Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT00647387
VPA
Closure of Muscular Ventricular Septal Defects with the Amplatzer™ Muscular VSD Occluder Post-Approval Study
Study Document No: CL00390
Version 10
Date: 20-Jul-2020

Sponsor

Abbott
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Clinical Investigational Plan

VPA

Closure of Muscular Ventricular Septal Defects

with the Amplatzer™ Muscular VSD Occluder

Post-Approval Study

Clinical Investigation Plan (CIP)

Sponsor

Abbott
5050 Nathan Lane North
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[redacted]

Clinical Protocol Signature Page

I have read and agree to adhere to the plan and all regulatory requirements applicable in conducting this clinical study. I will provide copies of this protocol and all pertinent information to study personnel and will discuss this information with them and ensure they are fully informed regarding the device and the conduct of the study according to 21 CFR parts 50, 54, 56 and 814, to other applicable regulations, to applicable laws, and to hospital Institutional Review Board (IRB)/Ethics Committee (EC) requirements.

Investigator:

_____
Print or Type Name

_____ _____
Signature Date

Table of Contents

[redacted]

I. Study Design

A. Introduction

The Amplatzer™ Muscular VSD Occluder was approved by the US Food and Drug Administration (FDA) on September 7, 2007. This study is designed to further evaluate the safety and effectiveness in subjects implanted with the Amplatzer Muscular VSD Occluder.

B. Device Description

The Amplatzer Muscular VSD Occluder is a self-expandable, double disc device made from a Nitinol wire mesh. The two discs are linked together by a short connecting waist corresponding to the size of the VSD. In order to increase its closing ability, the discs and waist are filled with polyester fabric. The polyester fabric is securely sewn to the device by a polyester thread.

C. Purpose

The purpose of this study is to further evaluate the safety and effectiveness of the Amplatzer Muscular VSD Occluder.

D. Disease to be Treated

The Amplatzer Muscular VSD Occluder is indicated for use in patients with complex ventricular septal defects (VSD) of significant size to warrant closure (large volume left to right shunt, pulmonary hypertension and/or clinical symptoms of congestive heart failure) who are considered to be at high risk for standard transatrial or transarterial surgical closure based on anatomical conditions and/or based on overall medical condition.

High risk anatomical factors for transatrial or transarterial surgical closure include patients:

- Requiring left ventriculotomy or an extensive right ventriculotomy;
- With a failed previous VSD closure;
- With multiple apical and/or anterior muscular VSDs ("Swiss Cheese Septum"); or
- With posterior apical VSDs covered by trabeculae.

E. Study Type

The objectives of this Amplatzer Muscular VSD Occluder Post Approval Study will be evaluated through a prospective, non-randomized, multi-site clinical study design. The primary safety and efficacy endpoints of this study are intended to be evaluated against the corresponding endpoints of the High Risk Cohort of the Muscular VSD Study.

F. Study Objectives

Primary Safety Objective

The primary safety objective is to evaluate the proportion of subjects experiencing a serious adverse event within 12 months of the procedure. Since the subject selection criteria will be similar to that used in the High Risk Cohort of the Muscular VSD Occluder Study, the proportion found in the post approval study will be compared for non-inferiority against the observed major adverse event rate from the High Risk Cohort.

Serious Adverse Event

A serious adverse event is defined as any untoward medical occurrence that:

- results in death;
- is a life-threatening adverse event;
- requires inpatient hospitalization or prolongation of existing hospital stay;
- results in persistent or significant disability/incapacity;
- results in congenital anomaly/birth defect;
- or results in a medically significant event, including laboratory abnormalities.

Primary Effectiveness Objectives

The effectiveness objective is to evaluate the proportion of subjects who experience technical success, closure success, and acute procedure success. Results for the three effectiveness endpoints will be reported separately and, like the safety endpoint, will be compared for non-inferiority against the corresponding results of the High Risk Cohort of the Muscular VSD Occluder Study.

