Abbott	Clinical Investigation Plan Cover Page

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AMPLATZER LAAO-PAS
AMPLATZER™ LAA Occluder Post Approval Study (PAS)
Study Document No: SJM-CIP-10122
Version C
Date: 19-NOV-2018

Sponsor

Abbott
5050 Nathan Lane North
Plymouth, MN 55442
USA

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AMPLATZER LAAO- PAS

AMPLATZER™ LAA Occluder Post Approval Study (PAS)
Clinical Protocol

[redacted]

Study Document No: SJM-CIP-10122

Version C

Date: 19NOV2018

Clinical Investigation Plan (CIP)

Sponsor:

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USA
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

AMPLATZER™ LAA Occluder Post Approval Study (PAS)

Study Document No: SJM-CIP-10122 Version C

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Principal Investigator

Printed name:
Signature:
Date:

Coordinating Investigator/ National Investigator

SIGNATURE PAGE

AMPLATZER™ LAA Occluder Post Approval Study (PAS)
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Coordinating Investigator/ National Investigator

Printed name:
Signature:
Date:

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1 Synopsis

Name of Study	**AMPLATZER™ LAA Occluder Post Approval Study**
Study Sponsor	**Abbott**
Device	Description: Abbott's transcatheter, self-expanding AMPLATZER™ LAA Occluders are made of nitinol mesh and a polyester patch. The lobe has stabilizing wires placed within the left atrial appendage (LAA) and a disc (to cover the LAA orifice) connected to the lobe by a central waist. The AMPLATZER™ Cardiac Plug™ and the AMPLATZER™ Amulet™ LAA Occluders are currently available in the following sizes: Sizes (lobe diameter): • 16, 18, 20, 22, 24, 26, 28 and 30 mm for the AMPLATZER™ Cardiac Plug™ • 16, 18, 20, 22, 25, 28, 31 and 34 for the AMPLATZER™ Amulet™ Future generation AMPLATZER™ LAA Occluders may be used in the study upon approval by Health Canada. Delivery System: AMPLATZER TorqVue™ 45x45 (sheath sizes 9,10,12,13 and 14 Fr)
Indications for Use	Abbott's AMPLATZER™ LAA Occluders are intended to prevent thrombus embolization from the left atrial appendage (LAA) in patients who have non-valvular Atrial Fibrillation (AF). The device may be considered for use in patients who have a high risk of stroke and bleeding and are deemed by their physician to have an appropriate rationale to seek a non-pharmacologic alternative to long term anticoagulants.
Study Objective	To compile real world outcome data on the use of the AMPLATZER LAA Occluder in subjects with non-valvular atrial fibrillation.
Study Design	This is a non-randomized multicenter study on patients who have undergone a procedure to implant an AMPLATZER LAA Occluder or will undergo an implant of an AMPLATZER LAA Occluder.
Randomization	Non-randomized
Sample Size	This study, and other AMPLATZER LAA Occluder post approval studies collecting similar data, will contribute to the overall sample size of 1000 subjects for analysis of study endpoints. Up to 100 sites worldwide will participate in this study.
Primary Endpoints	This study has three primary endpoints: • Efficacy Endpoint 1: The occurrence of the composite of stroke (including ischemic or hemorrhagic), systemic embolism, or cardiovascular or unexplained death at 24 months from the time of enrollment • Efficacy Endpoint 2: The occurrence of ischemic stroke or systemic embolism at 24 months from the time of enrollment • Safety Endpoint: The occurrence of one of the following events between the time of implant and within 7 days of the procedure or by hospital discharge, whichever is later: all-cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular repair
Secondary Endpoint	Comparison of the observed rate of ischemic stroke at 24months with the CHA_2DS_2-VASc predicted rate.
Descriptive Endpoints/Outcomes Measures	The following endpoints will be summarized descriptively: • Oral anticoagulant use over time • Device closure at the 2 month visit

[redacted]

