorter than 100 cm or taller than 240 cm.