Proposal No.: C-BSEAL-001
Date of proposal: V1.0/2019-11-18

Clinical Registry Study on Bactiseal Catheter

A Multi-center, Retrospective Registry Study on the Safety of Bactiseal Catheter

Product Name: Catheter

Model and Specifications:

Model	Description	Inner diameter (mm)	Outer diameter (mm)
823072	Ventricle and abdominal catheter	1.4/1.0	2.7/2.2
823073	Ventricle catheter	1.4	2.7
823074	Abdominal catheter	1.0	2.2

Proposal No.: C-BSEAL-001

Version No.: V1.0

Date of Version: November 18, 2019

Category of Test: Registry study

Lead Institution: Shanghai Children's Medical Center, School of Medicine, Shanghai Jiao Tong University

Sponsor: Integra LifeSciences (Shanghai) Co., Ltd.

Signature Page for the Review of the Study Protocol

Research Topic: Retrospective and Multi-center Registry Study on the Safety of Bactiseal Catheterization

Study No.: C-BSEAL-001

Date of Version: V1.0/November 18, 2019

The signatures of the following team members indicate that, prior to submission to the Ethics Committee (EC), this clinical study, including understanding of techniques involved, statistical methods, research procedures, regulatory compliance, and quality control, has obtained the internal approval of Integra LifeSciences.

Role	Name	Signature	Date
Author of the proposal	Henry TANG	Henry Tang	Nov 22, 2019
Sr Director, Global Clinical Operations, Integra LifeSciences Corporation	David SHELEHEDA		04 DEC 2019
Senior Vice President, Research and Development, Integra LifeSciences Corporation	William WEBER		11/27/19
Quality Assurance & Regulatory Affairs, Integra LifeSciences (Shanghai) Co., Ltd.	Jing CHEN		29 Nov. 2019
Biostatistics Analyst	Qian MAO		3 Dec 2019
Clinical Data Management, Integra LifeSciences Corporation	Lora LIU		12/04/2019

Signature Page for Investigator:

Research Topic: Retrospective and Multi-Center Registry Study on the Safety of Bactiseal Catheterization

Proposal No.: C-BSEAL-001

Date of Revision: V1.0/November 18, 2019

I, the signer, have reviewed the study proposal and its attachments. I will conduct this clinical study in accordance with the requirements of this proposal, Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki, and all applicable laws and regulations. I will provide a copy of this proposal and all relevant and permanent information to the participating research staff and supervise them.

_____

<Name> Investigator <Date>

_____

<Institution> Hospital

Contents

Summary of the Proposal

Research Topic:	A Multi-center, Retrospective Registry Study on the Safety of Bactiseal Catheterization
Research Purpose:	This study aimed to **continue** to evaluate safety information from subjects implanted with a catheter (trade name: Bactiseal) produced by Codman & Shurtleff, Inc. of the United States. Device safety would be assessed based on all the adverse events that occurred within one year after the subjects implanted the catheter.
No. of Subjects:	50
No. of Research Centers:	3 research centers
Research Design:	This study was designed to be single arm, multi-center, and retrospective. A total of 50 patients would be retrospectively enrolled. Information would be collected on adverse events of subjects enrolled within one year after the implantation of the Bactiseal Catheter from August 07, 2018 to January 31, 2021. The following information would be collected from subjects' medical records or hospitals' databases (if any): 1. General condition of the subjects 2. Intraoperative condition and catheter implantation 3. Information on the shunt product 4. Adverse events of subjects within one year after the operation and classification of the adverse events 5. Relevant examinations in case of postoperative infection 6. Other adverse event-related information (except anticipated adverse events)
Research Duration:	2020-
Inclusion Criteria:	Subjects who met all of the following inclusion criteria would be enrolled: 1. The informed consent was exempted by the Ethics Committee of a research center. Either a subject or his/her legal representative signed the informed consent form (ICF) prior to enrollment. 2. A subject had an indication suitable to use Bactiseal Catheter. 3. A subject received a hydrocephalus shunt at least one year ago.
Exclusion Criteria:	Subjects who met any of the following exclusion criterion were excluded:

	1. A subject didn't have an indication suitable to use the product. 2. A subject was known to be allergic to a component or ingredient of the product to be implanted, including silicone tubing, rifampicin, and clindamycin. 3. According to the comprehensive judgment of an investigator, a subject had an infection of the implant site when the shunt was implanted, such as ventriculitis, meningitis, peritonitis, and local implant skin infection. 4. A subject was simultaneously implanted with another shunt system different from Bactiseal Catheter. 5. A subject had a contraindication of the shunt operation. 6. A subject had uncorrected coagulopathy or any bleeding disorder.
Endpoint	1. Non-infection rate of a subject within one year 2. Type and incidence of adverse events of a subject within one year

Time and Data Collection Form

	Screening	Preoperative	Operation	Postoperative follow-up
Time of data collection	NA	-30 to -1 days	0	Days 1-365
Signed the ICF (if applicable)[1]	X			
Review of inclusion and exclusion criteria	X			
Medical History		X		
Laboratory examination		X		X+
Operative process			X	
Device application record			X	
Adverse events[2]			X*	X*
Serious Adverse Events			X*	X*
End of study/exit			X	X
Record of concomitant medication[3]		X*	X*	X*
Record of concomitant treatment[4]			X*	X*

+	Suspicious or proven infection
*	If any

Notes: 1. The ICF (if applicable) needed to be completed before screening.

