COVER PAGE

Protocol Title: Sundt™ Carotid Shunt Retrospective Post Market Clinical Follow-up Study (PMCF)

Protocol Number: C-SCS-001

Version / Date: Version 1.0 / 28-Nov-2018

NCT ID: 03816202

Sponsor:

Integra LifeSciences

Current Address:

1100 Campus Road,

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Plainsboro, NJ 08536

Sundt™ Carotid Shunt Retrospective Post Market Clinical Follow-up Study (PMCF)

PROTOCOL NO.: C-SCS-001

VERSION / DATE: Version 1.0 / 28-Nov-18

VERSION HISTORY: First

SPONSOR: Integra LifeSciences Corporation
311 Enterprise Drive
Plainsboro, NJ 08536, USA

HISTORY TABLE

Version Number #	Brief Summary of Updates	Date
Version 1.0	First	28-Nov-2018

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STATEMENT OF COMPLIANCE

By signing this document, I, the Investigator, certify that this trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, and 21 CFR Part 56)

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

The protocol associated with this trial will be submitted to an Institutional Review Board (IRB)/Ethics Committee (EC) for review and approval. Approval of the protocol must be obtained before any participant is enrolled.

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

Investigator Name

Investigator Signature Date

STUDY SYNOPSIS

PROTOCOL TITLE:	Sundt™ Carotid Shunt Post Market Clinical Follow-up (PMCF) Study
STUDY DESIGN:	Non-randomized, multi-center, single-arm, all-comers, retrospective Post Market Clinical Follow-up study
PRIMARY OBJECTIVE:	The primary objective of this study is to retrospectively investigate the safety and efficacy of the Integra Sundt™ carotid shunt during endarterectomy procedures.
PRIMARY ENDPOINT:	The primary endpoint of this study is evidence of injury to the artery or cerebral ischemia secondary to shunt placement and removal.
INDICATION:	The Integra Sundt™ carotid shunts are indicated for temporary carotid artery bypass during carotid endarterectomy procedures to help protect the cerebral hemispheres from ischemia during the period of carotid artery occlusion.
STUDY POPULATION:	100 subjects, both male and female, between the ages 18 to 80 in the United States will be recruited for this trial.
INCLUSION CRITERIA:	Subjects will be included in this study if they meet all of the following inclusion criterion: 1. Between the ages of 18-80 years old 2. Have undergone carotid endarterectomy with any Integra Sundt™ carotid shunt on or before date of study initiation 3. Availability of records on post-operative imaging of the carotid artery either by carotid duplex ultrasound or angiogram
EXCLUSION CRITERIA:	Subjects will not be included in this study if they meet the following exclusion criterion: 1. Insertion of a carotid shunt at the site of an infection

DESCRIPTION OF SITES:	A minimum of 3 sites and a maximum of 10 sites will participate in this study. A maximum of 40 consecutive patients will be enrolled at each site. This study will take place in the United States only.
STUDY DURATION:	The study duration from the first patient's chart review to the completion of the last patient's chart review is expected to be 1 year. The study will end when the data for 100 subjects have been collected.

DATA COLLECTION:	Retrospective review of patients who underwent carotid endarterectomy will include demographics, procedure details, safety events, and a post-operative assessment.
	• **Demographics**
	  ○ Age
	  ○ Gender
	  ○ Height
	  ○ Weight
	  ○ Relevant Past Medical History
	  • Transient Ischemic Attack (TIA)
	  • Stroke
	  • Asymptomatic Carotid Stenosis
	  • Bleeding Disorder
	  • Diabetes
	  • Smoking
	  • Other relevant past medical history per the investigator's opinion
	  ○ Relevant Past Surgical History
	  • Previous Head or Neck Surgery
	  • Previous Head or Neck Radiation
	  • Previous Vascular Surgery
	  • Other relevant surgical history per the investigator's opinion
	  ○ Diagnosis / Indication for Surgery
	  ○ Relevant Medications
	• **Procedure**
	  ○ Date of surgery