	• Procedural success • Technical success • Procedure duration • Device thrombosis • Transient ischemic attack • Death • Major bleeding
Enrollment Criteria	Prospective Enrollments Patients in whom an AMPLATZER LAA Occluder device is intended to be implanted Retrospective Enrollments Patients who underwent an AMPLATZER LAA Occluder implant attempt after the device was approved in the applicable geography
Clinical Follow-up Visits/Testing	Subjects will be followed through 2 years post implant. **Required Testing for Prospective Enrollments** • **Baseline evaluation:** Informed consent, history and physical, pregnancy testing for women of childbearing age, CHA2DS2-VASc score, HAS-BLED score, modified Rankin Scale, medication assessment • **Procedure:** Transesophageal echocardiogram (TOE), angiogram, adverse event assessment • **Post procedure/Pre-Discharge:** Transthoracic echocardiogram (TTE), medication assessment, adverse event assessment • **2M (+/- 45 days):** TOE, medication assessment, adverse event assessment • **6M (+/- 4 weeks):** Phone contact follow-up for medication assessment, adverse event assessment • **12M (+/- 6 weeks):** Medication assessment, adverse event assessment • **2yrs (+/- 12 weeks):** Medication assessment, adverse event assessment • **Interim/unscheduled visits:** per physician discretion Retrospectively enrolled subject data collection will include adverse events and standard of care (SOC) echo data previously collected by the site. Protocol required follow up visits will begin upon subject consent
Suspected Stroke / TIA Requirements	• Subjects suspected of a stroke should be seen by a stroke/TIA neurologist for evaluation and appropriate baseline neurological testing (i.e. magnetic resonance imaging (MRI), computed tomography (CT) • Modified Rankin Scale • TOE or ICE should be conducted within 7 days of confirmation of stroke to verify the presence of device related thrombus

1.1 Study Contacts

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USA
[redacted]

2. Introduction

This document is a clinical investigational plan for St. Jude Medical's AMPLATZER™ Cardiac Plug™ and AMPLATZER™ Amulet™ Left Atrial Appendage (LAA) Occluders (these devices are referred to as "AMPLATZER LAA Occluder"). The study is a post-approval study to compile real world outcome data on the use of AMPLATZER LAA occluders in patients with non-valvular atrial fibrillation who are at increased risk for stroke and systemic embolism. This is a worldwide study intended to fulfill Health Canada's post-approval requirements for the device. Future generation AMPLATZER™ LAA Occluders may be used in the study upon approval by Health Canada. A patient who was either implanted or had an attempt to implant with an AMPLATZER LAA Occluder may be retrospectively enrolled in the study if the device was approved in the applicable geography at the time of the procedure.

3. Background and Justification

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder[1]. During AF there are multiple simultaneous waves of contractions, which spread in a chaotic manner through both atria. This arrhythmia results in rapid, uncoordinated contractions, which decrease the blood pumped through the atria. The loss of mechanical efficiency during AF leads to insufficient contractions in the left atrium (LA)[2]. Stagnation of blood flow in the LA leads to hypercoagulability and thus increases the risk for thrombus formation in the LA or left atrial appendage (LAA). Approximately 90% of all the thrombi in subjects with non-valvular AF (NVAF) forming in the LA originate in the left atrial appendage[3]. The thrombus formation, in turn exposes the patient to thromboembolic events.

Echocardiographic risk factors for LAA thrombus formation include echocardiographic evidence of decreased LAA flow velocity and spontaneous echo contrast within the left atrium and left atrial appendage[4,5]. The normal flow pattern of the LAA is the ejection of blood from the appendage following atrial contraction at a velocity greater than 40cm/s^2. Agmon et al. found that the relative risk reduction of ischemic stroke was 2.6 times greater in patients with LAA flow velocities <20cm/s^2 than those with higher LAA velocites[6].

Non-valvular AF patients have been assessed to determine the risk of stroke based on the presence of independent risk factors. In a study by Gage et al. the $CHADS_2$ index was shown to be a tool to predict the risk of stroke in subjects with AF[7]. The $CHADS_2$ score assigns one point each for the presence of congestive heart failure, hypertension, age greater than 75 and diabetes mellitus and two points for history of stroke or transient ischemic attack (TIA). The study found that AF patients who were not treated with anti-thrombotic agents had an increased risk of stroke ranging from 1.9% to 18.2% as $CHADS_2$ scores increase from 0 to 6.

A study by Go et al. reviewed outcome data (11,526 patients) in a large primary care setting and confirmed that thromboembolic risk increases progressively with $CHADS_2$ score[8]. The study also noted that oral anticoagulation with warfarin reduces the risk of stroke in most patients with the exception of those at lowest risk ($CHADS_2$ score of zero) and highest risk ($CHADS_2$ >5) for stroke. The more recently developed CHA_2DS_2-VASc risk assessment scheme[9], which identifies truly low risk subjects, assigns two points to age ≥75 years and previous stroke, TIA or thromboembolism and one point each to congestive heart failure or left ventricular dysfunction, hypertension, diabetes, vascular disease, age between 65-74 years and female sex. A recent validation[10] of these risk schemes in more than 90,000 patients without oral anticoagulation (OAC) but on aspirin showed annual ischemic stroke rates ranging from 0.6% in CHA_2DS_2-VASc = 1 to 4.8% in CHA_2DS_2-VASc = 4, and more than 12% for CHA_2DS_2-VASc = 9.