2. A postoperative anticipated adverse event was not counted as an adverse event.

3. Only antibiotics and medications related to postoperative adverse events were recorded. Only the administration of antibiotics within seven days prior to the operation was recorded.

4. Only the treatment and operation associated with postoperative adverse events were recorded.

Abbreviations:

AE	Adverse events
CRF	Case Record Form
CV	Curriculum Vitae
EC	Ethics Committee
ICF	Informed Consent Form
IFU	Instructions for Use
GCP	Good Clinical Practice
NMPA	National Medical Products Administration
SAE	Serious adverse event
SDV	Source data verification
UADE	Unanticipated adverse device effect

1 Introduction

1.1 Background and principle

Abnormal enlargement of part or all of subarachnoid space or ventricles, the abnormal accumulation of cerebrospinal fluid (CSF) in subarachnoid space or ventricles is called hydrocephalus. It is a circulation disorder of CSF caused by many pathological reasons[1]. A shunt system mainly drains CSF from the accumulation site to the abdominal cavity, the lumbar cistern, and the atria through a catheter so as to address dilated ventricles and alleviate the pressure on the brain.

The earliest permanent CSF shunt operation occurred in 1893. A glass catheter was placed in a lateral ventricle of a patient with hydrocephalus, the end of which was placed under the skin. The head circumference of the patient was significantly reduced after the operation[2]. The principle of modern shunt operation can be dated back to the 1870s. Ventriculoperitoneal shunt operation had become a common treatment for hydrocephalus[3]. China released *Specialist Consensus on the Standardized Treatment of Hydrocephalus in China* in 2013, which regarded CSF shunt as an important operation for hydrocephalus and proposed suggestions on technical key points.

However, in terms of the treatment of neurosurgical diseases, the incidence of complications of shunt operations is the highest, mainly including shunt infection, obstruction or rupture of a shunt catheter, displacement of an intracranial or abdominal shunt catheter, excessive or insufficient drainage of CSF, intracranial hemorrhage, and epilepsy[1]. Infection is a common complication and important cause of revision. Its incidence rate is 3-29%. Approximately 90% of the cases occur within one year after the operation. If it is combined with ventriculitis, the mortality rate can be as high as 30-40%[3]. For children, even if the infection can be controlled, long-term complications, such as epilepsy, cognitive impairment, and physical and delayed psychological development, may occur[4].

From previous analysis of literatures, among a total of 8,588 shunt operations (3,291 cases with an antibiotic-impregnated catheter, 5,297 cases with a non-antibiotic-impregnated catheter), the postoperative infection of an antibiotic-impregnated catheter was 3.6%, while that of a non-antibiotic-impregnated catheter was 7.2%[5]. From most recent publication[6], (need to put reference here), 1605 cases were randomized to receive either a standard shunt (n=536), an antibiotic-impregnated shunt (n=538), or a silver shunt (n=531). Of those, 1594 had a shunt inserted without evidence of infection at the time of insertion (533 in the standard shunt group, 535 in the antibiotic shunt group, and 526 in the silver shunt group). The subjects were followed up for a median of 22 months (IQR 10¨C24; 53 withdrew from follow-up). 32 (6%) of 533 evaluable patients in the standard shunt group had a shunt revision for infection, compared with 12 (2%) of 535 evaluable patients in the antibiotic shunt group. The combined postoperative infection of an antibiotic-impregnated catheter was 3.2%, while that of a non-antibiotic-impregnated catheter was 7.1%.

In addition to infection, complications of CSF shunt operations include excessive and insufficient drainage of CSF associated with pressure regulation; obstruction of the shunt catheter, usually due to a poor position of an intracranial shunt catheter, the accumulation of red blood cells or brain tissues in the shunt pump, or wrapping of a shunt catheter by abdominal omentum majus; rupture of shunt catheter, mostly occurring at the junction of the catheter and the pump and a subcutaneous area; and rare complications, such as displacement of a shunt catheter, wound, intracranial hemorrhage, and symptoms of Parkinson's Disease[1].

Bactiseal Catheter manufactured by Codman & Shurtleff, Inc. in the United States is a silicon catheter impregnated in rifampicin and clindamycin. Thanks to the slow release of the two antibiotics on the surface of the catheter, the colonization of Gram-positive bacteria on the catheter is reduced. Meta analysis[7] demonstrated that Bactiseal can significantly reduce the infection rate after shunting.

Meanwhile, Bactiseal has been safely used around the world for more than a decade. However, there is a lack of data on the safety of the product in long-term follow-up and clinical application in the Chinese population.

1.2 Research-related devices

Devices verified in this study were catheters (trade name: Bactiseal) manufactured by Codman & Shurtleff, Inc., U.S.A. Its registration number is G.J20183132246. Please refer to the table below for the product specifications and models in this study.

