# Statistical Analysis Plan

# POST-MARKET CLINICAL FOLLOW-UP REGISTRY OF THE CODMAN AND INTEGRA EXTERNAL VENTRICULAR DRAINAGE PRODUCTS AND ACCESSORIES

## Short Title: External Ventricular Drainage PMCF Registry

**PROTOCOL NO.:** C-EXTVDR-001

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**Title:** **POST-MARKET CLINICAL FOLLOW-UP REGISTRY OF THE CODMAN AND INTEGRA EXTERNAL VENTRICULAR DRAINAGE PRODUCTS AND ACCESSORIES**

**Protocol No:** **C-EXTVDR-001**

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DD/MMM/YYYY

**Approved By:**

**Signature:** _____ **Date:** _____
DD/MMM/YYYY

# 1. VERSION HISTORY

| Date | Version | Primary Reason(s) for Amendment |
|---|---|---|
| 19 September, 2023 | Draft 1.0 | New release, Draft |
| 07 October, 2024 | Draft 1.1 | Draft, changes made from Protocol 5.0 |
| 7 March, 2025 | Final 1.0 | Final |

# 2. LIST OF ABBREVIATIONS

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| CMP | Clinical Monitoring Plan |
| CRAK | Cranial Access Kit |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CSF | Cerebrospinal Fluid |
| CTA | Clinical Trial Agreement |
| CT | Computed Tomography |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Forms |
| EDC | Electronic Data Capture |
| EDS | External Drainage Sets |
| EU | European Union |
| EVD | External Ventricular Drainage |
| FAS | Full Analyses Set |
| GCP | Good Clinical Practice |
| GCS | Glasgow Coma Scale |
| ICH | International Conference on Harmonisation |
| IDS | Integral Drainage Sets |
| ICP | Intracranial Pressure |
| ISO | International Organization for Standardization |
| ITT | Intent to Treat |
| MDCG | Medical Device Coordination Group |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MRI | Magnetic Resonance Imaging |
| MSE | Medical Safety Expert |
| NCT | National Clinical Trial |
| PMCF | Post-Market Clinical Follow-Up |
| PP | Per Protocol |
| PT | Preferred Term |
| QC | Quality Control |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| TBI | Traumatic Brain Injury |
| TMF | Trial Master File |
| VCAK | Ventricular Drainage Accessory Kits |
| YOB | Year of Birth |

# 3. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the statistical analyses planned to be implemented during the analysis C-EXTVDR-001 study. The methods and procedures are intended to support the generation of the clinical study report, including detailed descriptions of the populations and methodologies, as well as summary tables, listings and graphics.
This statistical analysis plan (SAP) is based on Version 5.0 dated 11-JUL-2024 of the Protocol # C-EXTVDR-001.

# 4. STUDY OBJECTIVES

## 4.1. Primary Objective

The primary objective of this registry is to capture clinical performance data to confirm the continued performance of the Integra External Ventricular Drainage Systems and Accessories.

## 4.2. Safety Objective

The safety objective of this registry is to capture clinical safety data to confirm the continued safety of the External Ventricular Drainage Systems and Accessories.

# 5. STUDY DESIGN

The External Ventricular Drainage Post-Market Clinical Follow-Up (PMCF) registry is an observational, multi-center, post-market study. Up to 15 sites in Europe will participate in this study.

## 5.1. Primary Endpoint

The primary endpoint is anticipated drainage (i.e., observed drainage consisting with the patient's clinical presentation) of cerebrospinal fluid (CSF) in the clinical setting until the EVD System is no longer required.

**Note:** Excessive drainage (e.g., more than 25 cc every hour) not attributable to the patient's condition, widely variable drainage over time inconsistent with the patient's clinical presentation, drainage levels inconsistent with concurrent neurological exams (e.g., GCS, NIHSS, etc.), and/or documented device deficiencies impacting drainage (e.g., breakage disconnection, etc.) are examples of unanticipated drainage of CSF that will be recorded as Adverse Events.

## 5.2. Secondary Endpoints

The secondary endpoint is the proportion of patients in whom the CODMAN Cranial Access Kit, when used with appropriate accessories, provided successful access to the intracranial space.

## 5.3. Tertiary Endpoints

The exploratory endpoints include following:

- Number of initial Catheter Insertion Attempts [Time Frame: Implantation of subject] Number of insertions needed to place initial Catheter
- Number of days the initial Catheter is in place.
- Number of Catheter and/or EVD System replacements during treatment, if applicable.

