POST-MARKET CLINICAL FOLLOW-UP REGISTRY OF THE INTEGRA EXTERNAL VENTRICULAR DRAINAGE SYSTEMS AND ACCESSORIES

Short Title: External Ventricular Drainage PMCF Registry

Protocol Number: C-EXTVDR-001

National Clinical Trial (NCT) Identified Number: NCT05652296

Protocol Version: V5.0

Protocol Date: 11-JUL-2024

Sponsor and Manufacturer:

Integra LifeSciences
1100 Campus Drive, Princeton, New Jersey, 08540

European Representative: Integra LifeSciences Services (France) S.A.S.
Immeuble Séquoia 2
97 Allée Alexandre Borodine
69800 Saint Priest
FRANCE
www.integralife.com

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A. AUTHORIZED SIGNATORIES FOR THE SPONSOR

Name	Position/Title	Signature/Date

B. MEDICAL EXPERT FOR THE STUDY

Jason M. Marzuola, MSN RN CNRN
Director, Global Medical Affairs
Phone : +1 609-433-1492
e-mail : jason.marzuola@integralife.com

C. STUDY INVESTIGATORS AND SITE MEDICAL STAFF

The contact information of all sites, study investigators and other site medical experts (if applicable) involved in conducting the registry study, can be found in the Trial Master File (TMF).

D. INVESTIGATION FUNDING AND INVESTIGATOR AGREEMENT OVERVIEW

This protocol is being funded by Integra Lifesciences, Corp. All lead investigators at study sites will become signatories on a study-specific Clinical Trial Agreement (CTA) which details the legal and regulatory roles and responsibilities of the Sponsor, investigator, and study site in carrying out the protocol.

E. CLINICAL LABORATORIES AND CONTRACT RESEARCH ORGANISATIONS

The list of laboratories and/or contract research organizations (CROs), if applicable, can be found in the TMF.

STATEMENT OF COMPLIANCE BY THE INVESTIGATOR

By signing this document, I, the Investigator, certify that this registry study will be carried out in accordance with Good Clinical Practice (GCP), the Declaration of Helsinki, and the following:

- Applicable laws and regulations as laid out by the European Union (EU) and/or by individual countries

AND, where applicable,

- EU 2017/745 (Medical Device Regulation)
- ISO 14155:2020

Additionally, I and any registry study site staff who are responsible for the conduct, management, or oversight of this registry study will complete Human Subjects Protection/ GCP Training.

The protocol, informed consent form(s), any recruitment materials, and/or all participant materials associated with this registry study will be submitted to an Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled.

Finally, I understand that any amendments to the protocol or consent forms will require review and approval by the EC before the changes are implemented to the study.

Investigator Name

Investigator Signature Date

1. PROTOCOL SUMMARY

1.1 Protocol Synopsis

Title:	Post-Market Clinical Follow-Up Registry of the Integra External Ventricular Drainage Systems and Accessories
Short Title:	External Ventricular Drainage PMCF Registry
Protocol number:	C-EXTVDR-001
Study Description:	This post-market follow-up registry will capture clinical data specific to the safety and performance of the Integra External Ventricular Drainage Systems and Accessories.
Background:	External Ventricular Drainage (EVD) Systems are a temporary system which allow drainage of cerebrospinal fluid (CSF) from the lateral ventricles of the brain. EVD Systems are commonly used within neurosurgery for the management of patients who require drainage of CSF. EVD Systems are regularly used in neurosurgery for diagnostic and therapeutic purposes. Complications of EVD Systems are well recognized, with infection and hemorrhage being the most common ones related to these procedures, followed by ventriculostomy occlusion. The rate of EVD-associated hemorrhage ranges from 18 to 41% in adults as reported in literature, and in pediatric population (single center), it has been found that incidence of hemorrhage at EVD placement to be 10%, and the incidence of hemorrhage on EVD removal to be 21.9%. Studies have demonstrated non patent EVDs in 19-47% of patients.
Pre/Post-Market:	Post-Market Clinical Follow-Up Registry
Study Design:	Observational, multi-center, post-market registry
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.
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.
Primary Endpoint:	The primary endpoint is 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.
Secondary Endpoint	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.
Tertiary Endpoints:	• Number of initial Catheter Insertion Attempts [Time Frame: Implantation of subject] Number of insertions needed to place initial Catheter • Number of days 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
Safety Endpoints:	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
Sample Size and Enrollment:	Approximately 120 patients at up to 15 study sites. Inclusion 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.
Device Identification:	All active External Ventricular Drainage Systems and accessories under the following product families will be included in the registry. ***EVD Systems*:*** • AccuDrain

	• Hermetic Plus • LimiTorr • MoniTorr • Codman EDS 3 / EDS 3C • Basic CSF Drainage System • External Ventricular Drainage System ***EVD Catheters *:*** • TraumaCath Ventricular Catheter Set • Hermetic Ventricular Catheter • Bactiseal Anti-Microbial Catheter **Note:** in this study, EVD Catheters will be considered as accessories to the EVD Systems. ***EVD Accessories **** ***Cranial Access*:*** • CODMAN Cranial Access Kit *Refer to APPENDIX I at the end of the protocol for product-specific Stock Keeping Units (SKUs) to be included in this post-market registry.
Indications for Use	**EVD Systems:** The AccuDrain is indicated for draining and monitoring of CSF flow from the ventricles of the brain or lumbar subarachnoid space in selected patients to reduce Intracranial Pressure (ICP), to monitor ICP, to monitor CSF, and to provide temporary CSF drainage. The Hermetic Plus is indicated for draining and monitoring of CSF flow from the lateral ventricles of the brain or lumbar subarachnoid space in selected patients to reduce Intracranial Pressure (ICP), to monitor ICP, to monitor CSF, and to provide temporary CSF drainage for patients with infected hydrocephalic shunts. The LimiTorr and MoniTorr System allow for drainage and monitoring of CSF from the lateral ventricles of the brain or lumbar subarachnoid space in selected patients to reduce ICP, to monitor CSF, to provide temporary drainage of CSF in patients with infected CSF shunts, and to monitor ICP. The Codman External Drainage Ventricular System is indicated for draining CSF from the cerebral ventricles or the lumbar subarachnoid

	space as a means of reducing intracranial pressure and CSF volume when the insertion of a permanent, internal shunt is not indicated. **Catheters:** TraumaCath and Hermetic Ventricular Catheters are indicated for drainage and monitoring of CSF from the lateral ventricles of the brain. The catheters may be used to reduce ICP, to monitor ICP, to monitor CSF, and in the management of hydrocephalic shunt infections. The Codman Bactiseal EVD Catheter and Codman Bactiseal Clear EVD Catheter Sets (Bactiseal EVD Catheters), are indicated for gaining access to the ventricles of the brain and can be used with dimensionally compatible devices for draining CSF and other fluids of similar physical characteristics as a means of reducing intracranial pressure (ICP) and CSF volume. **CRAK:** The Cranial Access Kits (CRAKs, Figure 2) allows for access to the subarachnoid space or the lateral ventricles of the brain. The kit is intended to be used with an external drainage and monitoring system in selected patients to reduce ICP, to monitor CSF, to provide temporary drainage of CSF, and to monitor ICP. The Ventricular and Integral External Drainage Sets (EDS) and Accessories are intended for CSF drainage, sampling, and collection. The EDS is intended to be connected to a ventricular or a lumbar catheter. Note: For the purposes of this study, only the ventricular use will be the focus. Refer to **Section 2.2** for further information of all indications for use.
Study Design Rationale:	The purpose of this study is to investigate whether the Integra External Ventricular Drainage Systems listed as part of this study do perform to clinical expectations. Additionally, this study will focus on the safety of these devices by collecting any device-specific Adverse Events (AEs) or Device deficiencies (DDs) seen when used during standard of care procedures. A registry is the most appropriate design for a study such as this because registries proactively collect study data, but do not needlessly expose patients to non-standard of care interventions or procedures.

	Additionally, registries include data from patients with complex medical histories which will generally provide more real-world evidence. Including multiple centers and nations will ensure that data collected is from a broad set of surgeons and countries, thereby increasing the generalizability of the outcomes and conclusions. Study outcomes will be summarized using descriptive statistics. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, ranges, and numbers of observations. A sample size of 120 patients will be enrolled with 8% potential drop-out assumed. Integra LifeSciences Corporation believes this study design and sample size is appropriate to confirm the continued safety and performance of these devices given their well-established nature and the existing clinical evidence base.
Description of Intervention:	Not applicable – This is a non-interventional, observational registry. Instead, data will be collected on the following devices following routine/standard of care use and in accordance with the Instructions for Use (IFU).
Study Population:	Consecutive patients of any age, and gender who underwent a procedure with one of the Integra External Ventricular Drainage Systems or Accessories.
Inclusion Criteria	1. Patient and/or legally authorized representative has agreed to participate in the study by signing the EC-approved consent form, where applicable. 2. Patients (of any age) who underwent or who plan to have a procedure with one of the Integra or Codman External Ventricular Drainage System. 3. For patients who have had the EVD System removed prior to study enrollment, have available follow-up data from implant until the EVD System is no longer required for drainage and monitoring of CSF.
Exclusion Criteria	1. The Patients in whom more than one EVD System were or are intended to be placed. 2. The Patient has sepsis. 3. The Patient has a history of poor wound healing. 4. The patient exhibits signs of scalp infection prior to implantation that would be contraindicated per the IFU.

	5. The Patient is otherwise determined by the Investigator to be medically unsuitable for participation in this Registry. 6. The Patient is currently enrolled in another device trial or has been previously entered in this trial. 7. The Patient is a prisoner or member of a different vulnerable population that should not be included in the study per the investigator. 8. The Patients known to have uncorrected coagulopathy. 9. The Patients with known hypersensitivity to rifampin or clindamycin hydrochloride (prior to implantation of Bactiseal catheters)
Registry Study Site & Investigator Selection:	Up to 15 sites in EU countries, UK and Switzerland will participate in this study. Sites will be chosen based upon their experience with the EVD System and accessories and their ability to fulfill general requirements in Sponsor's Standard Operating Procedures (SOPs).
Study Duration:	Total duration of data collection is expected not to exceed 25 months at any individual site. The number of sites postulated are sufficient to ensure adequate data collection within the stated timeframe.
Patient Duration:	This registry will collect data on patients from implant of the EVD System and accessories until the EVD System is no longer required for drainage and monitoring of CSF.
Study Visits:	• Not applicable – There are no study visits in this protocol for patients to attend.
Data for Collection:	The following data will be collected: **Patient Data:** • Basic demographic data (*e.g.*, gender, age) • Clinical diagnosis for requiring an External Ventricular Drain. **Device Related Data:** • EVD system and accessories information. • Details of EVD system and Catheter replacement(s), if applicable. **Clinical Performance– in accordance with the primary, secondary and tertiary endpoints:** • CSF drainage (daily total) • Intracranial access location • EVD system and accessories maintenance procedures • Number, type, and volume of flush(s) used to address occlusions, if applicable. • Concomitant neurosurgical and neuro-interventional procedures • Relevant concomitant medications **Safety Data – in accordance with the safety endpoints:**

	• EVD system and accessories or procedure related AEs • Noted device deficiencies during use of the EVD system and accessories
Statistical Methods & Analyses:	Study outcomes will be summarized using descriptive statistics. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, ranges, and numbers of observations. The primary endpoint of success rate will be evaluated against a pre-defined performance goal of 80%. The sample size of 120 patients will provide greater than 80% power to test the hypothesis. A P-value of less than 0.05 is considered statistically significant unless otherwise specified. The secondary endpoint will be summarized descriptively. Subgroup analyses will be performed for drainage systems. Descriptive statistics will be provided for the sub-groups.
Reference:	Integra's and Codman's External Ventricular Drainage Systems have been on the market for at least 15 years and to date, do not have any unanswered questions on safety or performance. Evidence from peer-reviewed literature has confirmed that these products are safe and perform as intended. The registry design was therefore chosen to capture real-world experience with device use. 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.