Table 1: Product Specifications and Models

Model	Description	Inner diameter (mm)	Outer diameter (mm)
823072	Ventricle and abdominal catheter	1.4/1.0	2.7/2.2
823073	Ventricle catheter	1.4	2.7
823074	Abdominal catheter	1.0	2.2

2. Benefits/Risks

2.1 Benefits

Bactiseal Catheter serves as a component of the shunt system of hydrocephalus treatment. Hydrocephalus shunt operations can alleviate or eliminate hydrocephalus and improve clinical symptoms and signs. Meanwhile, retrospective collection of data and experience of clinical safety can be used as a reference for investigators and enterprises and conducive to the diagnosis and treatment of future subjects. However, such data and experience had no extra benefits for the participants in this study.

2.2 Risks

This is a retrospective study. It did not intervene in subjects' normal treatment. It objectively collected patients' clinical data. Hence, there were no additional risks associated with participating in this study.

3 Research purpose

3.1 Indications

Bactiseal Catheter: Bactiseal Catheter serves as a component of the shunt system of hydrocephalus treatment.

3.2 Purpose

This study aimed to collect safety information from subjects implanted with a catheter (trade name: Bactiseal) produced by Codman & Shurtleff, Inc. of the United States. Device safety would be assessed based on all the adverse events that occurred within one year after the subjects were implanted with the catheter.

4. Research Design

This study was designed to be single arm, multi-center, and retrospective.

This is continued access study to enroll additional 50 new subjects, with total combined 150 subjects. The historical study is DPS-201501.

It would collect information on adverse events of subjects enrolled within one year after the implantation of Bactiseal Catheter from August 07, 2018 to August 31, 2019, through case review or hospital database (if any).

The following information would be collected from subjects' medical records:

1. General condition of the subjects

2. Intraoperative condition and catheter implantation

3. Information on the shunt product

4. Adverse events of subjects within one year after the operation and classification of the adverse events

5. Relevant examinations in case of postoperative infection

6. Other adverse event-related information (except anticipated adverse events)

Information on adverse events would be collected. And the safety of clinical application of the product would be assessed.

5. Endpoint

5.1 Endpoint

1. Non-infection rate of a subject within one year

2. Type and incidence of adverse events within one year of a subject

5.2 Safety indicators

The incidence of adverse events was observed in line with the IFU. Key attention should be paid to:

- Obstruction of a cerebral ventricular catheter
- Falling of a catheter
- Poor position of a catheter
- Intestinal perforation, abdominal and pseudocysts, umbilical fistula, pseudo-acute appendicitis, infection, and ascites
- Subcutaneous twist, rupture, distal obstruction, and distal retraction from the abdominal cavity
- Failure of a shunt catheter

- Mechanical failure
- Obstruction or infection of the shunt path
- Leakage of CSF in an implanted shunt catheter
- Excessive drainage
- Damage of intracranial or abdominal tissue
- Fibrous adhesion

6 Study Population

6.1 Selection of subjects

Subjects who received a hydrocephalus shunt operation between August 07, 2018 to August 31, 2019 and met the inclusion criteria were enrolled. As this was a retrospective study, it would apply for the exemption of informed consent from the Ethics Committee of a center. For the centers which did not exempt informed consent, the informed consent process would be completed prior to the start of data collection, either by telephone or by anyway approved by the Ethics Committees.

6.2 Inclusion criteria

Subjects who met all of the following inclusion criteria would be enrolled:

1. The informed consent was exempted by the Ethics Committee of a research center. Or a subject or his/her legal representative signed the informed consent form (ICF) prior to the enrollment;

2. A subject had an indication suitable to use Bactiseal Catheter;

3. A subject received hydrocephalus shunt at least one year ago.

6.3 Exclusion criteria

Subjects who met any of the following exclusion criterion were excluded:

1. A subject didn't have an indication suitable to use the product;

2. A subject was known to be allergic to a component or ingredient of the product to be implanted, including silicone tubing, rifampicin, and clindamycin;

3. According to the comprehensive judgment of investigator, a subject had an infection of the implant site, when the shunt was implanted, such as ventriculitis, meningitis, peritonitis, and local implant skin infection;

4. A subject was simultaneously implanted another shunt system excluding Bactiseal Catheter;

5. A subject had a contraindication of the shunt operation;

6. A subject had uncorrected coagulopathy or any bleeding disorder.

7 Research Process

The research process included: Screening and enrollment of subjects, Days -30 to -1 before the operation, Day 0, the day of operation, and one-year follow-up (Days 1-365) after the operation.

7.1 Screening and enrollment

7.1.1 Screening of subjects

Qualified and authorized investigators or clinical study coordinators reviewed the medical records of subjects to screen subjects eligible for this study.

7.1.2 Informed consent

As this was a retrospective study, it would apply for the exemption of informed consent from the Ethics Committee of a center. For the centers which did not exempt informed consent, the informed consent process would be completed prior to the start of data collection, either by telephone or by any means approved by the Ethics Committees. If informed consent was not obtained from a subject of a center which did not exempt informed consent, the subject could not participate in this study.

Research centers should maintain records of subjects who were screened to meet the general inclusion criteria and signed the ICF (in terms of a research center that did not waive informed consent).

7.1.3 Enrollment of subjects

If a subject met all the inclusion criteria and did not meet any exclusion criterion, he/she could be included in the retrospective analysis cohort. Subjects could be considered as enrolled in this study only if they met the following requirements:

1) A subject met all the inclusion criteria and did not meet any exclusion criterion; and

2) The ICF was signed (in terms of a research center that did not waive informed consent).