- Number of Catheter flushing interventions per each Catheter if a replacement Catheter is implanted.
- Length of Catheter Tunneling into the Brain [Time Frame: Implant of subject] Length of tunneling of EVD Catheter in the brain for each analysis population.
- Number of Days with initial Indwelling Catheter [Time Frame: Implant of subjects to the day of explant] Days Catheter was implanted in subjects
- Non-infectious Catheter Failure in the intent-to-treat (ITT) Population [Time Frame: Implant of subject to explant] Reasons for non-infectious Catheter malfunctions in the ITT population.
- CSF daily drainage.

### 5.4. Safety Endpoints

The safety endpoints include:

1. Device- or procedure related adverse events (AEs) during the use of the device in the patient
2. Noted Device Deficiencies during use of the device such as malfunction, use errors, or other issues related to the performance or safety of the External Ventricular Drainage Systems and Accessories.

## 6. SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Activities

| Procedures | Study Assessments |
|---|---|
| Informed consent[1] | X |
| Demographics/Patient data | X |
| EVD System and Accessories information/Details of Catheter and/or EVD System replacement(s), if applicable/Procedural data | X |
| Clinical Performance Data:<br>• Cerebrospinal fluid drainage (daily drainage)<br>• Intracranial access location<br>• EVD system and accessories maintenance procedures<br>• Number, type, and volume of flush(s) used to address occlusions, if applicable<br>• Concomitant neuro-surgical and neuro-interventional procedures<br>• Relevant concomitant medications | X |
| Safety Data:<br>• EVD system and accessories or procedure related AEs<br>• Noted Device Deficiencies during use of the EVD system and accessories | X |

1 Informed consent is captured once, prior or after implantation of the EVD System.

# 7. STATISTICL METHODS

## 7.1. Statistical Hypotheses

The primary hypothesis is to evaluate the anticipated drainage (i.e., observed drainage consistent with the patient's clinical presentation) of cerebrospinal fluid (CSF) in the clinical setting until the EVD System is no longer required.

**Note:** Excessive drainage (e.g., more than 25 cc every hour) not attributable to the patient's condition, widely variable drainage over time inconsistent with the patient's clinical presentation, drainage levels inconsistent with concurrent neurological exams (e.g., GCS, NIHSS, etc.), and/or documented device deficiencies impacting drainage (e.g., breakage disconnection, etc.) are examples of unanticipated drainage of CSF that will be recorded as Adverse Events.

The hypothesis is formulated as

$H_0$: $P \leq 80\%$ vs. $H_a$: $P > 80\%$

where P is the proportion of patients with clinical success.

The hypothesis will be evaluated using the exact method along with a two-sided 95% confidence interval. A P-value of less than 0.05 is considered statistically significant.

## 7.2. Determination of Sample Size

A sample size of 110 is estimated by pre-defined performance goal of 80% along with two-sided 95% confidence interval with 80% power for the primary endpoint. A total of 120 subjects will be enrolled with an 8% potential drop-out assumed. The registry will enroll patients who meet the eligibility criteria with an expected total sample size of 120 patients that underwent the procedure with one or more of the Integra devices at up to 15 study sites. Enrollment will be halted at sites that reach the 34% (40 subjects) inclusion cap. There will be no minimum number of subjects for a single study site.

The device systems have been on the market for more than 15 years and have substantial clinical evidence of safety and performance in the form of several peer-reviewed publications and post-market clinical experience data. In this study, data from multiple centers and nations will be included to ensure that the collected data is from a broad set of surgeons and countries, thereby increasing the generalizability of the outcomes and conclusions.

Integra believes this study design and size is appropriate to confirm the continued safety and performance of these devices given their well-established nature and the existing clinical evidence base.

## 7.3. Analysis Populations

The Intent to Treat (ITT) population consists of all patients who signed the written informed consent and are considered to meet all inclusion/exclusion criteria (patients included in the study) following the Intention to Treat principle whether patients have or not a procedure with one of the Integra or Codman External Ventricular Drainage System.

The Full Analysis Set (FAS) population consists of all patients included in the study who have a procedure with one of the Integra or Codman External Ventricular Drainage System.

The Per Protocol Set (PPS) population consists of all patients who have a procedure with one of the Integra or Codman External Ventricular Drainage System and meet all inclusion/exclusion criteria, and without major protocol deviation during the study. Primary and secondary endpoints analyses based on the PPS population will be supportive.

### 7.4. Missing Data and Sensitivity Analysis

Analysis of performance and safety data will be primarily performed on all observed (available) data. Missing data will be summarized, and multiple imputations on missing data may be used for sensitivity analysis to ensure study results are robust.

### 7.5. Accounting for Multiple Comparisons

There is only one primary hypothesis, therefore, no adjustments for multiple comparisons or multiplicity will be made for this study.

### 7.6. Interim analysis

There are no planned interim analyses.