Technical Success

Technical success is met for implant attempt subjects in whom a device is successfully deployed in the ventricular septal defect.

Acute Procedure Success

Acute procedure success is met for implant attempt subjects who meet shunt closure success (as defined in the next paragraph) at procedure.

Shunt Closure Success

Shunt Closure Success is met for subjects in whom the defect has less than or equal to two millimeters residual shunt. Shunt Closure Success will be evaluated at the post procedure, 30 day, 6-month, 12-month and annual follow-up visits through 5 years. The effectiveness endpoint for Shunt Closure Success will be based on the evaluation of the one year follow-up visit.

G. Eligibility Criteria

A subject is eligible to participate in the study if he/she meets all inclusion criteria and none of the exclusion criteria.

Patients who previously received an Amplatzer Muscular VSD Occluder following device approval on September 7, 2007, may be eligible to enroll in the study. Refer to **Section I, Part H**. for details.

Inclusion Criteria

1. The Amplatzer Muscular VSD Occluder is indicated for use in subjects with complex congenital muscular ventricular septal defects (VSD) of significant size to warrant closure. Subjects must meet at least one of the following:
    a. Large volume left to right shunt (Qp/Qs >2:1),
    b. Pulmonary hypertension (PA pressure >50% systemic),
    c. Clinical symptoms of congestive heart failure,
    d. Banding of the pulmonary artery(ies) and in the opinion of the treating investigator closure of the VSD is clinically warranted.

2. Subjects must meet at least one of the following criteria to be considered high risk for standard transatrial or transarterial surgical closure:
    a. Left ventriculotomy or an extensive right ventriculotomy, defined as: Due to the location of the VSD the surgeon would have difficulty visualizing and/or repairing the defect through a right atriotomy and therefore would require a ventriculotomy.
    b. Failed previous VSD closure,
    c. Multiple apical and/or anterior muscular VSDs ("Swiss Cheese Septum")
    d. Posterior apical VSDs covered by trabeculae.
    e. Overall medical condition
3. Subject/legally authorized representative has signed the informed consent
4. Subject/legally authorized representative is willing to complete the follow-up requirements of this study

Exclusion Criteria

1. Subjects with defects less than 4 mm distance from the semilunar (aortic and pulmonary) or atrioventricular valves (mitral and tricuspid)
2. Subjects with severely increased pulmonary vascular resistance above 7 Wood units and a right-to-left shunt and documented irreversible pulmonary vascular disease
3. Subjects with perimembranous (close to the aortic valve) VSD
4. Subjects with post-infarction VSD
5. Subjects who weigh < 5.2 kg
6. Subjects with sepsis (local/generalized)

7. Subjects with active bacterial infections
8. Subjects with contraindications to anti-platelet

If a subject does not meet at least one of the high risk anatomical conditions (inclusion criteria 2.a. – 2.d.) for standard transatrial or transarterial surgical closure and enrollment is based on overall medical condition (inclusion criteria 2.e.), the condition must be documented in progress notes or the medical record as the condition that meets enrollment criteria.

H. Subject Enrollment

Investigational sites will inform the subject/legally authorized representative of the study and invite them to participate. Informed consent/assent (if applicable) will be obtained from the subject/legally authorized representative prior to performing any study-specific testing per the clinical protocol. The person obtaining consent will verbally review the content of the Informed Consent Form/assent (if applicable) with the subject/legally authorized representative, allow adequate time for questions, and will provide the subject/legally authorized representative a copy of the consent form.

Prospective Patient Enrollment
Once the subject/legally authorized representative has read and understands the Informed Consent Form, he/she will indicate his/her willingness to participate in the study by signing the form. The site will document the informed consent process in the medical record. Following completion of the baseline testing, investigators will determine if the subject meets all of the inclusion criteria and none of the exclusion criteria.