7.2 Days -30 to -1 before the operation

The following information needed to be collected and recorded:

1. Demographic information and medical history of a subject before the operation: including patient age, gender, height, weight, preoperative diagnosis; past medical history, personal history; preoperative laboratory examination results: including white blood cells, red blood cell count, neutrophilic granulocyte count, hemoglobin content, platelet count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein, albumin, blood glucose, APTT, PT, and INR. If there were multiple laboratory tests before the operation, the latest results should be collected.

2. Concomitant medication: Only the administration of antibiotics within seven days prior to the operation was recorded.

7.3 Operation period (Day 0, the day of operation):

The following information needed to be collected and recorded:

1. Operation: surgeon, surgical procedure, start and stop time of the operation, blood loss during the operation, intraoperative complications, intraoperative shunt, and combined treatment;

2. Record of devices used during the operation: type, No. and batch No. of the cerebral ventricular shunt catheter; type, No. and batch No. of the pressure regulating valve; and type, No. and batch No. of shunt catheters at the abdominal cavity/the lumbar cistern/ the atria.

7.4 Postoperative follow-up period: Days 1-365

An adverse event (except an anticipated adverse event) discovered during the review of postoperative history or hospital database (if any) should be recorded:

The time, description, concomitant therapy, and outcome of an adverse event, information related to the operation and the product, if the implanted part was taken out due to an adverse event, and concomitant medication and treatment should be recorded.

Additional records were required for the following special adverse events:

1. Infection: Infection site which is usually classified into intracranial, skin, and abdominal infections. For intracranial infection, time of infection, white blood cell count, red blood cell count, neutrophilic granulocyte count, hemoglobin content, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein, blood glucose, traits and color of CSF, cell count, Pan's test results, contents of protein, sugar, and chloride in CSF, bacterial culture type, and bacterial susceptibility to rifampicin and clindamycin should be recorded. For skin infection and abdominal infection: white blood cell count, red blood cell count, neutrophilic granulocyte count, bacterial culture type, and bacterial susceptibility to rifampicin and clindamycin should be recorded.

2. Obstruction of catheter: site, reason (judged by an investigator), and nature of obstruction should be recorded.

3. Leakage of CSF: time and position of leakage should be recorded.

4. Mechanical failure: type of mechanical failure should be recorded, including falling out, displacement, twisting, and rupture.

A patient who died within one year was still considered as a complete case. The form of SAE should be completed. And the death should be specified in this study endpoint table.

8 Adverse Event Reporting

8.1 Adverse events

8.1.1 Adverse events

Adverse event (AE) refers to any adverse medical event of a subject, no matter if it is related to this study or a research-related device.

During the assessment of a subject enrolled to this clinical study, an investigator should each time determine whether there was an AE and collect information, including date, severity, treatment, prognosis, and analysis of the AE, and research-related device, operation, or drug, in as detailed a way as possible.

Information of all AEs, research-related device failures, and other product issues should be as much as possible collected from existing medical records, and entered into CRFs.

8.1.2 Anticipated operation-related adverse events

Anticipated AE refers to an event that occurred after the operation during hospitalization (relative to the baseline change of a subject), which was an anticipated consequence of the operation. If an anticipated AE occurred, it would not be reported to the sponsor.

Currently, postoperative anticipated AEs known include:

- Wound pain within 48 hours followed by agitation
- Fever lower than 38.5°C within 48h
- Abdominal distension and constipation within 48h
- A small amount of wound exudation within 48h
- Mild anemia (hemoglobin > 90g/L)
- Increase in white blood cells within 48h

8.2 Unanticipated adverse device effect

Unanticipated adverse device effect (UADE) refers to a serious adverse effect, a life-threatening issue, or death caused by or related to the devices, or a serious and unanticipated issue related to the rights, safety, or health of a subject and the devices. In addition, the nature, severity, or frequency of such an event was not specified in the study proposal, IFU, and clinical trial instructions.

8.3 Serious Adverse Events

Serious adverse event (SAE) refers to any of the following adverse events:

1) Cause Death,
2) Serious deterioration of a subject's health, including:
    a. A life-threatening illness or injury,
    b. Permanent damage of the body structure or a body function,
    c. Hospitalization or extension of the current hospital stay:
    d. Medical or surgical intervention required to avoid a life-threatening disease or prevent permanent damage to the body structure or a body function,
3) Fetal distress, fetal death, congenital malformation, or birth defects.

In this retrospective study, planned hospitalization or medical intervention due to a disease existing before the operation not followed by serious deterioration of health was not regarded as a serious adverse event.

8.4 Duration of follow-up after an adverse event

As this is a retrospective study, it did not intervene in subjects' normal treatment. Therefore, all adverse events were properly dealt with by an investigator based on medical requirements. And no additional

follow-up would be performed.

8.5 Adverse event reporting

Within one year after the shunt operation of a subject, all the adverse events (except anticipated adverse events) recorded in the medical records or hospital database (if any) should be reported. An investigator reported AEs to the sponsor via CRF.

An investigator should record the nature, severity, treatment and prognosis of an AE and determine the correlation with the devices, medication, or operation involved in this clinical study.