## 8. STATISTICAL ANALYSES

### 8.1. General Methods

All data collected in this study will be presented using summary tables, figures, and data listings. For categorical data, the number and percentage of subjects in each category will be presented. For continuous data, descriptive statistics, including sample size, mean, median, standard deviation, and range of values (i.e., minimum and maximum values) will be provided.

A significance level of 0.05 will be used for all statistical tests and p-value less than 0.05 will be considered statistically significant unless otherwise specified. The two-sided 95% confidence intervals will be presented whenever appropriate. Statistical analysis will be carried out using SAS software version 9.4 or higher, or other similar validated software.

By-subject listings will be presented for all subjects in the relevant analysis sets.

### 8.2. Study Subjects

#### 8.2.1. Disposition of Subjects

The disposition of all subjects in the study will be provided for all available data. The numbers of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all post-enrollment discontinuations will be summarized, for all centers combined and for each center separately. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

#### 8.2.2. Protocol Deviation

Protocol deviation will be summarized by category. Protocol deviation data will be listed for each subject. Major protocol violations will be summarized.

## 8.3. Demographics

Demographic and baseline characteristics are to be summarized. These variables include: age at ICF, and gender.

## 8.4. Medical History

Medical history data will be summarized and presented by count and percentage of subjects broken down by body systems, Pertinent Past Medical History Conditions, and medical history category as captured on the CRFs. Subjects reporting more than 1 condition within a body system will be counted only once for that body system. By subject listings will be provided for each subject.

## 8.5. Procedure

Procedure will be summarized and/or analyzed. These variables include details of initial and replacement (if applicable) catheter information, length of tunneling of EVD catheter in the brain, and EVD system and accessories usage.

## 8.6. Additional information

Additional questionnaires will be summarized using descriptive statistics, and by-subject listing will be provided. Data will be analyzed for the primary and secondary endpoints.

## 8.7. Concomitant Medications/Procedures

Concomitant Medications and/or Procedures information will be summarized using descriptive statistics by visit, by subject listing will be provided.

## 8.8. CSF Drainage

Total CSF Drainage volume will be summarized by subject. Data will be listed by catheter by subject.

## 8.9. Clinical Performance Analyses

All performance analyses will be primarily based on FAS. The Primary and Secondary endpoints analyses will also be performed based on PP.

### 8.9.1. Analysis of Primary Endpoint

The primary endpoint is anticipated drainage (i.e., observed drainage consisting with the patient's clinical presentation) of cerebrospinal fluid (CSF) in the clinical setting until the EVD System is no longer required.

**Note:** Excessive drainage (e.g., more than 25 cc every hour) not attributable to the patient's condition, widely variable drainage over time inconsistent with the patient's clinical presentation, drainage levels inconsistent with concurrent neurological exams (e.g., GCS, NIHSS, etc.), and/or documented device deficiencies impacting drainage (e.g., breakage disconnection, etc.) are examples of unanticipated drainage of CSF that will be recorded as Adverse Events.

The primary hypothesis will be tested using the exact (Clopper-Pearson) method along with two-sided 95% confidence interval. The null hypothesis will be rejected, and primary objective will be met if the lower bound of the 95% confidence interval is greater than the performance goal of 80%.

### 8.9.2. Analysis of the secondary Endpoints

The secondary endpoint is the proportion of patients in whom the CODMAN Cranial Access Kit, when used with appropriate accessories, provided successful access to the intracranial space. The number and percentage of patients with intracranial space success, along with two-sided 95% confidence interval of the percentage will be provided.

### 8.9.3. Analysis of the tertiary Endpoints

The exploratory endpoints include:

- Number of initial Catheter Insertion Attempts [Time Frame: Implantation of subject] Number of insertions needed to place initial Catheter
- Number of days the initial Catheter is in place.
- Number of Catheter and/or EVD System replacements during treatment, if applicable.
- Number of Catheter flushing interventions per each Catheter if a replacement Catheter is implanted.
- Length of Catheter Tunneling into the Brain [Time Frame: Implant of subject] Length of tunneling of EVD Catheter in the brain for each analysis population.
- Number of Days with initial Indwelling Catheter [Time Frame: Implant of subjects to the day of explant] Days Catheter was implanted in subjects
- Non-infectious Catheter Failure in the intent-to-treat (ITT) Population [Time Frame: Implant of subject to explant] Reasons for non-infectious Catheter malfunctions in the ITT population.
- CSF daily drainage

For categorical endpoints (Number of initial Catheter Insertion Attempts, Number of Catheter and/or EVD System replacements during treatment, Number of Catheter flushing interventions per each Catheter if a replacement Catheter is implanted, Non-infectious Catheter Failure in the intent-to-treat (ITT) Population), frequencies and percentages will be provided for each category. For continuous tertiary endpoints (Number of days initial Catheter is in place, Length of Catheter Tunneling into the Brain, Number of Days with initial Indwelling Catheter, CSF daily drainage), descriptive statistics, including sample size, mean, median, standard deviation, and range of values (i.e., minimum and maximum values) will be provided along with 95% confidence interval of the percentage.