A subject is considered enrolled in the study after he/she has provided informed consent, meets all inclusion criteria, meets no exclusion criteria, and the delivery system enters the subject's body in an attempt to implant the Amplatzer Muscular VSD Occluder (Implant Attempt). Investigational sites will keep a screening log to track screen failures. A screen failure is defined as a patient who signs the informed consent form but is not enrolled in the study.

Retrospective Patient Enrollment
In order for a previously implanted patient to be eligible for study participation, the following conditions must be met:

1) The participant met the eligibility criteria outlined in **Section I G. Eligibility Criteria, parts 1 and 2,** prior to the implantation of the Muscular VSD Occluder
2) The participant/legally authorized representative signs the study informed consent (and assent, if applicable)
3) The participant/legally authorized representative and site agree to follow the participant per the assessment schedule and complete all required assessments from the time of consent going forward
4) Only patients with the potential to provide a minimum of baseline, procedure, one-year, and five-year visit data, including echocardiographic data, will be considered for retrospective data collection.

All study related data, including safety and effectiveness endpoints, will be collected and reported on the corresponding Case Report Forms for those visits that have already occurred. Identification of adverse events in retrospectively enrolled subjects will adhere to the study's established guidelines and procedures. Future visits will occur per the assessment schedule and all data will be collected per the protocol requirements.

All eligible patients should be considered for retrospective enrollment.

I. Study Procedure and Assessments

Subjects will be required to undergo the tests noted in Table 1 at the indicated time periods.

If the delivery system enters the subject's body in an attempt to place a device but no device is implanted during the initial procedure, the subject will be discontinued from the study after a 30-day adverse event collection period. This subject will be discontinued from the study even if Re-intervention occurs within the 30-day period.

If the subject signs a consent form, but the delivery system does not enter the subject, the subject will be considered a consented screen failure, for which a discontinuation form must be completed.

If a subsequent catheterization procedure is performed to attempt to close a residual shunt or new muscular VSD with an Amplatzer Muscular VSD Occluder, this will be classified as a Re-intervention. Data regarding Re-intervention(s) will be captured on new Baseline/Procedure forms for all subjects who meet Technical Success at the initial implant procedure. All follow-up visits will be calculated based on the initial procedure date.

Table 1: Main Data Requirements

	Pre-Procedure	Procedure	Post procedure (+ one day)	30 days (+/- 7 days)	6 Months (+/- 30 days)	One Year (+ 60 days)	Two Year (+/- 180 days)	Three Year (+/- 180 days)	Four Year (+/- 180 days)	Five Year (+/- 180 days)
Physical Exam	✓		✓	✓	✓	✓	✓	✓	✓	✓
ECG	✓		✓	✓	✓	✓	✓	✓	✓	✓
Echo[1]	✓		✓	✓	✓	✓	✓	✓	✓	✓
Cardiac catheterization		✓								
TEE or ICE		✓								
AE Assessment		✓	✓	✓	✓	✓	✓	✓	✓	✓
Chest X-ray AP and lateral	✓		✓			✓	✓	✓	✓	✓
Fluoroscopy[2]						✓	✓	✓	✓	✓

[1] Echocardiographic data at Baseline/Procedure can include TTE, TEE and/or ICE. Echocardiographic image data must be submitted to the sponsor for one year visits.
[2] Fluoroscopy required if chest x-rays are read as "uncertain" with regard to wire fracture.

1. Implant Procedure

Reference the Amplatzer Muscular VSD Occluder and Delivery System Instructions for Use (IFU) for implant procedure techniques. The Amplatzer Muscular VSD Occluder is to be implanted percutaneously by catheter technique.

2. Closure Assessment

Assessment of VSD closure will be conducted post device deployment during the procedure, at the post procedure follow-up visit, at the 30-day follow-up visit, at the six month follow-up visit, at the one year follow-up visit and at annual visits until the five year visit is complete. Investigators are required to record echocardiographic data to document closure status and submit the data to the sponsor on case report forms in the remote data entry system. An independent Echocardiography Board or Core Laboratory will review the one-year echocardiograms to verify closure status.