1.2 Data Collection Scheme

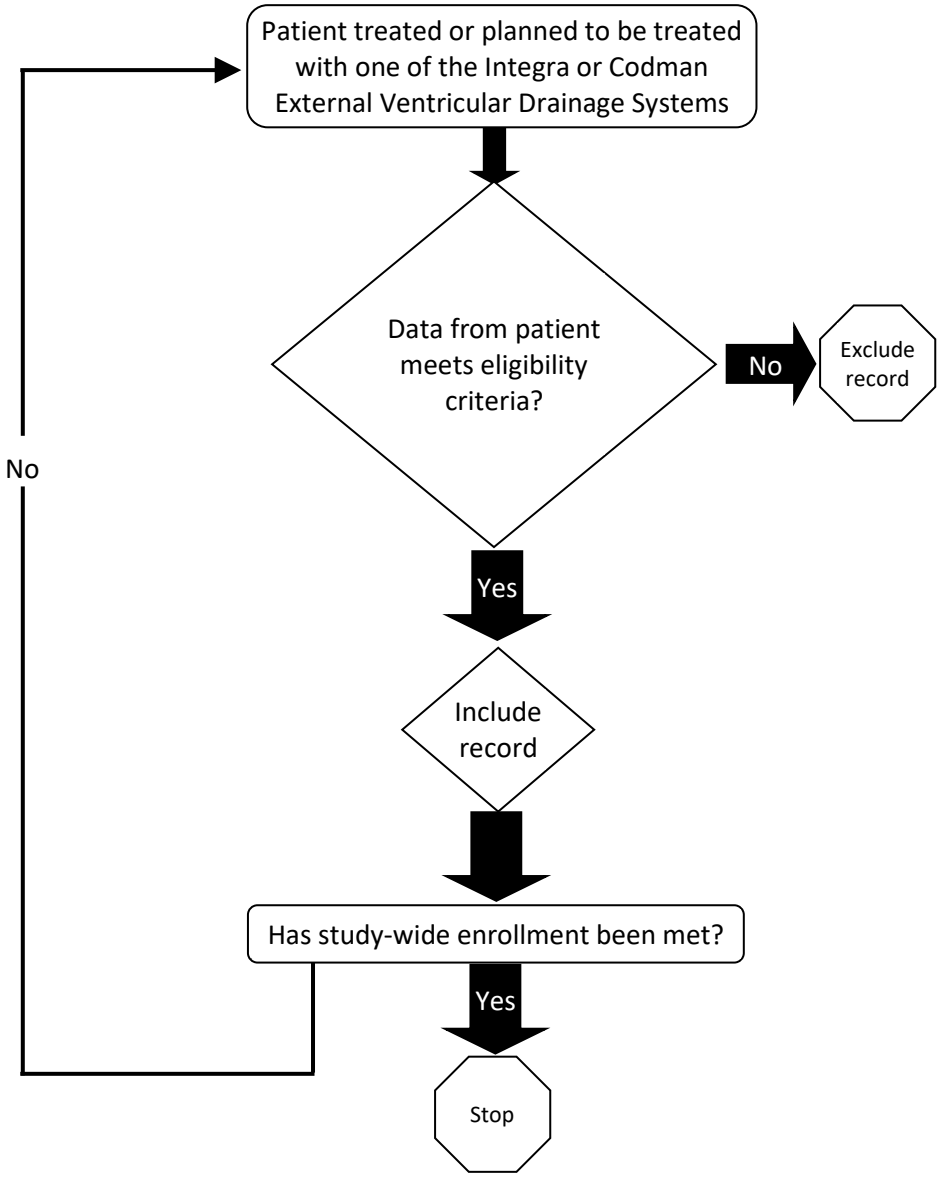


Figure 1. Enrollment Flowchart

1.3 Schedule of Activities

Table 1. Schedule of Activities[1]

Procedures	Study Assessments
Informed consent[2]	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: • Cerebrospinal fluid drainage (daily drainage) • Intracranial access location • EVD system and accessories maintenance procedures • Number, type, and volume of flush(s) used to address occlusions, if applicable • Concomitant neuro-surgical and neuro-interventional procedures • Relevant concomitant medications	X
Safety Data: • EVD system and accessories or procedure related AEs • Noted Device Deficiencies during use of the EVD system and accessories	X

[1] Details about all activities can be found in **Section 8**, unless otherwise specified.

[2] Informed consent is captured once, prior or after implantation of the EVD System.

2 INTRODUCTION

2.1 Background

The intracranial space is a fixed volume construct; the brain tissue, blood, and cerebrospinal fluid (CSF) are the components of this construct. Any change, therefore, in the volume of one of the components exerts deleterious pressure on the entire construct and stimulates compensatory measures to decrease the volume of the other components. This is the principle behind CSF drainage procedures conducted routinely in the neurocritical unit, often to reduce increased intracranial pressure (ICP) or intracranial hypertension. Conditions requiring CSF drainage may include hydrocephalus (a condition caused by excess buildup of CSF) and increased ICP following traumatic brain injury (TBI). CSF drains are also indicated for pre-and post-operative ICP monitoring in various cerebral conditions and in hydrocephalic shunt infections.

CSF drainage can be performed on a permanent or a temporary basis. The permanent means of CSF drainage involves shunting excess CSF to areas within the body. External drainage methods are usually temporary measures that drain CSF outside the body into a receptacle. The external CSF drainage systems are either designed to drain CSF from the ventricles of the brain (external ventricular drainage, EVD) or from the subarachnoid space of the lumbar spine (external lumbar drainage), though for this study only the EVDs are used External ventricular CSF drainage is done either continuously or intermittently for ICP management [1].

ICP monitoring is also routinely performed in the neurocritical unit either independently or in conjunction with CSF drainage. According to the Guidelines released by the Brain Trauma Foundation, ICP data can be used to predict outcomes and worsening intracranial pathology in severe TBI patients and are, therefore, useful in guiding therapy decisions [2, 3]. While ventricular ICP measurement is considered the reference standard, intraparenchymal, epidural, subdural, and subarachnoid spaces can also be used for effective ICP monitoring.

The External Ventricular Drainage Systems involve the combined functioning of monitors, drainage sets, Catheters, and other accessories. The present study is meant to confirm the continued safety and performance of the External Ventricular Drainage Systems as distributed by Integra. The following sections detail the types of products to be studied and their use.

2.2 Device Overview and Use

The devices used in this study are detailed in the Appendix I at the end of the protocol and are as follows:

2.2.1 Cranial Access

2.2.1.1 Codman Cranial Access Kits

The Cranial Access Kits (CRAKs, Figure 2) allows for access to the subarachnoid space or the lateral ventricles of the brain. The kit is intended to be used with an external drainage and monitoring system in selected patients to reduce ICP, to monitor CSF, to provide temporary drainage of CSF, and to monitor ICP.

The CRAK Kit consists of various accessories used during a burr hole procedure. The main components of the kit include a hand drill with variable chuck, and a variety of drill bits with depth guard. The depth guard allows accurate, secure, and easy to use adjustment of hand drill depth. Hand drill depth is selected by setting the depth guard to the required distance. The kit also contains various accessory instruments, including scalpels, needles, razor, syringes, skin marker and ruler, fenestrated drape, towels, sponges, and gauze.

Figure 2. Codman Cranial Access Kits

2.2.2 EVD Systems

EVD Systems allow for drainage and monitoring of CSF from the lateral ventricles of the brain and the lumbar subarachnoid space in selected patients to reduce ICP, to monitor CSF, to provide temporary drainage of CSF in patients with CSF shunts infected or not, and to monitor ICP. For the purposes of this study, only the ventricular use will be the focus on patients without infected CSF shunt.

Note: Although EVD Catheters are included as components in some EVD Systems in this study, EVD Catheters will be considered as accessories to the EVD Systems.

2.2.2.1 **LimiTorr Volume Limiting External CSF Drainage and Monitoring System**

The LimiTorr™ Volume Limiting External CSF Drainage and Monitoring System (LimiTorr, Figure 3) provides a closed system for drainage of CSF from the ventricles of the brain to an external drainage bag. The LimiTorr was designed to include a volume limiting valve mechanism which reduces the chances for excessive CSF drainage. The burette in the LimiTorr contains a volume limiting valve which stops drainage when the pre-determined volume (20 ml or 30 ml) is reached. The system includes an antimicrobial hydrophobic vent.

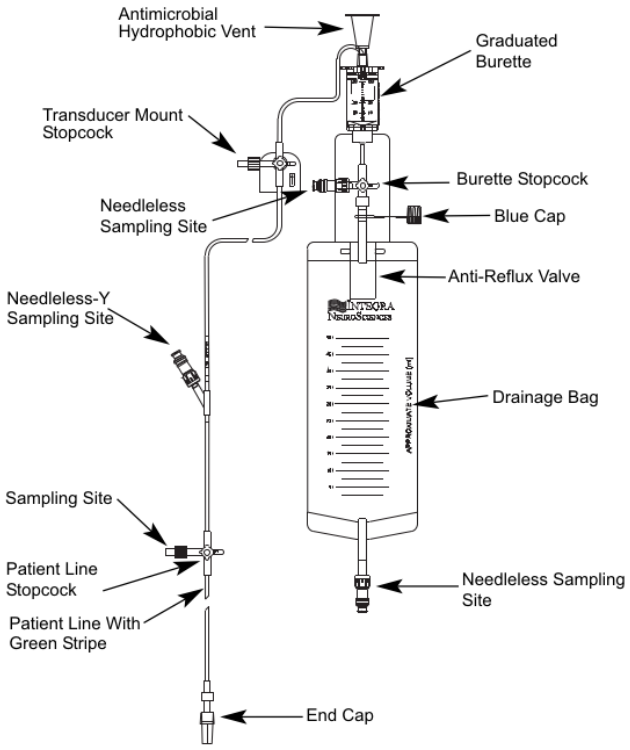


Figure 3. The LimiTorr™

2.2.2.2 **MoniTorr™**

The MoniTorr™ ICP External CSF Drainage and Monitoring Systems (Figure 4) includes MoniTorr CSF Drainage System with Patient Line One Way Valve (Product Code 10100), MoniTorr CSF Drainage System used with Pole Mount System (Product Code 10110 and INS1100), and MoniTorr CSF Drainage System Simple Bag and Line (Product Code 10150). The system may be used with a pole mounted assembly that allows for simple, quick, and accurate alignment with the patient and secure, positive or negative pressure level setting. The systems have also been designed to provide for ease of patient transport through a compact design and an antimicrobial hydrophobic vent feature that resists occlusion.