An investigator must report SAEs and UADEs to the sponsor (or a designated person) within 24h after their occurrence, and report them to the Ethics Committee in a timely manner. In the event of any request by the sponsor, additional information should be provided. The investigator should judge the time associated with the research product. The research center should report them to a local medical device adverse event monitoring organization. Death should be reported within 7 days, after it was known. A serious injury or an event that might result in death or a serious injury should be reported within 20 days after it was known. The sponsor would report to NMPA and/or a local medical device adverse event monitoring organization in line with the same requirements as those of the research center. If the adverse event had existed or been reported in the previous reporting system, it would be unnecessary to report it repeatedly.

The sponsor should regularly inform all the clinical investigators of this study of all SAEs and UADEs.

8.5.1 Severity criteria

The severity of an adverse event could be classified as mild, moderate, and severe according to the following criteria.

- Mild: It was transient and mild with no influence on daily life, and no special measures or treatment was required.
- Moderate: It had a slight impact on daily life. Measures or treatments were needed, if necessary.
- Severe: It had a serious impact on daily life. Special measures or treatment must be taken, and hospitalization was required, if necessary.

8.5.2 Determination of causal relationship

The relevance between any adverse event and a research-related device should be judged, according to the following criteria, including unrelated, possibly unrelated, possibly related, probably related, and definitely related. If an AE was judged to be possibly related, probably related, or definitely related to a research-related device, such an AE was related to the devices.

- Unrelated: An AE was not related to the devices.
- Possibly unrelated: An adverse event was more likely to be related to other factors, such as concomitant medication or disease. Or the timing of the AE indicated that it was unlikely to be caused by a research-related device.
- Possibly related: An AE might be caused by a research-related device. Other reasons were not excluded, such as concomitant medication or disease. When the occurrence of an AE and the use of a research-related device had a reasonable time sequence, the causal relationship between the

event and a research-related device could not be excluded.

- Probably related: An AE was probably caused by a research-related device. An AE and the use of a research-related device had a reasonable time sequence. For example, the causal relationship was proved after the device was taken out. There was unlikely to be another explanation, such as concomitant medication or disease.

- Definitely related: The type of an AE was identified as a side effect of a research-related device, which could not be explained by other reasons, such as concomitant medication and disease. The time of an AE strongly implied a causal relationship (e.g. reaction after the removal and re-implantation of a device).

9 Early Termination of the Study

9.1 Reason of early termination

Possible reasons of early termination include, but are not limited to, the following:

- Withdrawal of informed consent: (For a research center which required its subjects to sign the ICF) a subject decided to withdraw from this study. The decision must be "determined by the subject himself/herself" and recorded in the subject's research file;

- Early termination of this study: The sponsor might decide to suspend this study in advance for any reason.

9.2 Early termination of this study by a subject

For a research center which required its subjects to sign the ICF, if a subject terminated this study in advance, the reason must be recorded in the source document and the file of the research center and submitted via CRF.

A subject who terminated this study in advance could not be replaced, and his/her data would be included in the results analysis, unless the subject submitted a written request to withdraw the data.

9.3 Early termination of this study by the sponsor

The sponsor had the right to temporarily suspend or terminate in advance the research of a single research center, multiple research centers, or all the research centers at any time. The reasons include but are not limited to: Security or ethical issues, inaccurate or incomplete data records, non-compliance, or unsatisfactory quantity or quality of enrollment.

If this study was terminated or suspended, the sponsor or its representative should follow applicable regulatory requirements to inform investigators/their organizations and regulatory authorities of the reason. The sponsor or investigators/their organizations should comply with applicable regulatory requirements to notify the Ethics Committees and submit the reason.

10 Statistical Methods

10.1 Primary endpoint

The primary endpoint of the study is:

Non-CSF infection within one year post implant.

Incidence of adverse events within one year post implant, which includes:

- Obstruction of a cerebral ventricular catheter
- Bactiseal Catheter slipping
- Poor position of a catheter
- Intestinal perforation, abdominal and pseudocysts, umbilical fistula, pseudo-acute appendicitis, infection, and ascites caused by catheter
- Subcutaneous twist, rupture, distal obstruction, and distal retraction from the abdominal cavity
- Failure of a Bactiseal Catheter
- Mechanical failure
- Obstruction or infection of the shunt path
- Leakage of CSF in an implanted Bactiseal Catheter
- Excessive drainage
- Damage of intracranial or abdominal tissue
- Fibrous adhesion related to distal catheter

10.2 General considerations

The primary analysis will be descriptive in nature and will be based on information in the data collection form.

The extraction of the data from the medical records will be done by the investigators who care for the patients; in this way, the possible limitation of the study that is normally observed in other studies of review of clinical histories in which the information can be interpreted incorrectly is minimized.

10.3 Sample size

This study would provide the non-infection rate of Bactiseal Catheter within one year and assure the acceptable threshold of 95% confidence interval (CI). If the sample size was N_0 at first, the uninfected patients t year later would approximately be:

$$N(t) = N_0\, e^{-(r1+r2)\,t}$$

r1 and r2 represent the infection rate and the dropout rate.