	○ Procedure(s) performed ○ Duration of surgery ○ Device information, including lot number ○ Relevant Medications ○ Any complications noted in the operative report and in the investigator's opinion determined to be related to the device • **Post-operative Assessment (up to 60 days post-procedure)** ○ Evidence of cerebral ischemia as indicated by post-operative neurological exam ○ Evidence of injury to artery as seen on post-operative imaging of the carotid either by carotid duplex ultrasound or angiogram
STATISTICAL METHODS & ANALYSES:	The post marketing clinical follow up study is a retrospective chart review. All analyses will be descriptive in nature. No formal statistical analyses will be conducted.

1 INTRODUCTION

1.1 Background

Stroke affects nearly 800,000 individuals in the United States per year and is the fifth leading cause of death[1]. Carotid artery stenosis—the narrowing of the carotid arteries due to atherosclerotic plaques—is one of the leading causes of stroke. The annual risk of stroke in individuals with asymptomatic carotid stenosis (ACS) is about 1 to 3%, but the risk is around 4 to 12% for individuals with symptomatic stenosis (SCS) without carotid intervention[2]. Early treatment of carotid stenosis (CEA) has the potential to prevent or delay the occurrence of strokes.

Carotid endarterectomy (CEA) is a surgical procedure to remove the stenosis together with unstable plaque, thereby reducing the risk of stroke[3]. It has been found to be effective in patients with high-grade symptomatic (~70%) or asymptomatic (< 60%) internal carotid artery stenosis and has been proven to be superior to medical management alone[4]. Most perioperative strokes are ischemic in nature, some of which may be caused by the temporary interruption of blood flow during CEA when the carotid artery is clamped[3]. A carotid shunt may be used to minimize this interruption of blood flow and ensure sufficient cerebral perfusion during carotid cross clamping, which may decrease the incidence of perioperative stroke. Carotid shunting can either be used in all patients undergoing CEA (routine shunting) or in a proportion of patients who are at a high risk of developing cerebral ischemia during carotid clamping (selective shunting). However, there is no conclusive evidence of the superiority of one method over the other, and it often depends on the surgeon's preference and familiarity with the method[3–5].

1.2 Study Device

1.2.1 Device Description

The Integra Sundt™ internal and external (Loop) Carotid Endarterectomy Shunts are designed to provide temporary carotid bypass for cerebral circulation during carotid endarterectomy procedures.

The Sundt™ internal and external Carotid Endarterectomy shunts are constructed of silicone elastomer with stainless steel spring reinforcement to minimize kinking and occlusion of the cannula lumen and to aid in the ease of insertion of the proximal and distal ends. The ends of the shunts have cone-shaped bulbs to facilitate fixation of the shunt in the vessel. Quite frequently in the internal type shunt a distal tourniquet is not required because, if the proper shunt size is selected, the bulb fits firmly enough against the wall of the vessel that there is no bleeding around the distal bulb. A tourniquet is always required on the proximal end of both the external and internal shunts and usually on the distal end of the external shunt

1.3 Intended Use

The carotid endarterectomy shunts are indicated for temporary carotid artery bypass during carotid endarterectomy procedures in order to help protect the cerebral hemispheres from ischemia during the period of carotid artery occlusion. These shunts are designed as temporary indwelling catheters and are not intended for permanent placement.

1.4 Sponsor Contact Information

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2 OBJECTIVE AND ENPOINTS

2.1 Primary Objective

The primary objective of this study to retrospectively investigate the safety and efficacy of the Integra Sundt™ carotid shunt during endarterectomy procedures.

2.2 Primary Study Endpoint

The primary endpoint of this study is evidence of injury to the artery or cerebral ischemia secondary to shunt placement and removal.

3 STUDY DESIGN

This is a non-randomized, multi-center, single-arm, all-comers retrospective Post Market Clinical Follow-up study investigating subjects who received a Sundt™ carotid shunt during a carotid endarterectomy before study initiation at the site.

3.1 Study Duration

The study duration from the first patient's chart review to the completion of the last patient's chart review is expected to be 1 year. The study will end when the data for 100 subjects has been collected.