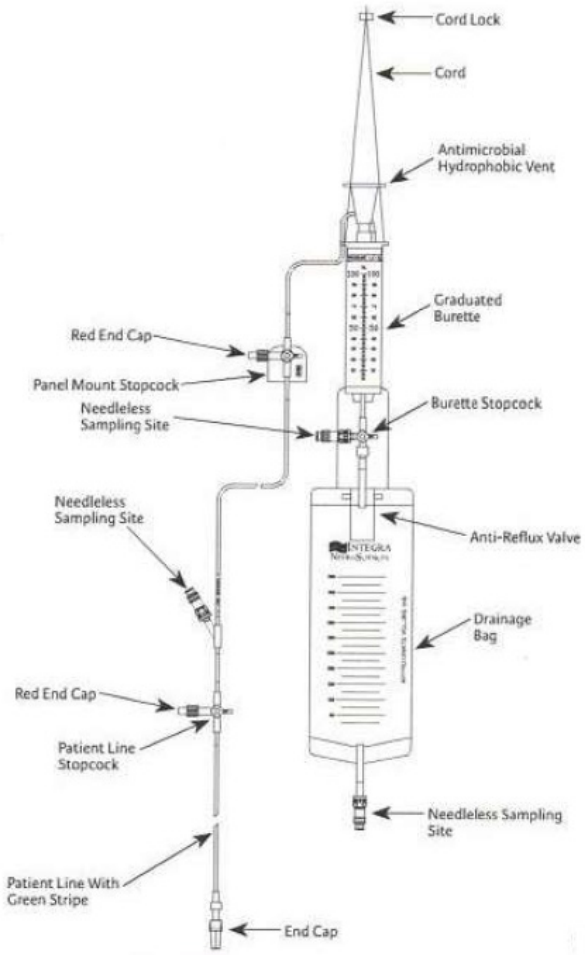


Figure 4. MoniTorr™ ICP External CSF Drainage and Monitoring Systems

2.2.2.3 **AccuDrain™ External CSF Drainage System without or with the Anti-Reflux valve**

The AccuDrain™ External CSF Drainage System may be used without (Product Code INS8400) or with the Anti-Reflux valve (Product Code INS8401) (Figure 5).

Monitoring of ICP is usually performed in selected patients with severe head injury, subarachnoid hemorrhage, Reyes syndrome or similar encephalopathies, hydrocephalus, hydrocephalic shunt infections, intracranial hemorrhage and pre and/or post-operative monitoring.

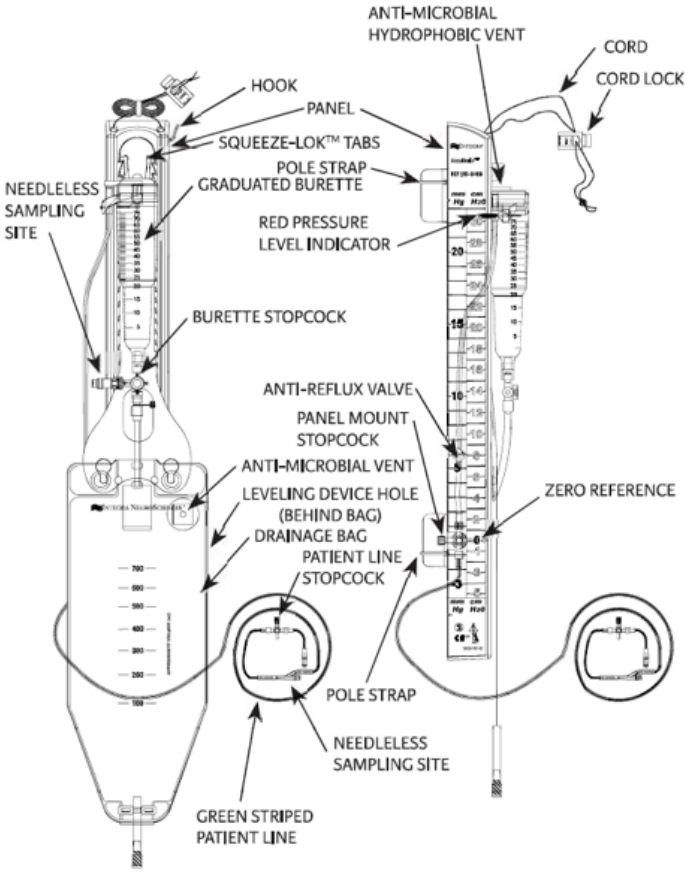


Figure 5. AccuDrain® System Components

2.2.2.4 Hermetic Plus™ External CSF Drainage Systems with reflux valve

The Hermetic Plus™ External CSF Drainage Systems with reflux valve (Product Code INS8301) (Figure 6) provide a sterile fluid path resistant to microbial particles and is a closed integral system.

Monitoring of ICP is usually performed in selected patients with severe head injury, subarachnoid hemorrhage, Reyes syndrome or similar encephalopathies, hydrocephalus, intracranial hemorrhage, and under physician supervision and discretion when drainage is to be used as a therapeutic maneuver.

Monitoring can also be used to evaluate the status pre-and postoperatively for space-occupying lesions.

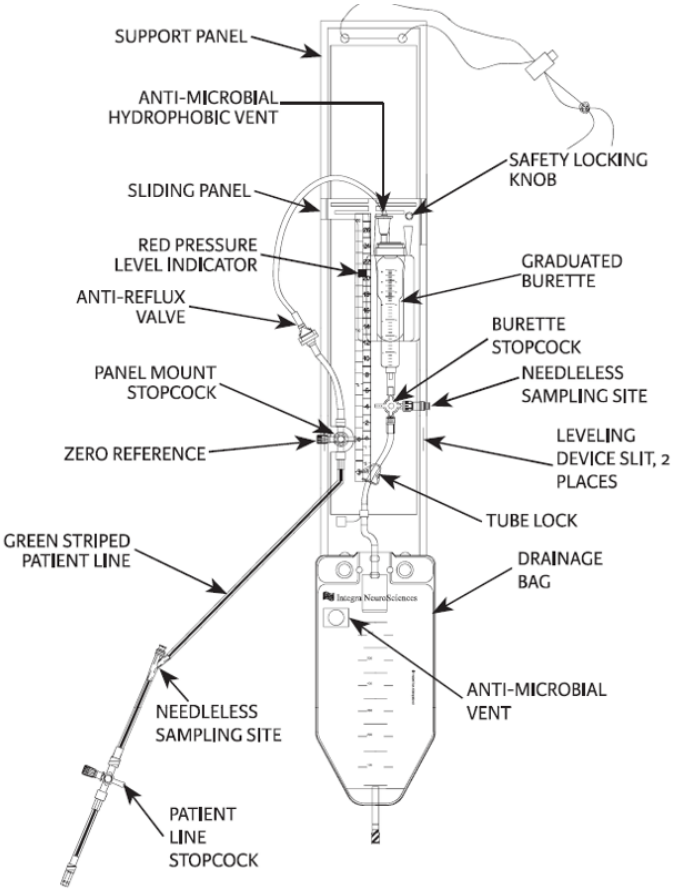
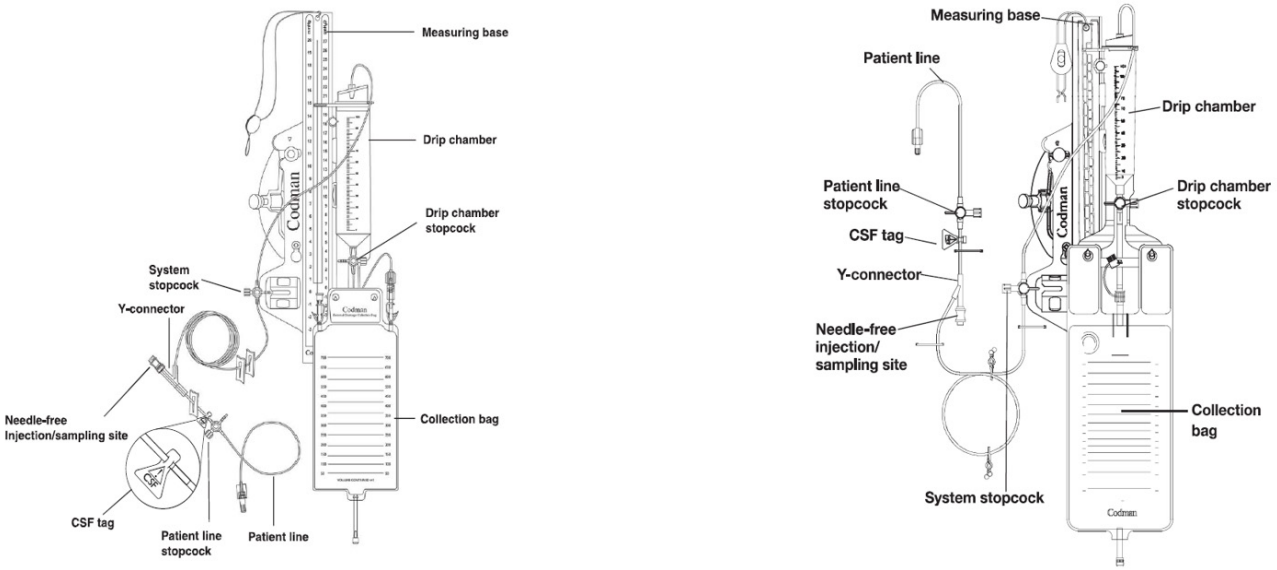


Figure 6. Hermetic Plus System Components

2.2.2.5 Codman® EDS 3™ CSF External Drainage System (EDS 3) without or with Ventricular Catheter

Use of the Codman® EDS 3™ CSF External Drainage System (EDS 3) may be used without (Product Code 821731 and 821731C) or with Ventricular Catheter (Product Code 821730C) (Figure 7). The system is indicated for draining CSF when the insertion of a permanent, internal shunt is not indicated



Product Code 82-1731 ***Product Code 82-1730C and 82-1731C***

Figure 7. Codman® EDS 3TM CSF External Drainage System

2.2.2.6 **Ventricular Drainage Systems**

The Ventricular Drainage System Product Code NL850-500V (Figure 8), provides a sterile fluid path for the drainage of the CSF from an intraventricular Catheter to a collection bag. System components facilitate ventricular drainage, fluid injection, CSF sampling and ICP monitoring when used in conjunction with Camino® Ventricular Pressure Monitoring Kits.