In a meta-analysis conducted by Andersen et al., warfarin was found to be superior to aspirin and placebo in reducing the risk of systemic embolism in subjects with NVAF[11]. Hart et al. reported that adjusted dose warfarin reduces stroke by 64% (6 trials) and antiplatelet agents reduce stroke risk by 22%[12]. The study also reported that risk of intracranial hemorrhage was doubled with adjusted-dose warfarin compared with aspirin.

Recently, new drugs (known as novel oral anticoagulant, or NOAC) have been developed with less dietary and pharmacological interactions than warfarin and less stringent requirements for frequent INR monitoring. Major trials such as RE-LY and ROCKET AF demonstrated that dabigatran and rivaroxaban are non-inferior to warfarin in the prevention of stroke or systemic embolism[13, 14]. The ARISTOTLE trial demonstrated Apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality in subjects with atrial fibrillation[15]. The ENGAGE AF-TIMI[16] trial demonstrated both once daily dose regimens of Edoxaban were non-inferior to warfarin with respect to the preventions of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes[17]. A number of characteristics that increase a patient's risk for stroke also increase the patient's risk for bleeding; therefore an alternative to warfarin and NOAC drugs is needed.

Left atrial appendage occlusion (LAAO) is considered a viable alternative to oral anticoagulation (OAC) therapy for stroke prevention in patients with NVAF[15-25]. Published evidence supporting LAAO is provided in large part by the major randomized controlled trials PROTECT AF and PREVAIL[15-18]. Five-year results of PROTECT AF showed superiority of the WATCHMAN™ device in mortality and stroke reduction compared to optimal medical treatment with warfarin[18].

The AMPLATZER Cardiac Plug demonstrated favorable feasibility and safety in observational studies in Europe[26-28]. Additionally, Park et al. reported the results of an investigator-initiated retrospective study to report on the initial European experience in patients treated with the AMPLATZER Cardiac Plug device between December 2008 and November 2009. SJM's AMPLATZER Cardiac Plug Registry results were also presented at EURO PCR in 2012 and 2014[29-30]. In addition, results from a multicenter study involving 22 sites and 1047 consecutive patients undergoing implant of the AMPLATZER Cardiac Plug device showed a high procedural success rate and a favorable outcome for the prevention of AF related thromboembolism[31].

In a comparative study between the AMPLATZER Cardiac Plug and the WATCHMAN devices (40 patients each), Chun et al.[32] found the devices to perform similarly. The rate of successful implantation achieved with the ACP device was greater than with the WATCHMAN device (100% vs. 95%) although the difference was not statistically significant. TEE at follow-up revealed a significantly higher incidence of residual peri-device flow (jet > 5 mm) for the WATCHMAN device compared to the ACP device, although this was not associated with an increased incidence of thromboembolic events. This finding is consistent with other reports on the ACP device[33].

In conclusion, percutaneous LAAO devices have emerged as an alternate option for stroke reduction in non-valvular AF patients at high risk for stroke.

See **Appendix A for a listing of abbreviations used throughout this document*

4. Study Design

4.1 Purpose

The AMPLATZER LAA Occluders are transcatheter, self-expanding nitinol devices intended for use in preventing thrombus embolization from the LAA. The purpose of this study is to compile real world outcome data on the use of an AMPLATZER LAA Occluder in subjects with non-valvular atrial fibrillation (NVAF).

4.2 Study Design and Scope

The AMPLATZER LAA Occluder devices will be clinically evaluated through this post approval study. This is a multicenter, non-randomized observational post-approval study in subjects who meet one of the following criteria:

Prospective Enrollments
Patients in whom an AMPLATZER LAA Occluder device is intended to be implanted

Retrospective Enrollments

[redacted]

Patients who underwent an AMPLATZER LAA Occluder implant attempt after the device was approved in the applicable geography

4.2.1 Subject population

The subject population will include participants that are ≥ 18 years old and diagnosed with NVAF.