3.2 Study Sample Size

100 patients will be enrolled at up to 10 centers, with up to a maximum of 40 consecutive patients enrolled at each center. Patients will be enrolled at a minimum of 3 centers. This study will take place in the United States only.

4 SUBJECT POPULATION

4.1 Inclusion Criteria

Subjects will be included in this study if they meet all of the following inclusion criteria:

1. Between the ages of 18-80 years old
2. Have undergone carotid endarterectomy with any Integra Sundt™ carotid shunt before the date of study initiation
3. Availability of records on post-operative imaging of the carotid artery either by carotid duplex ultrasound or angiogram

4.2 Exclusion Criteria

Subjects will not be included in this study if they meet the following exclusion criterion:

1. Insertion of a carotid shunt at the site of an infection

5 STUDY PROCEDURES

This study is a retrospective review of patients who have undergone a carotid endarterectomy procedure with the use of the Sundt™ carotid shunt prior to study initiation.

Eligible subjects for the study should be identified by the 3-digit site number followed by the 3-digit subject ID. Numbering of the subjects should be done in a reverse chronological order with the most recent subject being 001 followed by the second most recent being 002 and so forth.

Required information will be collected through a review of the patient chart or electronic medical records (EMR) by the Principal Investigator or delegated personnel. The delegated staff

member shall collect demographics, details surrounding the procedure, and the post-operative assessment.

- **Demographics**
  - Age
  - Gender
  - Height
  - Weight
  - Relevant Past Medical History
    - Transient Ischemic Attack (TIA)
    - Stroke
    - Asymptomatic Carotid Stenosis
    - Bleeding Disorder
    - Diabetes
    - Smoking
    - Other relevant past medical history per the investigator's opinion
  - Past Surgical History
    - Previous Head or Neck Surgery
    - Previous Head or Neck Radiation
    - Previous Vascular Surgery
    - Other relevant surgical history per the investigator's opinion
  - Diagnosis / Indication for Surgery
  - Medications
- **Procedure**
  - Date of surgery
  - Procedure(s) performed
  - Duration of surgery
  - Device information, including lot number
  - Medications
  - Any complications noted in the operative report and in the investigator's opinion determined to be related to the device
- **Post-operative Assessment (up to 60 days post-procedure)**
  - Evidence of cerebral ischemia as indicated by post-operative neurological exam
  - Evidence of injury to artery as seen on post-operative imaging of the carotid artery either by carotid duplex ultrasound or angiogram

5.1 Device Performance

The delegated site staff will collect information regarding the device performance.

The following device performance questions will be part of the case report form and will be collected from the patient medical record including both the operative note and the anesthesia record for the procedure. For the "yes / no" questions below, if the medical record is silent on the answer to the question it will be assumed that the answer is "no".

1. Was the shunt use routine or selective? If selective, specify the test and the result that led to use of the shunt.

2. Was there any delay in surgery or complication due to preparation of the device for surgery? If yes, please explain.

3. What was the clamping method type for shunt insertion?

4. How long was the carotid artery cross clamped for shunt insertion?

5. Was there any device-related damage to the artery during insertion of the shunt? If yes, please explain.

6. Was there evidence of clot formation within the shunt at any point during the procedure? If yes, describe how this was detected and what was the remedy. What was the impact to the procedure?

7. Was there any evidence of reduced flow within the shunt other than clot formation (e.g. due to kinking, malposition within the artery)?

8. Was there any evidence of excessive bleeding around the shunt after initial placement? If yes, what was the remedy and the result of that remedy?

9. Did removal of the shunt cause vessel injury or complicate closure? If yes, please explain.

10. Was there evidence of post-operative cerebral ischemia noted in the neurological exam?

11. Did the subject experience injury to the artery due to the device as evidenced by the imaging of the carotid artery either by carotid duplex ultrasound or angiogram?

12. Were there any other device-related complications not previously recorded in the case report forms? If yes, please explain.