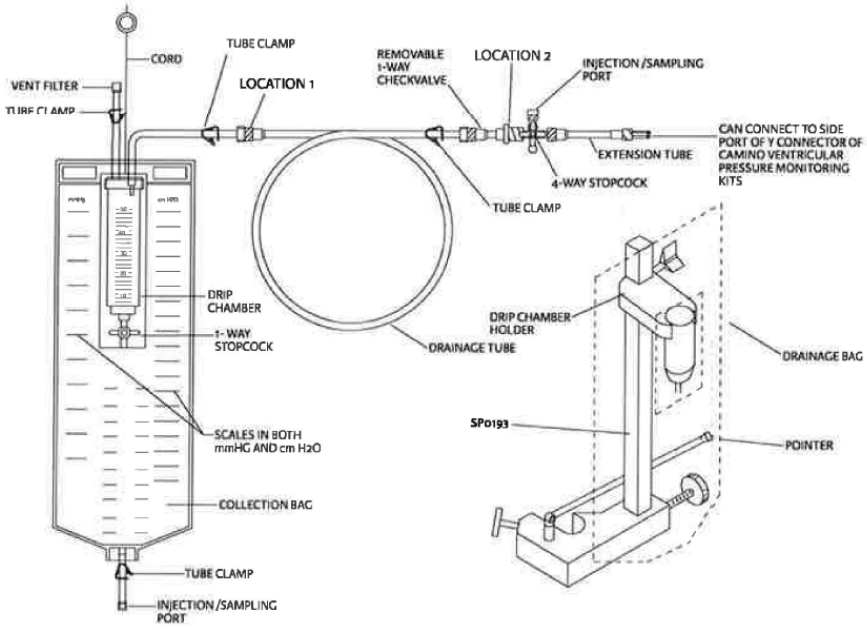


Figure 8. Ventricular Drainage Systems

2.2.2.7 External CSF Drainage Systems and Accessories

The External CSF Drainage Systems and Accessories include the CSF Drainage System w/Blue Stripe Tubing & 1-way V (Product Code INS8600) (Figure 9) and the Hermetic External CSF Drainage System with pressure tubing (Product Code INS8601) (Figure 10)

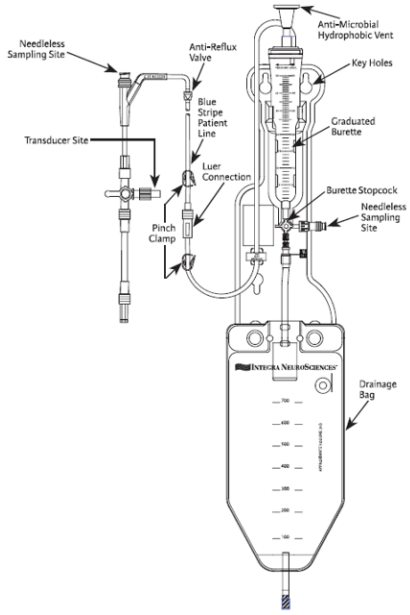


Figure 9. CSF Drainage System Components with large bore blue striped tubing assembly

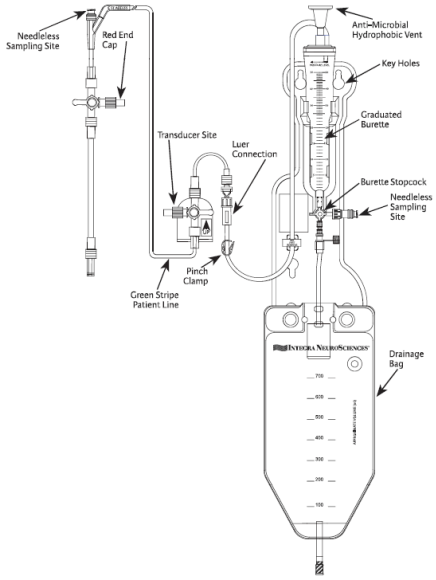


Figure 10. *Hermetic External CSF Drainage System Components with pressure tubing*

2.2.3 Catheters

Acute hydrocephalus is one of the most common indications for EVD, whether due to subarachnoid hemorrhage, intraventricular hemorrhage, intraparenchymal hemorrhage, infection, brain tumors, or shunt failure. Additional indications for EVD include post hemorrhagic ventricular dilation and post hemorrhagic hydrocephalus in premature infants. The importance of CSF drainage, managed by EVD using ventricular drainage, is also included in the Brain Trauma Foundation Guidelines for the management of severe TBI [2]. While it is well recognized that EVD can be a life-saving intervention, EVD insertion is associated with a number of complications, including CSF infections, hemorrhage, and misplacement of the device [1, 4].

2.2.3.1 **Bactiseal External Ventricular Drainage Catheters**

The Codman Bactiseal EVD Catheter and Codman Bactiseal Clear EVD Catheter Sets (Bactiseal EVD Catheters), are indicated for gaining access to the ventricles of the brain and can be used with dimensionally compatible devices for draining CSF and other fluids of similar physical characteristics as a means of reducing intracranial pressure and CSF volume.

Each of the Bactiseal EVD Catheters is a 35 cm silicone Catheter. The Catheter is marked with numbers or rings at each centimeter between 3 cm and 15 cm from the proximal tip (Figure 11). These markings serve as a scale to determine depth of insertion. The Catheter characteristics vary by catalog number (Appendix I).

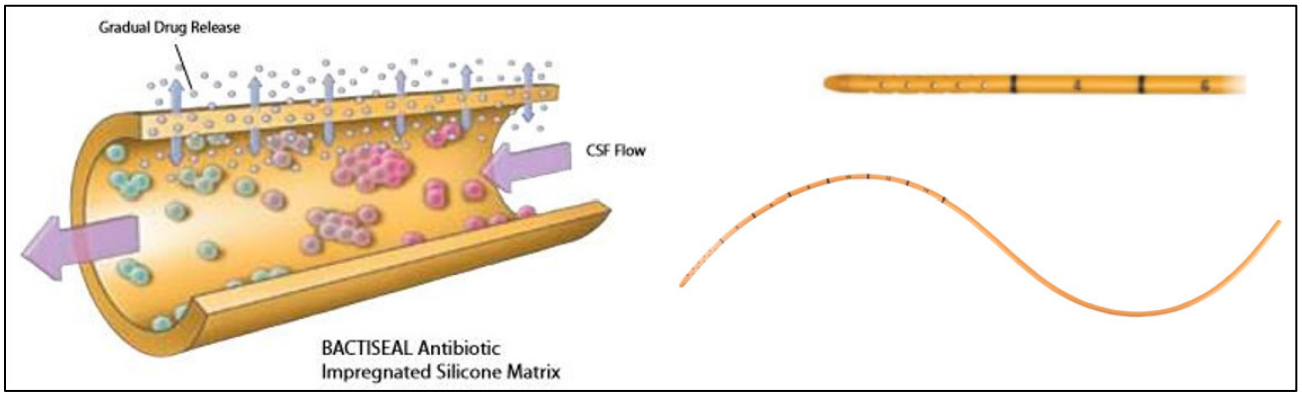


Figure 11. The Codman Bactiseal EVD Catheter

2.2.3.2 External Ventricular Drainage Catheters

External ventricular drainage Catheters (Figure 12) are indicated for drainage and monitoring of CSF from the lateral ventricles of the brain. The Catheters may be used to reduce ICP, to monitor ICP, to monitor CSF and in the management of hydrocephalic shunt infections.

The Ventricular Catheters are designed for diverting fluid from the ventricles through a series of drainage holes near the Catheter tip. The Catheters can be inserted into the ventricular cavity with the stainless-steel stylet. A trocar is supplied with the Catheters to facilitate subcutaneous tunneling away from the burr hole. The external portion of the Catheter may be secured to the scalp by the suture collar.

All external ventricular Catheters have markings from 3 to 15 cm ± 1.5 mm with numbers located at odd markings and dots located at even markings. All Catheters have a radiopaque tip: The Product Code INS-8220 Catheter is barium impregnated and the Product Code INS-4000, INS-4500 and INS-8420 are barium striped. An overview of all EVD Catheters and Accessories is provided in APPENDIX I.

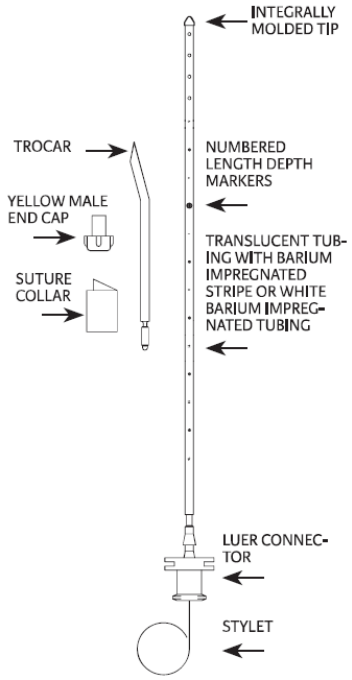


Figure 12. External Ventricular Drainage Catheters

2.2.3.3 Codman® EDS 3™ Clear Ventricular CSF Catheter

The Codman® EDS 3™ Clear Ventricular CSF Catheter is indicated for gaining access to the ventricles of the brain. It is a 35cm clear silicone Catheter with a radiopaque strip.

2.2.4 EVD Accessories

2.2.4.1 Pole Mount Assemblies and Accessories

The MoniTorr ICP™ Pole Mount Assembly provides support and alignment for External Ventricular Drainage Systems. The Pole Mount Sliding Bracket can be used with the Integra External Ventricular Drainage Systems and may also be used as a replacement assembly or accessory component (Figure 13). The Pole Mount Sliding Bracket is used to secure the External Ventricular Drainage System to the rail of the Pole Mount Assembly. The Pole Mount Assembly incorporates a removable rail graduated in cm H_20 and/or mmHg, a sliding bracket which facilitates secure attachment of the External Ventricular Drainage System through 2 keyholes located at the top of the system panel, and a pointer that is extendible to approximately 75 cm is attached to the bracket for easy alignment to patient's Foramen of Monro.

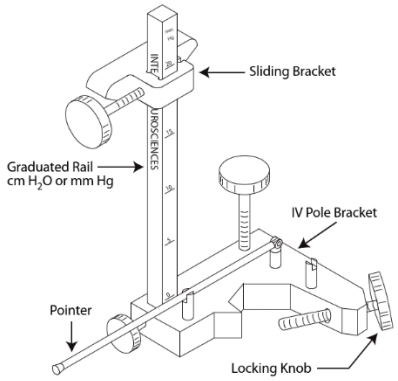


Figure 13. *Pole Mount Assembly*

2.2.5 Contraindications

Refer to the Instructions for Use for the contraindications specific for each device.

2.3 Intended Purpose in the post-market clinical follow-up registry

The External Ventricular Drainage Systems and Accessories will be used within label in this registry and the registry is of observational nature. There will be no specific medical or surgical procedures involved in the use of the study device, other than the standard of care. A full description of the medical and surgical procedures related to the External Ventricular Drainage Systems are available in the Instructions for Use.

2.4 Required training and experience

The External Ventricular Drainage Systems and Accessories will be used within label in this registry study. The investigators working with these systems have been previously trained on the use of the devices and should be familiar with their use prior to taking part in this registry study. Integra LifeSciences Corporation does not train, nor dictate, the shunt implantation technique. All investigators must meet certain expectations per Sponsor Standard Operating Procedures (SOPs).

2.5 Device Accountability

Given the post-market design of this registry, no device accountability will be performed for the purposes of this registry study.

2.6 Device Traceability

Devices will be tracked by Model, SKU, and LOT numbers, as applicable, which will be part of the data entered into the database of this registry.

3 OBJECTIVES AND ENDPOINTS

3.1 Primary Objective

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

3.2 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.

3.3 Primary Endpoint

The primary endpoint is 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.

3.4 Secondary Endpoint

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.

3.5 Tertiary Endpoints

- Number of initial Catheter Insertion Attempts [Time Frame: Implantation of subject] Number of insertions needed to place Catheter.

- Number of days 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 ITT Population [Time Frame: Implant of subject to explant] Reasons for non-infectious Catheter malfunctions in the intent to treat population.
- CSF daily drainage.

3.6 Safety Endpoints

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.

4 RISKS AND BENEFITS OF THE REGISTRY STUDY

4.1 Anticipated Clinical and Device Benefits

There are no anticipated clinical benefits for the patient as a result of participation in this registry. An increased review of a patient's procedural and follow-up data in addition to standard of care may be beneficial to the patient but is not guaranteed.