3. Follow-up Compliance Measures

Abbott (ABT) will have a dedicated staff to train and manage sites on the importance of protocol compliance, assist sites with reminders, and compensate sites to help ensure adequate subject follow-up. ABT will send reminders to each site regarding upcoming visits. Each enrolled subject will receive a visit notification card. Whenever possible, the site should schedule the next subject follow-up visit at the time of the current visit. Sites will be compensated for the time it takes for the investigator to complete the case report forms. As part of CRF completion reimbursement, sites will be compensated for time spent notifying and reminding subjects of upcoming follow-up visits. If a site becomes non-compliant, enrollment may be halted until the site initiates the appropriate steps to correct compliance.

4. Device Explant

If a subject has a device explanted during the study, the timing of the explant determines whether the subject is followed further or discontinued from the study. If the device explant occurs before the 12-month visit and a Serious Adverse Event (SAE) is associated with the device explant, the subject will be discontinued on the date the device is explanted. (In this case, the subject is considered a failure for all endpoints except Technical Success.) If a device explant is not associated with a SAE, the subject will continue to be followed through the 12-month visit. The subject will then be discontinued at the 12-month visit.

If a subject has a device explanted after the 12-month visit, the subject will be discontinued on the date of the explant procedure.

J. Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical study. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical study or the subject withdraws from the clinical study.

<u>For subjects that do not receive a device</u>
If the delivery system enters the subject's body in an attempt to place a device but no device is implanted, the patient will be followed for reportable adverse events for 30 days. The subject should attend a 30-day (+/- 7 days) visit for an adverse event assessment and then be discontinued.

Adverse event data will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

For the purposes of this study, the following event types will be reported:

- All serious adverse events

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below. For retrospective subjects, the reporting timeframe does not apply to SAEs that occur prior to the informed consent date.