6 STATISTICAL ANALYSIS

The PMCF is a retrospective chart review. All analyses will be descriptive in nature. No formal statistical analyses will be performed. The study objectives will be presented by summary statistics.

Summary statistics (mean, standard deviation, quintiles, counts, and percentages) will be presented for all demographic (i.e. age, gender, etc.), clinical baseline characteristics (diagnosis, medical history, medications), surgical procedures (procedures performed, duration of surgery) and complications.

The primary objective will be evaluated by summarizing the incidence of injury to the artery or cerebral ischemia secondary to shunt placement.

All statistical analysis will be conducted using SAS.

7 ETHICS AND REGUALTORY REQUIREMENTS

7.1 Confidentiality

In order to observe the confidentiality of personal data, each patient will be allocated a confidential identification code consisting of the investigator site number followed by a 3-digit patient number. CRFs or any other documents submitted to the sponsor will identify the patient by this identification code. Each investigator will maintain a patient identification list which would detail the identification code along with the corresponding patient identifiers (name and date of birth).

Each subject should be numbered in reverse chronological order from 001 as the most recent subject prior to study initiation at the site.

7.2 Waiver of Consent

A waiver of informed consent is key to perform this retrospective chart review study. Informed consent will not be possible to obtain as the care has already been provided by the surgeon/investigator and it is unlikely the patient will return to the surgeon for a clinical visit. In addition, this chart review involves no more than minimal risk to the subjects and the waiver will not affect the rights and welfare of the subjects since care has already been given.

7.3 Waiver of HIPAA Authorization

Waiver of HIPAA authorization is key for the success of this chart review. Not only will it be difficult to obtain the authorization since the care has already been provided by the surgeon/investigator and it is unlikely that the patient will return to the surgeon for a clinical visit, but the use or

disclosure of protected health information involves no more than a minimal risk to the privacy of the individuals.

8 STUDY FINANCES

The study will be funded by Integra Lifesciences Corporation. The Sundt™ internal and external (Loop) Carotid Endarterectomy Shunt is considered a pre-amendment device and is FDA registered under the device listing D024713.

9 RETENTION

Study records must be retained by the Investigator for 2 years following the conclusion/ termination of the study and the publication (if applicable). Study records should not be destroyed without prior written agreement between the Sponsor and the study Investigator. At the completion of the study, details of the archival process must be provided to the Sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

10 PUBLICATION PLAN

A report will be prepared under the responsibility and according to the Integra LifeSciences Corporation SOPs. It will include the study objectives, the methodology, statistical analysis and raw data listings, and the conclusions of the study.

The sponsor is not allowed to use investigator's name in any publication without prior written consent. The investigator is not allowed to use sponsor's name in any publication without prior written consent.

11 REFERENCES

1. Sardar P, Chatterjee S, Aronow HD, et al. Carotid Artery Stenting Versus Endarterectomy for Stroke Prevention: A Meta-Analysis of Clinical Trials. *J Am Coll Cardiol*. 2017;69(18):2266-2275. doi:10.1016/j.jacc.2017.02.053
2. Heo SH, Bushnell CD. Factors Influencing Decision Making for Carotid Endarterectomy versus Stenting in the Very Elderly. *Front Neurol*. 2017;8(May). doi:10.3389/fneur.2017.00220
3. Chongruksut W, Vaniyapong T, Rerkasem K. Routine or selective carotid artery shunting for carotid endarterectomy (and different methods of monitoring in selective shunting). *Cochrane Database Syst Rev*. 2014;2014(6). doi:10.1002/14651858.CD000190.pub3
4. Kret MR, Young B, Moneta GL, et al. Results of routine shunting and patch closure during carotid endarterectomy. *Am J Surg*. 2012;203(5):613-617. doi:10.1016/j.amjsurg.2011.12.005
5. KATANO H, YAMADA K. Comparison of Internal Shunts during Carotid Endarterectomy under Routine Shunting Policy. *Neurol Med Chir (Tokyo)*. 2014;54(10):806-811. doi:10.2176/nmc.oa2013-0218