The parameters of K-M survival analysis (e.g., non-infection rate) were estimated according to Peto. The two-sided confidence interval threshold of 95% of K-M survival t years after the operation was defined as S(t) in accordance with the following formula:

$$margin = 1.96\sqrt{[S(t)]^2[1-S(t)]/N(t)}.$$

According to a literature review, the annual infection rate of a catheter with antibiotics was 3.2% (95% CI 1.3-4.4%). By taking into account the differences among centers and of operating standards, the lower limit of 95% confidence interval of the infection rate was considered as the anticipated infection rate. The annual infection rate of a catheter with antibiotics was 4.3%. Therefore, the non-infection rate was 95.7% within one year. If 150 (100 subjects historical data from DPS-201501 study with additional 50 new subjects enrollment) subjects and the dropout rate was 10%, according to the first formula, the sample size of infected subjects one year after the operation, N(1), would be:

$$N(1) = N_0\, e^{-(r1+r2)} = 150 * e^{-(0.044+0.1)} = 130.$$

The threshold of 95% CI of non-infection rate within one year would be:

$$margin = 1.96\sqrt{[95.7\%]^2[1-95.7\%]/130} = 3.4\%.$$

The precision of 3.4% is considered acceptable for this study.

10.4 Criteria of qualification/disqualification of the trial results

This study aimed to collect post-marketing safety data on the Chinese population implanted Bactiseal Catheter, according to product registration requirements. It described the occurrence, type, severity, frequency of all AEs occurring during the research, as well as the correlation between AEs and the product. Hence, criteria of qualification/disqualification were not applicable.

10.5 Interim analysis

No interim analysis is planned for this study.

10.6 Analysis plan

All study data collected in this study will be presented in subject data listings. Statistical analyses will be performed using SAS 9.3 or later version. Other valid software might also be used as appropriate.

Data analysis will be carried out primarily using descriptive statistics. In general, mean, standard deviation, median, minimum and maximum will be calculated for continuous variables, and frequencies and percentages will be presented for categorical variables. If necessary, additional descriptive statistics may be calculated.

Analysis population

The primary analysis population for this study is the Per Protocol (PP) populations. The PP population will include all subjects who meet the inclusion/exclusion criteria

Subgroup analyses

The main subgroups that will be analyzed, in addition to the total population per protocol, will be adults and children.

Endpoint analysis

The primary endpoint of1-year infection free survival rate will be estimated by the Kaplan-Meier method, the 95% confidence width for the survival rate will be estimated by the Peto method. The Kaplan-Meier survival curve will be presented.

10.7 Report

After the data of all subjects were completely collected (within one year after the operation), a clinical study report would be compiled and submitted to NMPA for review as material supporting the extension of product registration.

11 Research Management and Administration

11.1 Responsibilities of investigators and the sponsor

11.1.1 Responsibilities of investigators

An investigator should ensure that all the work and services herein or incidental matters of all the work and services herein were implemented in accordance with the highest standards of medical and clinical study practice. An investigator should perform his/her duties according to all applicable laws and regulations. An investigator should provide a copy of the current study proposal to all assistant investigators or research staff of other research centers in charge of research implementation, and ensure all research staff are qualified, trained, and competent.

An investigator should submit the progress report, the safety report required by local regulations or national regulatory requirements, and study completion notice to the EC within the specified time limit.

11.1.2 Responsibilities of the sponsor

The sponsor should be solely responsible for the implementation of this study. The sponsors should ensure compliance with all applicable regulations and guidelines during this study.

The sponsor should properly monitor clinical study centers, obtain subjects' informed consent, provided quality data in compliance with regulations, notify investigators, ECs, and regulatory authorities of AEs, revocation of ethical approval, a list of current investigators (if necessary), and relevant safety issues, in accordance with international and local guidelines, and describe proposal deviation, as appropriate. The sponsor should write the safety report, the progress report, and the final clinical study report.

11.2 Assessment, initiation, monitoring, and close of visits

11.2.1 Assessment visits

The main requirements for which a research center and an investigator are selected and continue to

participate in this study include: They have sufficient experience in relevant research areas and all research operations, and adhere to safety commitments and the study proposal. The number of subjects should also be consistent with what is specified in the study proposal. The sponsor and its designated personnel should select qualified investigators, obtain a copy of signed research agreement from the latter, and provide the latter with the information necessary to implement this study, including any amendment or update to the research information specific to this study.

11.2.2 Initiation visits

At the beginning of this study, the monitor designated by the sponsor would visit research centers to confirm that all investigators personnel and research-related items were in place. The monitor would offer research-related training to investigators, including study proposals, informed consent procedures (if applicable), complaint of adverse events and research-related devices, completion of CRF, maintenance of research documents, responsibility of immediate notification to the sponsor of investigator changes, monitoring process, and GCP. During the initiation of visits, all preparations for subjects enrolled should be carried out.

11.2.3 Monitoring visits

At all research centers, the monitoring of this study should be carried out by the sponsor or personnel designated by the sponsor. Monitoring should ensure:

- Rights and health of subjects were protected;
- This study was conducted in accordance with all applicable regulations and guidelines;
- The study proposal and corresponding amendments were complied with;
- The accuracy of data recorded should be confirmed by verifying source documents.