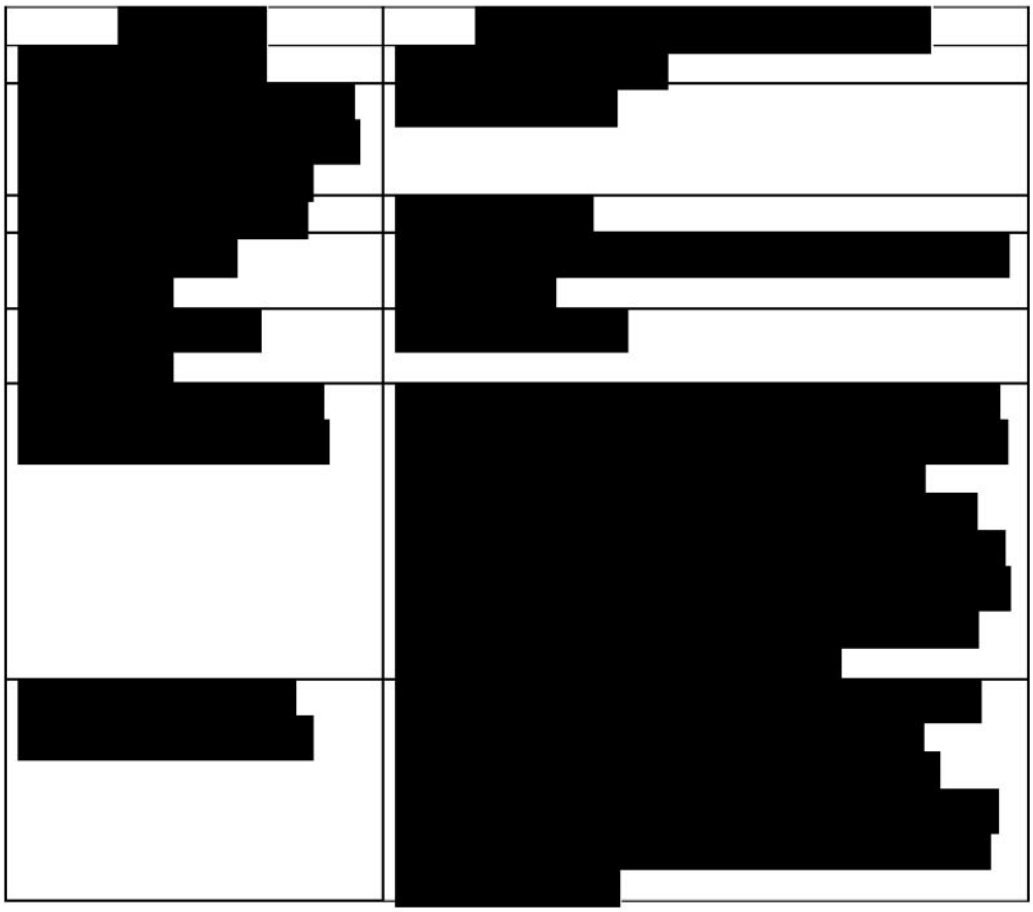
Clinical Site	Reporting timelines

All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined above.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

K. Study Duration

This study will enroll [redacted] Each study subject receiving a device will be followed for 60 months post-procedure, unless the device is explanted (See Section I.5 regarding Device Explant).



L. Investigator Selection

Qualified investigators will be selected and adequate information and training will be assessed and provided, if needed, to ensure best conduct of the study.

M. Risk Assessment of the Amplatzer Muscular Occluder Device:

The subjects who receive the Amplatzer Muscular VSD Occluder will be exposed to potential risks of this permanent implant. See Amplatzer Muscular VSD Occluder and Delivery System Instructions for Use for more details on observed adverse events and potential risks.

II. Statistical Analysis

Analysis will include prospectively and retrospectively enrolled subjects, unless otherwise specified.

The primary safety objective is to evaluate the proportion of subjects experiencing a serious adverse event within 12 months of the procedure. [redacted]

[redacted]

[redacted]

[redacted]

Similarly, the three effectiveness objectives are the proportion of subjects who experience technical success, acute procedure success, and shunt closure success. In [redacted]

Note: technical success analysis will include only prospectively enrolled subjects.

[redacted]

[redacted]

The analysis of technical success and acute procedure success will be conducted on all subjects who have an attempted device placement (defined as the delivery system enters the subject's body in an attempt to place a device). The analysis of shunt closure success will be conducted on the study population who has a 12-month follow-up visit. The serious adverse event endpoint will be evaluated on all subjects who have a 12-month follow-up visit or who had a serious adverse event prior to the 12-month visit. For all analyses, a secondary analysis will be conducted on the entire study population, including subjects that are classified as lost to follow-up. In the situation classified as lost to follow-up, subject's last known (reported) status will be used in the calculations.

[redacted]

[redacted]

III. Study Management

A. Investigators and Sites

A list of institutions and investigators will be completed and sent to the FDA or other regulatory authorities upon request and as required by applicable regulations.

B. Monitoring Procedures

Monitoring will be conducted according to the ABT Clinical Monitoring standard operating procedure.

Prior to beginning the study, ABT will contact the investigator or designee to discuss the study and data requirements. An ABT monitor will periodically review the subject records and associated source documents.

The investigator shall make subject and study records available to the clinical monitor for monitoring.

C. Data

1. Source Data and Documentation

All study findings must be documented as source data. Source data are all information in original records (or certified copies of original records) of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, evaluation checklists, recorded data from automated instruments, study worksheets, or subject files). The investigator uses source documentation to complete the Case Report Forms (CRF). The investigator is required to verify that he/she has reviewed the recorded data. It will be the responsibility of the Investigator to verify all case report forms and ensure data is submitted to ABT in a timely fashion.