4.2 Anticipated Adverse Device Effects/Residual Risks

The External Ventricular Drainage Systems and Accessories will be used according to standard of care. Expected side-effects for patients participating in this registry are therefore not different than expected side-effects without participation.

4.3 Risks Associated with Participation in the Registry study

The External Ventricular Drainage Systems and Accessories will be used within label in this registry study and the study is of observational nature. Patients will not be asked to change their medical or medication treatments other than standard of care. There are no device-related risks for this study. There are, however, privacy (loss of confidentiality) risks associated with participation in the registry.

4.4 Risk Control/Mitigation

This registry does not add any additional risk compared to the risks associated with the use of the External Ventricular Drainage Systems and Accessories outside of this study.

Participation in the study does not submit the patient to any additional procedures or exams outside the customary standard of care. Patient confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor. The patient's data will be given a code in order to assure that the data can only be traced with the use of an identifier. The identifier will be stored securely in the local research institute. Data that is shared with the Sponsor will only contain the code and the name and any other identifiable information will be omitted. Please refer to **Section 12.1.3** for additional information. Therefore, there is no additional risk for taking part in this study.

4.5 Risk/Benefit Analysis

The participation in the registry does not add risks to the patients, thus the benefit is judged to outweigh the overall residual risks.

5 STUDY DESIGN

5.1 Overall Design

The External Ventricular Drainage Post-Market Clinical Follow-Up (PMCF) registry is an observational, multi-center, post-market study.

5.2 Description of Sites

Up to 15 sites in EU countries, UK and Switzerland will participate in this study. Sites will be chosen based upon their experience with the EVD System and accessories and their ability to fulfill general requirements in the Sponsor's SOPs.

5.3 Rationale for Study Design

The purpose of this study is to investigate whether the Integra External Ventricular Drainage Systems listed as part of this registry do perform to clinical expectations.
Additionally, this study will focus on the safety of these devices by collecting any device-specific AEs or DDs seen when used during standard of care procedures.

A registry is the most appropriate design for a study such as this because registries proactively collect study data, but do not needlessly expose patients to non-standard of care interventions or procedures. Additionally, registries include data from patients with complex medical histories which will generally provide more real-world evidence.

Including multiple centers and nations will ensure that data collected is from a broad set of surgeons and countries, thereby increasing the generalizability of the outcomes and conclusions.

Study outcomes will be summarized using descriptive statistics. Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, ranges, and numbers of observations.

A sample size of 120 patients will be enrolled for this registry. Inclusion 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.

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

5.4 End of Study Definition Overview

The end of the study is defined as completion of case report forms for the last subject in the registry study.

5.5 Primary Study Hypothesis

The primary hypothesis is to evaluate the success rate of CSF drainage against a pre-defined performance goal of 80% (with an expected success rate of 90% or higher). The hypothesis will be tested based on patients of all ages using the exact method along with two-sided 95% confidence interval.

6 STUDY POPULATION

6.1 Inclusion Criteria

In order to be eligible to participate in this study, Patients must meet all of the following criteria:

1. Patient and/or legally authorized representative has agreed to participate in the study by signing the EC-approved consent form, where applicable.
2. Patients (of any age) who underwent or who plan to have a procedure with one of the Integra or Codman External Ventricular Drainage as distributed by Integra System.
3. For patients who have had the EVD System removed prior to study enrollment, have available follow-up data from implant until the EVD System is no longer required for drainage and monitoring of CSF.

6.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from participation in this study:

1. The Patients in whom more than one EVD System were or are intended to be placed.
2. The Patient has sepsis.
3. The Patient has a history of poor wound healing.
4. The patient exhibits signs of scalp infection prior to implantation that would be contraindicated per the IFU.
5. The Patient is otherwise determined by the Investigator to be medically unsuitable for participation in this Registry.
6. The Patient is currently enrolled in another device trial or has been previously entered in this trial.
7. The Patient is a prisoner or member of a different vulnerable population that should not be included in the study per the investigator.
8. The Patients known to have uncorrected coagulopathy.
9. The Patients with known hypersensitivity to rifampin or clindamycin hydrochloride (prior to implantation of Bactiseal catheters)

6.3 Point of Enrollment & Enrollment Period

This is an observational study, and the patients will only provide informed consent to allow use of their data. All consented patients are assigned a study identification (ID) number and screened for eligibility in the study. The study will collect data on each patient from (1) the start of the procedure involving External Ventricular Drainage Systems or Accessories until the EVD System is no longer required for drainage and monitoring of CSF, and (2) in patients who have met all eligibility criteria. Patients eligible for the study are identified and informed consent is obtained prior or after the start of treatment with the devices. In case informed consent is obtained:

- Prior to the start of the treatment with the EVD System and Accessories, the data will be prospectively collected from the implantation procedure until the EVD System is no longer required for drainage and monitoring of CSF.
- After the implantation of the EVD System and Accessories and before the EVD System is no longer required for drainage and monitoring of CSF, the data will be retrospectively collected from the implantation procedure until the point of informed consent and prospectively collected until the EVD System is no longer required for drainage and monitoring of CSF.
- After the EVD System is no longer required for drainage and monitoring of CSF, the data will be retrospectively collected from the implantation procedure until the EVD System is no longer required for drainage and monitoring of CSF.

This registry study is anticipated to have an enrollment period of 25 months.

6.4 Comparison of Study Population to Target Population

The registry aims to collect information from patients that represent all ages, demographics, and regions to ensure that the data and conclusions generated from this study are as generalizable as possible while still matching the intended patient population as defined in the Instructions for Use. The patient population of this study will reflect patients who have had a TBI, undergone a major neurosurgical procedure, or some other traumatic, ischemic or hemorrhagic incident requiring EVD.

6.5 Screen Failures and Failures

Participants who are consented to participate in the registry, who do not meet one or more criteria required for participation in the study during the screening procedures, are considered screen failures.

Participants who underwent or undergo a replacement of the Integra or Codman EVD System with an EVD System other than an Integra or Codman EVD System are considered failures and will be discontinued from the date of the Integra or Codman EVD System replacement. The data collected up to the date of the Integra or Codman EVD System replacement will be included as part of the registry study results, as permitted by national laws and regulations.

7 STUDY INTERVENTION/INVESTIGATIONAL PRODUCT

Not applicable – This is a registry; no interventions or investigational products will be used.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Informed Consent

Informed consent will occur prior to data collection. **Section 12.1.1.** should be consulted for this process.

8.2 Performance Data to be Collected

Completion of Worksheets/Case Report Forms (CRFs). Sites will transcribe/transmit the information outlined below in study worksheets and CRFs. This information will originate from existing medical and other patient records.

Patient Data:

- Demographics:
  - Gender
  - Year of Birth (YOB)
- Prescribed clinical diagnosis for CSF drainage (e.g., reason the physician prescribed CSF drainage)

Procedural Data:

- Procedural Information CSF drainage:
  - Dates of EVD System and Accessories placement and removal.
  - Details of Catheter and/or EVD System replacement(s), if applicable.
  - Number of initial Catheter Insertion Attempts i.e., number of insertions needed to place Catheter
  - Length of Catheter Tunneling into the Brain i.e., length of tunneling of EVD Catheter in the brain
  - External Ventricular Drainage System and/or accessories used:
    - Brand name
    - Model, SKU, and LOT number(s), if documented

Clinical Performance Data:

- Daily CSF drainage until the EVD System is no longer required for drainage and monitoring of CSF.
- Intracranial access location
- EVD System and Accessories maintenance procedures
- Number, type, and volume of flush(s) used to address occlusions, if applicable.
- Concomitant neuro-interventional and neurosurgical procedures
- Relevant concomitant medications
- Whether the patient required a permanent shunt after the EVD System is no longer required for drainage and monitoring of CSF, if so (name, model)
- In the case of a malfunctioning EVD system and/or Accessories, the component(s) responsible for malfunction or reason for malfunction (where possible)

8.3 Safety and Other Assessments

- Assessment of events related to EVD system and accessories or procedure
  - Medical records will be reviewed for all events that occurred between index procedure and until the EVD System is no longer required for drainage and monitoring of CSF. See

Section 9.1 for complete definitions and information on assessing and documenting events.

- Assessment of noted Device Deficiencies during use of the EVD system and accessories
    - Medical records will be reviewed for device deficiencies (DD) that were documented that occurred between index procedure and until the EVD System is no longer required for drainage and monitoring of CSF. See **Sections 9.1.3 and 9.7.3** for complete definitions and information on assessing and documenting device deficiencies.

8.4 Concomitant Medication Review

The patient's relevant concomitant medications (i.e. current medication) will be recorded. Medication is considered relevant when associated with an adverse event related to the device or procedure as determined by the investigator.

The relevant medications will be documented from device implant until the EVD System is no longer required for drainage and monitoring of CSF. All medications as part of AE treatment must be noted as such on the AE CRF and on the ConMed CRF. If there was a change in dose, frequency, or route of medication, this change must be entered into the ConMed CRF as a new medication. The previous medication will be noted as being stopped.

9 SAFETY

9.1 Definitions

9.1.1 Adverse Device Effect (ADE)

Adverse event related to the use of an investigation medical device.

NOTE 1: This includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device.

NOTE 2: This includes any event resulting from use error or from intentional misuse of the investigational device.

9.1.2 Adverse Events (AE)

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether related to the investigational medical device or not and whether anticipated or unanticipated.

NOTE 1: This includes events related to the investigational medical device.

NOTE 2: This includes events related to the procedure involved.

NOTE 3: For users or other persons, this definition is restricted to events related to the use of the investigational medical device.

9.1.3 Device deficiency

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety and performance.

NOTE 1: Device deficiencies include malfunction, use error, and inadequacy in the information supplied by the manufacturer including labelling.

9.1.4 Incident

Any malfunction or deterioration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect.

9.1.5 Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instruction for use.

9.1.6 Serious Adverse Device effect (SADE)

Adverse device effect that has resulted in any of consequences characteristic of a serious adverse event

9.1.7 Serious Adverse Events (SAE)

AE that led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
c) fetal distress, fetal death or a congenital abnormality, or birth defect including physical or mental impairment.

Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a SAE.

9.1.8 Unanticipated Serious Adverse Device effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence severity or outcome has been identified in the risk assessment.

9.1.9 Unanticipated Serious Incident

Any incident that directly or indirectly led, might have led or might lead to any of the following:

a. the death of a patient, user or other person,
b. the temporary or permanent serious deterioration of a patient's, user's or other person's state of health,
c. a serious public health threat

9.2 Classification

9.2.1.1 **Severity of Event**

All events will be described by their severity level. In this study, one of the following levels will be assigned by the investigator:

- Mild – Symptoms barely perceptible to the subject, do not affect his/her performance or activity, do not normally require the administration of drugs for relief of the symptoms, but they may, however, be administered depending on the subject's needs.
- Moderate – Symptoms sufficiently serious to cause patient discomfort, having impact on the performance of daily activities; the subject may be able to continue in the study, but it may be necessary to treat the symptoms.
- Severe – Symptoms cause serious discomfort and they may be serious to a degree that the patient may not be able to continue in the study; treatment may be administered for the symptoms and/or the patient hospitalized.