Throughout the clinical study period, all effective research centers should be regularly monitored and visited to ensure that investigators fulfilled their obligations. These visits were to ensure that the research centers met requirements for facilities, follow the study proposal and all amendments, informed their ECs of changes to the proposal as required, maintain complete records, report to the sponsor and their ECs appropriately and in a timely manner, and that investigators were implementing all agreed matters.

11.2.4 Closing visiting of research centers

At the completion of the clinical study (Data were completely collected from all subjects enrolled. All CRFs were completed. And all data queries were resolved), the sponsor or designated personnel should inform research centers to end this study and close their visit to the centers.

At the last visit to research centers, all unused research materials should be collected and returned to the sponsor or destroyed at research centers. The monitor and investigator should ensure that the investigator folder and other research-related materials were up-to-date and complete, and that all outstanding issues of previous visits were resolved. During this visit, others issues to be reviewed included: storage of research materials, possibility of audit of research centers, open policies, and notice to ECs about the end of this study.

If a research center failed to enroll any subject for any reason, and the sponsor decided that the research center should stop further participation in this study, before the end of this clinical study, the last visit to the research center could be planned. In this case, the sponsor should instruct investigators to

complete the notification to the EC of the participation of the research center in this study and prepare the final documents required by the sponsor.

11.3 Documents required

Before enrolling subjects, at least the following documents should be submitted to the sponsor or designated personnel:

- The confidentiality agreement;
- Signed signature page of the study proposal;
- CVs of primary investigators and assistant investigators recently signed and dated; The CVs should clearly describe the qualifications and experience of research personnel;
- A copy of the written approval of the study proposal by ECs (including version number and date) and informed consent (including version and date) (if applicable);
- A list of current EC members, including name, title, occupation, and name of any organization of each member;
- Signed research contract.

11.3.1 Source documents

Regulations state that investigator should maintain the information in subjects' medical records (i.e., source documents). Such information could verify the data collected in CRFs. In order to comply with these regulatory requirements, the following information should be stored and available upon request by the monitor and/or inspectors of regulators:

- Information on medical history/physical condition of a subject that could prove the subject met the inclusion criteria of this study before participating in this study;
- Records on the informed consent process (if applicable);
- Description of implantation;
- All exam results and follow-up information;
- Dated and signed exam reports (e.g., X-ray);
- Description of an adverse event (description, severity, date, and duration of the adverse event, correlation with a research-related device, prognosis and treatment of the adverse event, and concomitant medication);
- Condition of a subject at the completion of or withdrawal from this study.

Source documents of a subject should include at least but not be limited to the above information.

11.3.2 Source data verification (SDV)

During visits, the monitor should check all the following key items in accordance with CRF entries of 100% of the subjects: all inclusion/exclusion criteria, the ICF (if applicable), demographic information of a subject, all events that met the criteria of reporting of adverse events (the inducing factor that

indicated the occurrence of an event), safety and efficacy endpoints, use of devices, re-operation, and all device failure/complaint reports. The monitor should check the other data of 50% of the subjects. For complete and details of verification of source data, please refer to the monitoring plan.

During a visit by the monitor, a research coordinator and/or an investigator should be present. The research coordinator or the investigator should ensure that the monitor could review source documents and provide the latter with an appropriate environment to review relevant documents. All inconsistencies should be identified and discussed with the investigator or designated personnel for resolution.

11.3.3 Case Record Form (CRF)

The CRF of each subject should be completed by an authorized investigator or another authorized personnel of research center. All the data on subjects required must be collected in CRFs. CRFs could not be used as a source document. The monitor should check completed CRFs at a research center to confirm the accuracy of the data collected in CRFs. All corrections to CRFs should be carried out by an authorized investigator or another authorized personnel of research center.to CRFs should be carried out by authorized investigator or other authorized personnel of the research center. The investigator /assistant investigator must sign and date at a specific part of CRF to prove that he/she had reviewed the data and ensured the data were complete and accurate.

A investigator should complete CRFs as soon as possible after a subject was screened or relevant information was collected. This would facilitate timely monitoring visits.

11.3.4 Archive and data retention

After being informed of the end of all research, a investigator should keep all research records, reports, and source documents supporting the completion of CRFs for at least 10 years and could continue to keep the data in line with the local and international guidelines specified in the clinical study agreement.

Investigators should be able to provide the document records at the request of regulators and the sponsor (designated personnel). Before the transfer of the documents, the sponsor or designated personnel must approve in writing the filing or transfer of the documents so as to relocate the documents. Investigators must notify the sponsor in writing of the location of the transfer and duration and procedures of reviewing the documents. Before destroying any records and reports related to this study, an investigator must contact the sponsor or designated personnel to confirm that the records and reports were no longer to be retained.

If an investigator no longer shouldered the main responsibility of storage of research records due to retirement, relocation, or other reasons, the investigator must transfer in writing the right of storage to the sponsor or designate personnel and indicate the name and address of the person with the primary responsibility.

11.3.5 Audit and inspection

In the case of an audit initiated by the sponsor (or its designated personnel), or a regulator, an investigator should ensure that auditors and inspectors had access to the original medical records during their audit or inspection, and provide all necessary information. In the case of an audit initiated by a regulator, an investigator should notify the sponsor immediately.