4.2.2 Number of study subjects

This study, and other AMPLATZER LAA Occluder post approval studies collecting similar data, will contribute to the overall sample size of 1000 subjects for analysis of study endpoints. Up to 100 sites worldwide, will participate in this study. [redacted]

4.2.3 Enrollment period and study duration

[redacted]

4.3 Endpoints

4.3.1 Primary endpoints

This study has three primary endpoints:

1. Efficacy Endpoint 1: The occurrence of the composite of stroke (including ischemic or hemorrhagic), systemic embolism and cardiovascular or unexplained death at 24 months
2. Efficacy Endpoint 2: The occurrence of ischemic stroke or systemic embolism at 24 months
3. Safety Endpoint: The occurrence of one of the following events between the time of implant and within 7 days of the procedure or by hospital discharge, whichever is later: all cause death, ischemic stroke, systemic embolism, or device or procedure-related events requiring open cardiac surgery or major endovascular repair*

* NOTE: Percutaneous catheter drainage of pericardial effusion, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm and nonsurgical treatments of access site complications will not be included in the assessment of the third primary endpoint.

4.3.2 Secondary endpoint

The secondary endpoint is a comparison of the observed rate of ischemic stroke at 24 months with the CHA_2DS_2-VASc predicted rate.

4.3.3 Descriptive Endpoints/Outcomes Measures

The following endpoints will be summarized using descriptive statistics.

- Oral anticoagulant use over time
- Device closure
  - Defined as residual jet around the device ≤ 5mm at the 2-month visit documented by transoesophageal echocardiogram (TOE)
- Procedure success
  - Procedural success-defined as implantation of the AMPLATZER LAA Occluder with no serious adverse events prior to hospital discharge
- Technical success
  - Technical success-defined as delivery and release of the AMPLATZER LAA Occluder.
- Procedure duration

[redacted]

- Device thrombosis
- Transient Ischemic Attack
- Death
- Major bleeding defined as Type 3 or greater based on the Bleeding Academic Research Consortium (BARC - **Appendix H**: Major Bleed classification/definition)

4.4 Enrollment Criteria

This study will enroll patients in whom an AMPLATZER LAA Occluder device is either intended to be implanted or underwent an implant attempt after the device was approved in the applicable geography

All patients who sign the informed consent will be assigned a study identification number and this will be recorded on a baseline electronic case report form (eCRF). The subject ID number will be unique to each individual and will allow the participant to be linked if necessary, to name, alternative identification or contact information. To ensure subject privacy and confidentiality of data, subject ID numbers will be used and maintained by study site personnel for the duration of the study.

4.5 Informed Consent Process

The process for obtaining informed consent must comply with the ethical principles defined in the current version of the Declaration of Helsinki (**Appendix C**).

Prior to enrollment in the clinical study, all subjects will be consented, as required by applicable regulations and the site's Institutional Review Board (IRB) or ethics committee (EC). The consent form must be signed and dated by the subject and by the person obtaining the consent, where applicable.

The principal investigator (PI) or his/her authorized designee will conduct the informed consent process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate, and the subject should be allowed adequate time to review and ask questions.

Documentation that informed consent was obtained will be recorded on the eCRF and in the subject's medical record. The signature date on the consent form should be referenced. The original signed informed consent should be filed in the subject's study chart and a copy of the signed consent form given to the subject per IRB/EC requirements.

A template of the informed consent form is provided in **Appendix E**: Sample Informed Consent. Any changes to the informed consent must be approved by Abbott prior to ethics committee review and approval.

A subject cannot be consented for the study prior to IRB/EC approval of the informed consent form. The subject shall be provided the informed consent form that is written in a language understandable to the subject and has been approved by the site's IRB/EC.

The subject is enrolled in the study when consent has been obtained and vascular access initiated, (prospective), or when consent is obtained after a subject underwent a study device implant attempt that may have been successful or unsuccessful (retrospective). Failure to obtain informed consent from a subject must be reported to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB/EC's reporting requirements.

5. Device

5.1 Device Descriptions

The AMPLATZER Cardiac Plug (ACP) (**Figure 1**) and AMPLATZER Amulet Occluder (**Figure 2**) are constructed from a nitinol mesh and consist of a lobe and a disc connected by a central waist. These devices are percutaneous transcatheter devices intended to prevent thrombus

embolization from the left atrial appendage (LAA) in patients who have non-valvular atrial fibrillation. These devices may be considered for use in patients who have a high risk of stroke and bleeding and are deemed by their physician to have an appropriate rationale to seek a non-pharmacologic alternative to long term anticoagulants.