If the severity of an event changes at any time in its duration, the site should update the related CRF accordingly.

9.3 Relationship to Study Intervention

All reported events must have their relationship to study intervention assessed by the clinician who examines and evaluates the subject based on temporal relationship and his/her clinical judgement. The Sponsor and the investigators will use the following definitions to assess the relationship of the AE to the investigational medical device or procedures (Medical Device Coordination Group [MDCG] 2020-10/1, May 2020).

Not related: relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the event does not follow a known response pattern to the medical device or procedure(s) (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;

- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment, or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis[3], when applicable.

To establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Possible: the relationship to the use of the investigational device, or the relationship with investigational procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

Probable: the relationship to the use of the investigational device, or the relationship with procedures, seems relevant and/or the event cannot reasonably be explained by any other cause.

Causal relationship: the event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis[3], when applicable.

To establish the relatedness, not all the above listed criteria must be met at the same time, depending on the type of device/procedures and the event.

[3] If an investigational device gives an incorrect diagnosis, the patient might, for example, receive an unnecessary treatment and incur all the risks that accompany that treatment, or might be incorrectly diagnosed with a serious disease. In other cases, the patient might not receive an effective treatment (thereby missing out on the benefits that treatment would confer), or might not be diagnosed with the correct disease or condition.

The Sponsor and the investigators will distinguish between the events related to the investigational device and those related to the procedures (any procedure specific to the registry study). An event can be related both to procedures and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related. Similarly, several routine diagnostic or patient management procedures are applied to subjects regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also not related.

In some cases, the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the investigators will make the maximum effort to define and categorize the event and avoid these situations. Where an investigator's assessment is not available and/or the Sponsor remains uncertain about classifying the event, the Sponsor should not exclude the relatedness; the causality of the event should be classified as "possible" and the reporting should not be delayed.

Special attention shall be given to the causality evaluation of unanticipated serious adverse (device) events. The occurrence of unanticipated events could suggest that the registry study places subjects at increased risk of harm than was to be expected beforehand.

9.4 Expectedness

The investigator and the Sponsor will be provided an initial assessment as to the expectedness (i.e., whether an event is anticipated or unanticipated) of an event. An event will be considered unanticipated if the nature, severity, or frequency of the event is not consistent with the risk information described for the External Ventricular Drainage Systems or accessories, or the surgical procedure. A list of anticipated AEs can be found in the following section.

Important: Anticipated and unanticipated designations do not revolve around whether the investigator/Sponsor thought an event would happen in a particular patient. Expectedness only speaks to whether the investigator/Sponsor has seen this type of event before with the use of the product (or class of products) or as a result of a procedure. Please see the decision tree below (Figure 7) to assist in determination.

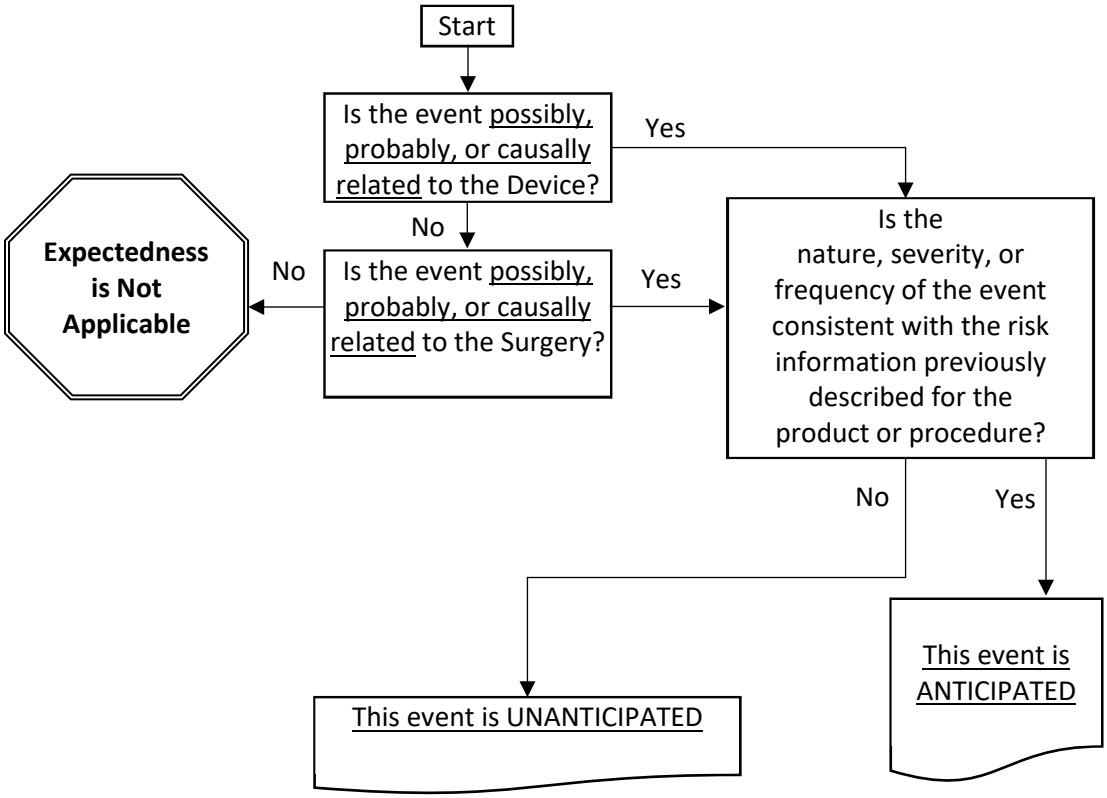


Figure 14. *Expectedness determination of investigational device or procedure related AEs*

9.4.1 Anticipated Adverse Device Effects

Complications which may result from the use of the EVD systems include the risks associated with the medications and methods utilized in the surgical procedure, as well as the patient's degree of intolerance to any foreign object implanted in the body.

The principal complications associated with cerebrospinal fluid drainage are Catheter obstruction, infection (including meningitis and ventriculitis), intracranial hypotension/hypertension, migration of ventricular Catheters, ventricular collapse, and intracerebral hemorrhage.

Excessive lowering of ICP in infants may result in complications which include subdural hematomas, markedly sunken fontanelles, overriding of cranial bones, and conversion of a communicating to a non-communicating hydrocephalus.

Ventricular Catheters may be obstructed by particulate matter such as blood clots, fibrin, or brain fragments. If not properly located in the lateral ventricle, the ventricular Catheter may become embedded in the ventricular wall or choroid plexus. Less commonly, the ventricular Catheter may be obstructed by the excessive reduction of ventricular size to slit like proportions.

Complications that are specific for the use of the Cranial Access Kits are improper use of the hand drill including failure to properly secure the drill bit to the variable chuck or failure to properly secure the depth guard to the drill bits. Improper use of the hand drill may result in serious injury. Bleeding may occur at the site of the drill hole, originating from the scalp, bone, dural, or cerebral areas. Due to the possibility of cerebral or extra cerebral hemorrhage or any other complication of this procedure, drill hole placement is the sole responsibility of the attending neurosurgeon.

9.5 Adverse Event Coding

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding platform.

9.6 Time Period and Frequency for Event Assessment and Follow-Up

As previously described, investigators and/or their staff will review the patient's medical record for events that occurred from device implant until the subject exits the study.

All events will be captured on the appropriate CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event (i.e., [possible] influenza instead of chills, fever, and vomiting). The investigator or designee should, to the best of their ability, endeavor to document an outcome/resolution for the event. If no resolution can be found in the medical record, the site will note it as ongoing.

Any medical condition that is present at the time that the subject is screened will be considered as baseline (i.e. medical history and/or conditions) and not reported as an event. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an event. Any procedures/surgeries should be documented on the Concomitant Neurosurgical and Neuro-interventional Procedures Log from device implant until the until the subject exits the study.

Changes in the severity of an event will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Events characterized as intermittent require documentation of onset and duration of each episode.

9.7 Event Reporting

All AEs and SAEs information will be collected on all subjects regardless the AE or the SAE is procedure- or device related. AE and SAE recording will start at the point of device implant until the subject exits the study.

Each event must be described as follows in the Electronic Data Capture (EDC) system:

- Event Term: A medically defined diagnosis/symptom. Use the highest level of evidence available.
  - Level 1: Diagnosis
  - Level 2: Symptoms
  - Level 3: Signs
- Event Description: Explain the circumstance of becoming aware of the event, how the subject explained the circumstances surrounding the onset of the event, the underlying cause (the diagnosis), coexisting disease, or other condition or complaint involving the event.
- Event Duration: Document by entering the date of onset (start date) and date of resolution (stop date).
- Event Attribution/Causality: Document causal relationship between event and the investigational product (e.g., causally related, probable, possible, unrelated).
- Event Seriousness: Document as serious or not serious.
- Event Severity: Document as mild (transient and easily tolerated by the subject), moderate (discomfort and interrupts normal activities), or severe (incapacitating with inability to work or do usual activity).
- Treatment: Document as none, medication, hospitalization, surgical, and/or other. Any prescribed medication should be noted in the subject's medical records and transcribed onto the event and Concomitant Medications CRFs. If a surgical or invasive procedure is required for an event, document the procedure on the Procedure Log.
- Outcome: Document as recovered without sequelae, recovered with sequelae, ongoing, death, or other. Events will be followed until a resolution has occurred, until a resolution is no longer expected, the pre-existing condition returns to baseline conditions, or the subject exits the study.

9.7.1 Event Reporting to Regulatory Authorities

All events will be communicated directly to the Sponsor by the investigator or designee. Event reporting will be collected since the time of implant and reported in the EDC. event information will be collected for all events. Event information will be collected on all patients.

Integra LifeSciences Corporation is responsible for the management of the device vigilance database and shall notify the relevant competent authority of incidents that occurred during the registry study, in accordance with Integra LifeSciences Policies and SOPs, the requirements and all applicable regulations.

9.7.2 Reporting to Ethics Committees

Prior to initiation of the registry study, reporting requirements for each Ethics Committee (EC), where applicable, will be verified and documented. Reporting will occur according to the requirements set forth by each involved EC and/or national requirements, where applicable, whichever is the most stringent.

9.7.3 Reporting of Device Deficiencies (DDs)

The principal investigator shall record every observed DD together with an assessment. All DDs including the analysis of used or explanted investigational devices, where applicable, shall be documented throughout the registry study and managed by the Sponsor.

In this study, review of potential DDs in a patient's medical records will occur from the date of implant to the date of explant.

The Sponsor is responsible for the classification of events and ongoing safety evaluation of the registry study and shall review all DDs. The investigator and Sponsor will determine and document whether the DD could have led to a serious adverse device effect (SADE). In case of disagreement between the Sponsor and the principal investigator(s), the Sponsor shall communicate both opinions to concerned parties described further below in this section.

Every attempt should be made by the Site to save or collect the defective device and packaging, if appropriate, for return to the Sponsor. A qualified company representative will investigate and determine root cause and corrective actions as applicable, and directives will be provided to the site if warranted.

The investigator shall:

- report to the Sponsor, without unjustified delay, all DDs that could have led to a SADE via the supplied CRF (definition in section 9.1).
- report to the EC any DDs that could have led to a SADE, if required by the national regulations or by the EC,
- report to regulatory authorities any DDs that could have led to a SADE, as required by the national regulations, and
- supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

It should be noted that no documents should be submitted to any regulatory agency/ EC without approval by the Sponsor beforehand to assure accuracy and completeness of the information.