11.4 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

The recruitment of the study centers and the extraction of data from patients' medical records will be closely monitored to reach the proposed sample sizes. The study investigators will be asked to extract the data from the medical records of all patients implanted with Hakim programmable shunt system for the study in their respective centers. Integra Clinical Operations will follow up with the centers during the data collection process when appropriate to ensure a rapid completion of the data collection process.

Hardcopies of the study visit CRFs will be provided for use to collect data for each subject enrolled in the study. Data recorded in the CRFs derived from any source documents should be consistent with the data recorded on those source documents.

Clinical data (including AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Microsoft Access Database by Sponsor by double data entry. The data will be reviewed and validated. Queries for any missing, inconsistent or illogical data points will be forwarded to the research center for resolution. After all data queries are resolved, the data will be transferred to a biostatistician for analysis.

12 Ethical and Regulatory Requirements

12.1 Ethics Committee

Before enrolling subjects, a research center should submit the study proposal, the ICF (if applicable), and other applicable documents related to this study to its EC, obtain a written approval from the latter, and submit the approval to the sponsor or designated personnel.

An investigator should immediately report any change to the appointment of primary investigator s and all unanticipated issues related to risk of subjects. Without the consent of the EC, an investigator was not allowed to alter the study proposal, excluding necessary changes to eliminate immediate hazards to subjects. Amendments involving significant risks or changes requiring EC approval and the written approval by an EC must be submitted to the sponsor or designated personnel.

12.2 Informed consent

If informed consent was not exempted by a research center, before any research-related action outside of routine treatment or nursing was implemented, each subject (or their legally authorized representative) must complete the informed consent process in line with the requirements of the EC of a research center, after having the nature of this study fully explained to them. At a research center which did not exempt informed consent, for a subject younger than 18 years old, an investigator should obtain a signed ICF from either of the parents or the statutory guardian. A subject aged between 6 and 18 should also sign a relevant version of ICF in person.

The voluntary process of informed consent demonstrated that a subject (or his or her statutory guardian) was willing to participate in this study. Before an ICF was signed, investigator must explain all aspects of this study to and answer all questions raised by a subject (or his/her statutory guardian). Investigator and/or designated personnel must clearly document the process of obtaining informed consent in a subject's clinical record. An investigator should ensure that the informed consent process was implemented in accordance with all applicable regulations and requirements of the EC.

12.3 Subject confidentiality

Throughout the clinical study period, all data should be traceable to the original records; and subject data should be kept confidential. To this end, unique subject identification numbers (research center number and subject number) were used, via which all data reported on each subject could be identified.

If data were encrypted and subjects' privacy was protected, information related to this study could be used by third parties (e.g. regulatory authorities during inspection).

12.4 Revision of the study proposal

Changes to the study proposal could be submitted by the sponsor or designate personnel to an investigator or by an assist investigator to his/her EC. Before any change to the study process was implemented, all major amendments must be approved by the EC of a research center.

If it was likely to significantly impact the following items, an amendment would be a major amendment:

- The safety or physical or mental health of a subject;
- Scientific value of the trial;
- Implementation or management of the trial;
- Quality or safety of equipment used in the trial.

12.5 Proposal deviation

Proposal deviation stands for the deviation of actual implementation of the study proposal from a particular part of the study proposal (e.g. non-compliance with inclusion/exclusion criteria). This study only retrospectively collected data. An exam item required in the proposal yet missing was not regarded as a proposal violation.

No matter if it was medically sound, or if a violation was made to protect a subject in an emergency, the violation should be reported to the sponsor. An investigator should follow procedures as well as reporting policies and requirements of the EC of the research center to report a violation to the EC.

Relevant regulations required an investigator 's records should be accurate, complete, and up-to-date, including documentation recording the date and cause of each proposal violation.

Proposal violation could be classified into primary proposal violation and secondary proposal violation. A violation related to inclusion/exclusion criteria or informed consent (if applicable), or affecting the endpoint would be regarded as a primary proposal violation. Other violations other than primary proposal violations were secondary proposal violations.

The final confirmation of a proposal violation should be agreed by investigator, data analyst, and the sponsor.

13 Publication Policies

At the end of this study, an article reflecting the results of the multi-center study would be published

in prestigious scientific journals. Prior to the compilation and publication of the multi-center study results, any main results of any single research center in this study were not allowed to be published. Exceptions to this rule were subject to prior approval by the sponsor and the primary investigator. Other pre-defined and non-pre-defined endpoint analysis would be implemented by the data management department. Secondary analysis and other proposed research studies were subject to the approval by the primary investigator and the sponsor. In order to promptly extract and publish statements, secondary publication would be delegated to a relevant main author. The final analysis and review of all multi-center data should be approved by the primary investigator and the sponsor.

14 Devices

14.1 Count of research-related devices

This is a retrospective study. Devices were implanted. Hence, this entry does not apply.

14.2 Return of research-related devices

This is a retrospective study. Devices were implanted. Hence, this entry does not apply.

14.3 Complaint about devices

An investigator should immediately notify the sponsor or designated personnel of an issue regarding authenticity, identification, quality, and performance of the research product.

14.3.1 Complaint about devices

Relevant personnel of the sponsor must report the complaint to the email of the Custom Service China of Integra LifeSciences (Shanghai) Co., Ltd. within 24 hours after receiving a complaint about the research product: custsvcchina@integralife.com

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