2. Data Collection and Processing

Remote data entry will be used to collect all subject data during the study. The investigator, or an individual designated by him/her, is responsible for completing the appropriate CRFs. ABT will handle data per current standard operating procedures. Edit checks built into the database will help ensure data integrity.

Subject information shall be de-identified prior to sending any source documents to ABT. Data collected during this study will be analyzed by ABT or its contractors and submitted to the FDA.

3. Confidentiality and Protection of Study Files

Hard copy information will be stored in controlled files when not in use. Electronic data protection and confidentiality will be ensured by use of passwords allowing different levels of access to computer files based on necessary access (e.g., read only vs. data entry access).

D. Records and Reports

1. Case Report Forms

The investigator, as well as the support staff, will be instructed on content of the case report forms. Case report forms should be submitted via the remote data entry system as soon as possible after implantation and after the subsequent follow-up visit(s). A record will be created in a database for each subject in the study. Records will be updated as the study progresses.

2. Lost-to-Follow-Up

Thorough documentation for contact attempts must be completed for subjects considered by the investigator/site to be lost-to-follow-up. A minimum of three attempts to contact the subject must be made, with at least one of them via certified/signature required mail to the subject's last known address.

3. Investigator Records

Investigators are responsible for maintaining records as required per applicable laws, regulations, and IRB/EC requirements. Records include the following:

- Correspondence with the FDA, other regulatory authorities, the sponsor, IRB/ EC, and other investigators relating to this investigation.
- Subject records, including informed consent, electronic case report forms, and supporting documents (echo reports, etc.).
- Protocol and documentation of, and reasons for protocol deviations.

4. Investigator Reports

Investigators are responsible for preparing and submitting all records as required per applicable laws, regulations, and IRB/EC requirements.

5. Sponsor Records & Reports

ABT is responsible for maintaining records and completing reports as required per applicable laws, regulations, and ABT standard operating procedures.

6. IRB/EC Records

Each reviewing IRB/EC must maintain records as required per applicable laws, regulations, and IRB/EC requirements.

E. Protocol Adherence

1. Protocol Deviation

Deviations from the investigational plan may be identified at the site or by in-house ABT personnel, and will be recorded on the Deviation CRF. The site is responsible for notifying their IRB/EC of deviations as applicable.

Examples of deviations from the investigational plan include:

- Required testing not completed or done outside window
- Subject seen outside of protocol-defined window
- SAE not reported
- Protocol-required testing done prior to signing the Informed Consent Form
- Inclusion/exclusion criteria not met
- Required subject follow-up not completed
- Subjects enrolled after expiration or during a lapse of IRB/EC approval
- Depending on IRB/EC requirements, continued follow-up of subjects after expiration of IRB/EC approval (or during a lapse in approval)

Investigator compliance will be continuously assessed by the Clinical Affairs management team and compliance will be secured when applicable.

2. Regulatory Documents

The FDA regulations, as well as ABT policies, require that certifications and other regulatory documents be kept up-to-date at all times during the conduct of a clinical investigation.

3. IRB/EC Approval and Continued Renewal

Written documentation of IRB/EC approval for the protocol and sponsor-approved informed consent including HIPAA authorization for the study must be received by ABT prior to enrollment of subjects. The IRB/EC must review and approve the continuation of the study at a minimum of annually from the initial approval date until the study is officially closed out at a site.

4. Approval to Enroll

Investigators must receive written approval from ABT prior to enrolling study subjects.

F. Review Boards

1. CEC

An independent Clinical Events Committee (CEC) will be utilized to adjudicate reported adverse events. Members of the CEC will have no affiliation with the Muscular VSD Clinical Study. This committee will be composed of at least three

clinicians with expertise in VSD closure. The CEC will review and adjudicate events reported by investigators as defined in the CEC charter.

2. Echocardiography Board

An independent Echocardiography Board or Core Laboratory will review one year echocardiograms to verify closure status. The Board or Core Laboratory may also evaluate echocardiographic images as necessary for analysis of endpoints.