All DDs related to the identity, quality, durability, reliability, usability, safety or performance of an investigational device including the analysis of used or explanted investigational devices, where applicable, shall be documented throughout the registry study and managed by the Sponsor through internal SOPs.

10 PATIENT DISCONTINUATION OF CONSENT FOR THE STUDY

IMPORTANT: This section is only applicable to sites and/or patients who have consented to have their data collected as part of this registry.

Patient participation in the registry study is considered complete when the EVD System is no longer required for drainage and monitoring of CSF. The registry study is considered complete upon the EVD System is no longer required for drainage and monitoring of CSF of the last patient.

A patient may withdraw consent for data to be collected in the registry study at any time during the registry study. The patient does not have to give a reason for withdrawal of consent. The investigator may exclude a patient if the patient or the patient's data does not fulfil the eligibility criteria (**Section 6.1-6.2**). The investigator may also decide to stop collecting a patient's data for the registry study if the investigator feels it is in the patient's best interest.

The Sponsor or its representative shall be notified immediately when a patient's consent is withdrawn or discontinued for any reason. Premature registry study end date and reason (if known) shall be documented on the CRF.

The data collected up to the date the patient has withdrawn consent will be included as part of the registry study results, as permitted by national laws and regulations. Additional safety information may be requested from a withdrawn or discontinued patient if it is considered clinically relevant.

11 STATISTICAL CONSIDERATIONS

11.1 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

$$H_0: P \leq 80\% \quad \text{vs.} \quad H_a: P > 80\%$$

where P is the proportion of patients with clinical success.

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

11.2 Sample Size Determinations

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 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.

11.3 Populations for Analyses

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 primary endpoint and all other endpoints analyses will be based on the FAS population.

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. Endpoints analyses based on the PPS population will be supportive.

11.4 Statistical Analyses

11.4.1 General Approach

Descriptive statistics will be presented (e.g., number of observations, percentage, mean with standard deviation, median, range). Individual patient summaries will be tabulated in data listings. All observed data will be included.

Descriptive summaries will be the basis of study reports to generate an overall summary of the population characteristics and outcomes. Continuous outcome variables will be presented as means and standard deviations, as well as medians and ranges as appropriate. For categorical outcome variables, counts and percentages of subjects by category will be provided. Descriptive tables will be produced where applicable.

Statistical analyses will be performed using SAS/STAT software, Version 9.4 or higher of the SAS System for Windows.

Additional details on the analysis as well as any changes from the analysis plans presented in the protocol are provided in the Statistical Analysis Plan (SAP).

11.4.2 Measures to Minimize Bias

Potential for bias during this registry has been minimized by a well-controlled design, expected conduct under the terms of an approved clinical investigation plan and prospectively defined methods of data analysis. All patients meeting the criteria will have all available data relevant to the registry objectives collected. No blinding/masking will be conducted. Any known or foreseeable factors that may compromise the outcome of the registry study or the interpretation of results have been accounted for by the design of the registry study.

11.4.3 Analysis of the Primary Endpoint

The primary endpoint of this registry is 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.

The number and percentage of patients with 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 will be presented. The primary hypothesis will be tested using the exact (Clopper-

Pearson) method along with two-sided 95% confidence interval. The primary objective will be met if the lower bound of the 95% confidence interval is greater than the performance goal of 80%.

11.4.4 Analysis of the Secondary Endpoint

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.

11.4.5 Analysis of the Tertiary Endpoints

The tertiary endpoints include:

- Number of initial Catheter Insertion Attempts [Time Frame: Implantation of subject] Number of insertions needed to place initial Catheter
- Number of days 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

Descriptive statistics will be provided to summarize the secondary endpoints. Continuous outcome variables will be presented as means, standard deviations, medians, and ranges as appropriate. For categorical outcome variables, counts and percentages of subjects by category will be provided along with 95% confidence interval of the percentage.

11.4.6 Safety Analyses

The safety endpoints of this study are:

- Device- or procedure-related adverse events (AEs) during the use of the device in the patient
- 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

AEs will be coded using the MedDRA terminology for data summaries. Each AE will be coded with 2 levels including Preferred Term (PT) and System Organ Class (SOC).

The total number of EVD system and accessories-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 EVD system or accessories within each SOC and PT. A listing of EVD system and accessories-related AEs and SAEs will be presented respectively.

The total number of DDs as well as the percentage of patients with at least one DD will be presented overall and by drainage system. A listing of DDs will be presented.

11.4.7 Baseline Descriptive Statistics

The baseline patient characteristics will be summarized using descriptive statistics (continuous outcome variables will be summarized using means and standard deviations, as well as medians and ranges; categorical outcome variables will be summarized by presenting the number and percentage of subjects in each category).
A patient listing of this data will also be provided.

Other data pertinent to the EVD System and Accessories or relevant patient care may be summarized.

11.4.8 Planned Interim Analysis

There are no planned interim analyses.

11.4.9 Sub-Group Analyses

Subgroup analyses will be performed for drainage systems for primary endpoint and secondary endpoint. The purpose of the subgroup analysis is not to reach statistically significant results within each subgroup, but rather to assess the consistency and robustness of the treatment effects across the subgroups. Descriptive statistics will be used for the subgroup analysis. Two-sided 95% confidence intervals will be reported as appropriate for reference purpose only. No multiplicity adjustment will be considered for the subgroup analysis.

EVD Systems:

- AccuDrain
- Hermetic Plus
- LimiTorr
- MoniTorr
- Codman EDS 3 / EDS 3C
- Basic CSF Drainage System
- External Ventricular Drainage System

11.4.10 Tabulation of Individual Participant Data

Individual patient data will be listed by measure and time point where appropriate.

11.4.11 Exploratory Analyses

Any exploratory analyses will be pre-specified in the SAP.

11.4.12 Missing Data

Analysis of performance and safety data will be primarily performed on all observed (available) data. No imputation methods on missing data will be performed. Based on the primary point, missing data is expected to be minimal. Reasonable efforts will be made to obtain complete data for all subjects. If despite these efforts, missing data occurs, reasons for missing data will be summarized, including withdrawal of consent.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 Informed Consent Process

12.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms will be EC-approved, where applicable, and the participant or their legally authorized representative will be asked to read and review the document and provide written authorization via signature to participate in the registry study.

12.1.1.2 Vulnerable population

Patients will be receiving CSF Drainage as part of standard of care and no additional risks or procedures will be conducted outside of standard of care.

There may be situations where patients are treated with the External Ventricular Drainage Systems, but where the patients are not able to provide informed consent for data collection prior to treatment. This may be the case in situations such as, but not limited to, post-traumatic hydrocephalus, post-hemorrhagic stroke, or intercranial tumor. These situations are expected to happen relatively frequently, and data referring to the use of the device in these situations are considered of value for the evaluation of clinical safety and performance of the device.

However, for these patients, their willingness to volunteer in data collection for the purposes of the registry study cannot be confirmed, and these patients thus meet the criteria of vulnerable population as defined in ISO 14155, Section 3.55. Therefore, in these cases, informed consent may be obtained by the patient's legal authorized representative.

12.1.1.3 Consent Procedures and Documentation

Non-vulnerable population

Patients must be fully counseled and informed of their options, risks and benefits, and should have every opportunity to ask questions about participation in the registry study. This process includes a thorough explanation of the patient information letter and informed consent form that the patient will be asked to sign acknowledging that they understand and desire to participate in the registry study.

The investigator is responsible for assuring that written informed consent is obtained from each patient prior to participation in the registry study. Should the investigator delegate the responsibility of

conducting the informed consent process to a designee, the investigator must ensure and document appropriate training of the authorized designee.

The investigator will use an EC approved informed consent form, where applicable, that was prepared in accordance with this clinical investigation plan, ISO 14155 and regulatory requirements.

Informed consent must always be obtained from a patient prior to initiation of any data collection dictated by the clinical investigation plan. A copy of the signed and dated statement of informed consent, as well as any other written information, will be provided to the patient.

If new information regarding the investigational device becomes available and/or the clinical investigation plan changes and this information can significantly affect a patient's future health and medical care, patients will be informed of the information and may be asked to sign a revised informed consent form.

Vulnerable population

Patients' legally authorized representative must be fully counseled and informed of the options, risks and benefits, and should have every opportunity to ask questions about participation in the clinical investigation. This process includes a thorough explanation of the patient information letter and informed consent form that the legally authorized representative will be asked to sign acknowledging that they understand the requirements of participation in the clinical investigation.

The investigator is responsible for assuring that written informed consent is obtained from each legally authorized representative prior to participation in the clinical investigation. Should the investigator delegate the responsibility of conducting the informed consent process to a designee, the investigator must ensure and document appropriate training of the authorized designee.

The investigator will use an EC approved informed consent form that was prepared in accordance with this clinical investigation plan, ISO 14155 and regulatory requirements.

Informed consent must always be obtained from the legally authorized representative prior to initiation of any data collection dictated by the clinical investigation plan. A copy of the signed and dated statement of informed consent, as well as any other written information, will be provided to the patient and the legally authorized representative.

If new information regarding the investigational device becomes available and/or the clinical investigation plan changes and this information can significantly affect a patient's future health and medical care, patients and their legally authorized representative will be informed of the information and may be asked to sign a revised informed consent form.

12.1.2 Study Discontinuations and Closure

This study may be suspended temporarily or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to investigators. Those study patients who consented to participate will be notified by their respective investigators, if required. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform their EC and provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Unanticipated operational difficulties or other unforeseen occurrences

The study may resume if resolution of identified problems can be resolved.

Upon study closure or termination, the patients will not be able to have access to the devices studied in this registry unless warranted by medical necessity outside of the scope of this registry. The rationale for this is that this is a non-interventional study. All treatments with the devices occurred outside of the registry and for standard of care use.

12.1.3 Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating investigators, their staff, and the Sponsor and their collaborators (e.g., contract research organizations [CROs]). Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data resulting from the procedures, will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitors (i.e., Clinical Research Associates), other authorized representatives of the Sponsor, representatives of the EC, regulatory agencies or CROs may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and imaging records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing EC, Institutional policies, or Sponsor requirements, but no less than two (2) years after the end of the study.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Sponsor via an EDC system. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Sponsor research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor.

12.1.4 Future Use of Stored Data

Data collected during the study may be stored for as long as needed and can be used as basis for future studies or regulatory filings. All data used in this manner will remain deidentified in accordance with Sponsor SOPs and national and local regulations.

12.1.5 Site Selection, Corrective and Preventative Actions, Investigator Disqualification

Procedures governing site selection, corrective and preventive actions, and criteria for investigator disqualification can be located in current SOPs at Integra LifeSciences. Details about these procedures can be provided upon request.

12.1.6 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of participating subjects are protected, that the reported registry data are accurate, complete, and verifiable, and that the conduct of the registry is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by internal Sponsor representatives or by qualified external personnel contracted from a CRO.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- In brief, on-site and/or centralized review of source documents will occur after completion of the data collection of the final patient enrolled in this registry. All monitoring criteria can be found in the most current CMP for the study.
- All personnel conducting monitoring visits will be trained on the study, Sponsor SOPs, and the study-specific CMP ahead of the visit.
- It is not anticipated that Sponsor-lead audits will be conducted as part of this study; however, the Sponsor reserves the right to conduct audits or to hire an external firm to perform audits if cause is demonstrated.