## 8.10. Safety Analyses

All safety summaries will be presented for the FAS population. No formal statistical testing is planned on safety endpoints.

### 8.10.1. Adverse Events

All AEs and complications occurring from the time of subject enrollment until study termination or study completion include intra-operative AEs and complications. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology for data summaries. Each AE will be coded with 2 levels including Preferred Term (PT) and System Organ Class (SOC). The severity of all adverse events will be reviewed and adjudicated and classified as mild, moderate or severe.

The total number of device-related AEs as well as the percentage of patients with at least one device-related AE will be presented overall and by SOC and PT. AEs will also be tabulated by severity and by relationship to device within each SOC and PT. A listing of device-related AEs and SAEs will be presented respectively.

### 8.10.2. Device Deficiencies

Device deficiencies will be summarized using descriptive statistics. A listing of device deficiencies will be presented.

## 8.11. STATISTICAL ANALYSIS AND GENERAL DATA ISSUES

### 8.11.1. General Calculations and Data Conventions

**Relative Day**

The date the EVD device placement will be considered relative day 0, and the day before the device placement will be relative day -1. Relative days will be calculated as follows only when the full assessment date is known (i.e., partial dates will have missing relative days): For days on or after the device is implanted: Relative Study Day (Rel Day) = Date of Assessment – Date of implant. For days before the device is implanted: Relative Study Day (Rel Day) = Date of Assessment – Date of implant.

**Age**

Age will be presented as the number of years between date of birth and date of signing the informed consent. Age is computed in whole years as follows:

Age (years) = year of informed consent – year of birth

**Length of Time**

Except for age, the length of time between 2 reference dates will be calculated as the number of Calendar days between the two dates. When the length of time between 2 reference dates is expressed in months, the number of months will be calculated as the number of calendar days between the 2 dates divided by 30.4 days. When the length of time between 2 reference dates is expressed in weeks, the number of weeks will be calculated as the number of calendar days between the 2 dates divided by 7 days.

**Clinical Trial Duration**

Clinical Trial duration will be calculated as the total number of days each subject is in the clinical trial.

Clinical Trial Duration (days) = (date of last clinical or adverse event visit or withdrawal – date of EVD placement) + 1

**Duplicate Data**

For unscheduled duplicate data within a protocol-specified visit, the last measured value will be used for the analysis. If it is not possible to identify the “last measured value” the average of the duplicate values will be used.

**Partial AE and medication date**

For partial start dates:

1. If the year is unknown, then do not impute the date but assign a missing value
2. If the month is unknown, then:
    a. If the year matches the year of initial EVD placement, then impute the month and day of the EVD placement date.
    b. Otherwise, assign "January."
    c. If the day is unknown, then
    d. If the month and year match the month and year of the initial EVD placement date, then impute the day of the surgery date.
    e. Otherwise, assign "01."

For partial end dates:

1. If the year is unknown, then do not impute the date but assign a missing value.
2. If the month is unknown, then assign " December."
3. If the day is unknown, then assign the last day of the month.

# 9. REFERENCES

1. American Association of Neuroscience Nurses, *Care of the Patient Undergoing Intracranial Pressure Monitoring / External Ventricular Drainage or Lumbar Drainage*, in *AANN Clinical Practice Guideline Series*. 2011, AANN: http://files.mmintensivecare.webnode.pt/200000471-ad055ad4d0/Intracranial%20Pressure%20Monitoring.pdf.

2. Brain Trauma Association, *Guidelines for the Management of Severe Traumatic Brain Injury*, in *Brain Trauma Association*. 2016, Brain Trauma Foundation: https://braintrauma.org/uploads/03/12/Guidelines_for_Management_of_Severe_TBI_4th_Edition.pdf.

3. Brain Trauma Foundation, *Guidelines for the Management of Severe Traumatic Brain Injury*, in *Brain Trauma Foundation*. 2007: https://www.braintrauma.org/uploads/11/14/Guidelines_Management_2007w_bookmarks_2.pdf.

4. Atkinson, R., et al., *Silver-impregnated external-ventricular-drain-related cerebrospinal fluid infections: a meta-analysis.* Journal of Hospital Infection, 2016. **92**(3): p. 263-272.