12.1.7 Quality Assurance and Quality Control

Each investigational site will be responsible for quality management of study conduct, data and if applicable biological specimen collection, analysis, documentation and completion in keeping with GCP, national, and local regulations. If applicable, sites will follow their internal SOPs in regard to biological specimen collection and analysis.

Quality control (QC) procedures have been implemented with regard to the EDC (i.e., the database) system in keeping with the Sponsor's SOPs. Data QC checks that will be run on the database will be generated and documented in accordance with the Sponsor's SOPs. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution. Sites should aim to resolve these queries as soon as possible in the EDC system.

The investigational site will provide direct access to all clinical investigation related sites, source data/documents, and reports for the purpose of monitoring and/or auditing by the Sponsor, and inspection by local and regulatory authorities. All sites will follow their institutional procedures for collection and storage of medical records that will become part of this dataset.

Data processing will be performed in compliance with the EU General Data Protection Regulation (GDPR) 2016/679 and all applicable national laws.

12.1.8 Data Handling and Record Keeping

12.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical investigation staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring that all data recorded meets ALCOA documentation standards; that is, data should (to the best of the site's ability) be:

- Attributable – It should be clear who has documented the data.
- Legible – Readable and signatures identifiable.
- Original – Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
- Accurate – Accurate, consistent and real representation of facts.
- Enduring – Long-lasting and durable.
- Available and accessible – Easily available for review of treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
- Complete – Complete till that point in time.
- Consistent – Demonstrate the required attributes consistently.
- Credible – Based on real and reliable facts.
- Corroborated – The data should be backed up by evidence.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each subject enrolled in the study. Clinical data will be entered directly from the source documents. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) will be entered into an EDC system provided by the Sponsor. The EDC system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the sites' source.

12.1.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the formal discontinuation of clinical registry. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

If deemed necessary by the investigational site, records may be placed in off-site storage; however, the Sponsor should be made aware of any off-site storage arrangements made by the site. If storage changes

before the limits of the retention period, the Investigative site is responsible for communicating those changes with the Sponsor.

12.1.9 Protocol Deviations

A protocol deviation is an Instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (ISO 14155 Definition). The investigator is not allowed to deviate from the protocol without first receiving approval in writing from the Sponsor, involved EC, and applicable regulatory authorities. Deviations from the protocol to protect the rights, safety, and well-being of human subjects under emergency circumstances or situations beyond the investigator's control (such as subjects not attending scheduled follow-up visits, etc. may proceed without prior approval of the sponsor and the EC.

Approval for deviations shall be documented in writing and maintained in the investigator and clinical investigation files.

The use of waivers from the protocol is prohibited.

A Major Protocol Deviation is defined as an event that resulted in an increased risk to a subject or others; affected the right, safety, or welfare of a subject; or affected the scientific integrity of the clinical investigation. Major Protocol Deviations might include, but are not limited to, the following list:

- Failure to obtain informed consent prior to subject enrollment
- Enrolled subject did not meet the inclusion/exclusion criteria
- Impacts subject safety or alters risks to subjects

Any other events or omissions that do not comply with the requirements of the protocol will be considered Minor Protocol Deviations. Minor Protocol Deviations might include, but are not limited to, the following list:

- Incorrect version of the informed consent form used.
- Follow-up visit was outside the required window.

All Major Protocol Deviations from the protocol must be reported promptly, but in no event later than 5 business days, to the appointed Sponsor representative/clinical investigation monitor via e-mail, regardless of whether they were medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. In addition, Investigators will also adhere to procedures for reporting deviations to the involved EC in accordance with their specific reporting policies and procedures.

As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Integra or its representatives will record and evaluate all deviations from the protocol during monitoring visits or when notified of the protocol deviation by the investigation site. Individual event corrective and preventive actions may be recommended at that time the deviations are recorded. In addition, deviations occurring across investigational sites will be reviewed by Integra on a periodic basis to determine if more global preventive actions may be required.

Subjects will receive standard of care in case a protocol deviation leads to the end, temporary halt, or early termination of the investigation. The standard of care is defined by the applicable treatment protocol(s) for the disease at the investigational site.

12.1.10 Publications and Data Sharing Policy

Publication and data sharing policies are contained within the Investigative site's clinical trial agreement (CTA).

Integra will register this study with public clinical investigation registries in accordance with applicable laws and regulations and will report the results of the study publicly in accordance with guidelines set by those registries.

12.1.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the device industry, is critical. Therefore, and in accordance with an investigational site's CTA, any actual conflict of interest (COI) of persons who have a role in the design, conduct, analysis, publication, or any aspect of this registry will be disclosed and managed by the Sponsor and their institution. Furthermore, persons who have a perceived COI will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this registry. It is incumbent upon the investigator to disclose COI to their respective facilities in accordance with their policies and procedures.

12.2 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
CMP	Clinical Monitoring Plan
COI	Conflict of Interest
CRAK	Cranial Access Kit
CRF	Case Report Form
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CTA	Clinical Trial Agreement
DD	Device Deficiency
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDS	External Drainage Sets
EU	European Union
EVD	External Ventricular Drainage
GCP	Good Clinical Practice
ICP	Intracranial Pressure
IFU	Instruction For Use
ISO	International Organization for Standardization
IQR	Interquartile Range
ITT	Intent-To-Treat
MDCG	Medical Device Coordination Group
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
OR	Operating Room
PMCF	Post-Market Clinical Follow-Up
PT	Preferred Term
QC	Quality Control
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SKU	Stock Keeping Unit
SOC	System Organ Class
SOP	Standard Operating Procedure
TBI	Traumatic Brain Injury
TMF	Trial Master File
USADE	Unanticipated Serious Adverse Device effect
VCAK	Ventricular Drainage Accessory Kits
YOB	Year of Birth

12.3 Protocol Amendment History

Version	Date	Summary of Changes/Affected Sections
Version 1.0		N/A – First Version
Version 2.0	14-JUN-2022	The primary endpoint clinical success has been defined, and the sample size has been recalculated per primary endpoint hypothesis. The Exclusion criteria 7 has been adjusted
Version 3.0	09-NOV-2022	The Subgroup Analyses and Missing Data sections are updated.
Version 4.0	10-JUL-2023	The safety objective was changed to collect safety data until the EVD system is no longer required and not limiting the timeframe to 30 days if the device was not removed in this timeframe. The primary endpoint was changed to better evaluate the safety and performance of the EVD system rather than the disease that being treated. The secondary endpoint was added to evaluate the successful access to the intracranial space.
Version 5.0	11-JUL-2024	The inclusion cap was changed to 34% (40 subjects per site). The study duration at any individual site was changed to 25 months. Protocol section “12.1.9 Protocol Deviation” was amended in line with the Sponsor’s new procedures for recording protocol deviations.

13 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*.
2. Brain Trauma Association, *Guidelines for the Management of Severe Traumatic Brain Injury*, in *Brain Trauma Association*.
3. Brain Trauma Foundation, *Guidelines for the Management of Severe Traumatic Brain Injury*, in *Brain Trauma Foundation*.
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.
5. Yuen J, Selbi W, Muquit S, Berei T. Complication rates of external ventricular drain insertion by surgeons of different experience. Ann R Coll Surg Engl. 2018 Mar;100(3):221-225. doi: 10.1308/rcsann.2017.0221. Epub 2018 Jan 24. PMID: 29364007; PMCID: PMC5930101.
6. Mansoor N, Madsbu MA, Mansoor NM, Trønnes AN, Fredriksli OA, Salvesen Ø, Jakola AS, Solheim O, Gulati S. Accuracy and complication rates of external ventricular drain placement with twist drill and bolt system versus standard trephine and tunnelation: a retrospective population-based study. Acta Neurochir (Wien). 2020 Apr;162(4):755-761. doi: 10.1007/s00701-020-04247-3. Epub 2020 Feb 4. PMID: 32020298; PMCID: PMC7066093.
7. Chung DY, Olson DM, John S, Mohamed W, Kumar MA, Thompson BB, Rordorf GA. Evidence-Based Management of External Ventricular Drains. Curr Neurol Neurosci Rep. 2019 Nov 26;19(12):94. doi: 10.1007/s11910-019-1009-9. PMID: 31773310; PMCID: PMC7383112.

14 APPENDIX I

14.1 External Ventricular Drainage Systems included in this registry study

Product Code	Device/Part Name
INS8401	AccuDrain with Anti-Reflux Valve
INS8400	AccuDrain without the Anti-Reflux valve
821731	Codman EDS3 Drainage System without Ventricular Catheter
821730C	Codman External Drainage System 3 with Ventricular Catheter
821731C	Codman External Drainage System 3 without Ventricular Catheter
NL850500V	CSF Drainage System
INS8600	CSF Drainage System with Blue Stripe Tubing & 1-way V
INS8601	Hermetic External CSF Drainage System with pressure tubing
INS8301	Hermetic Plus EVD System with Reflux Valve
INS9020	LIMITORR VOLUME LIMITING EVD 20 ML
INS9030	LIMITORR VOLUME LIMITING EVD 30 ML
10150	MoniTorr CSF Drainage System Simple Bag and Line
10110	MoniTorr CSF Drainage System used with Pole Mount System
INS1100	MoniTorr CSF Drainage System used with Pole Mount System
10100	MoniTorr CSF Drainage System with Patient Line One Way Valve

14.2 External Ventricular Drainage Catheters included in this registry study

Product Code	**Device/Part Name**
821735	Codman Clear Ventricular CSF Catheter Kit
82-1745	Codman BACTISEAL EVD Catheter Set
82-1749	Codman BACTISEAL EVD Large Lumen Catheter Set
82-1750	Codman BACTISEAL Clear EVD Catheter Set
INS4000	Hermetic Ventricular Small Catheter Set
INS4500	Hermetic Large Style Ventricular Catheter Set
INS8220	Hermetic Catheter Set, 35CM
INS8420	TraumaCath, 35CM

14.3 Cranial Access included in this registry study

Product Code	Device/Part Name
826617	CODMAN CRANIAL ACCESS KIT With/Without
826607	MicroSensor Hand Drill Disposable
826608	MicroSensor Drill Bit O 5.8mm Disposable

14.4 External Ventricular Drainage Accessories included in this registry study

Product Code	Device/Part Name
10210	Drain Bag Replacement w/ Reflux Valve
INS2100	MoniTorr Drain Bag Replacement w/ Reflux Valve
INS2101	LimiTorr DRAINAGE BAG WITH ANTI REFLUX VALVE AND BLUE CAP
821732C	EDS 3™ Collection Bag Kit - 5 Bags
821733	EDS 3™ Leveling Device
INS8700	701 ml Replacement Drainage Bag
INS-301	Integra® Pole Mount Sliding Bracket
INS-400	Evolution pole mount assembly with cm H_2O and mm Hg Rail with Laser Level and Line Level
INS-400CM	Evolution pole mount assembly with cm H_2O Rail, Laser Level and Line Level
INS-410	Evolution Pole Mount Assembly with cm H_2O and mm Hg Rail with Laser Level and negative scale of -25 cm H_2O/-18 mm Hg and Line Level
INS-410CM	Evolution Pole Mount Assembly with cm H_2O Rail and negative scale of -25 cm H_2O, Laser Level and Line Level
INS-8903	Line Level