Depending on the device, the lobe ranges in diameter from 16 to 34 mm (**Table 1**) and has stabilizing wires for device placement and retention. The disc is larger in diameter than the lobe, ranging from 20 to 41 mm; both the disc and the lobe contain polyester fabric to facilitate LAAO. There are threaded screw attachments at either end of the device for connection to the delivery and loading cable. Radiopaque markers at either end of the device and at the location of the stabilizing wires allow for predictable placement of the device. The stabilizing wires and polyester patch are secured to the device using polyester thread. A platinum/iridium thread is attached to the nitinol braid.

Accessories packaged with the AMPLATZER LAA Occluder device include the loader, loading cable, loading cable vise, delivery cable, delivery cable vise, and hemostasis valve.

Figure 1: The AMPLATZER Cardiac Plug and key components

A. Screw attachments
B. Waist of device
C. Lobe
D. Marker Bands
E. Stabilizing wires
F. Platinum/iridium thread
G. Disc

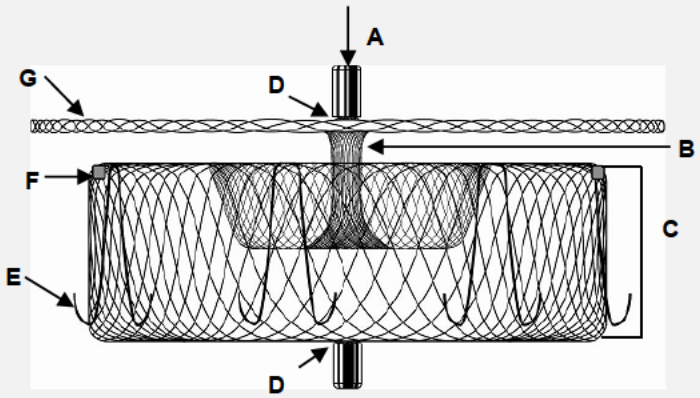

Figure 2: AMPLATZER Amulet Occluder key components

A. Screw attachments
B. Waist of device
C. Lobe
D. Marker Bands
E. Stabilizing wires
F. Platinum thread
G. Disc

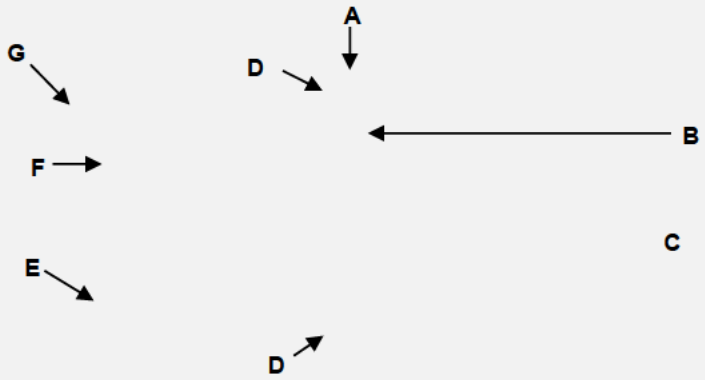

Table 1: Model numbers and key dimensions of the AMPLATZER LAA Occluders and delivery system

Reference	ACP Lobe/ Device Size (mm)	Left Atrial Disc Size (mm)	Lobe Length (mm)	Usable Length (cm)	Sheath size
AMPLATZER CARDIAC PLUG					
9-ACP-007-016	16	20	6.5	80	9F
9-ACP-007-018	18	22	6.5	80	10F
9-ACP-007-020	20	24	6.5	80	10F
9-ACP-007-022	22	26	6.5	80	10F
9-ACP-007-024	24	30	6.5	80	13F
9-ACP-007-026	26	32	6.5	80	13F
9-ACP-007-028	28	34	6.5	80	13F
9-ACP-007-030	30	36	6.5	80	13F
AMPLATZER Amulet Occluder					
9-ACP2-007-016	16	22	7.5	80	12F
9-ACP2-007-018	18	24	7.5	80	12F

[redacted]

Reference	ACP Lobe/ Device Size (mm)	Left Atrial Disc Size (mm)	Lobe Length (mm)	Usable Length (cm)	Sheath size
9-ACP2-007-020	20	26	7.5	80	12F
9-ACP2-007-022	22	28	7.5	80	14F
9-ACP2-007-025	25	32	10	80	14F
9-ACP2-007-028	28	35	10	80	14F
9-ACP2-007-031	31	38	10	80	14F
9-ACP2-007-034	34	41	10	80	14F

Future generation AMPLATZER™ LAA Occluders may be used in the study upon approval by Health Canada.

5.2 Device Accountability

The AMPLATZER LAA Occluder devices are market released in the countries where this study will be conducted. Therefore, there are no tracking requirements for this study. Information regarding opened, introduced, and implanted devices will be recorded on the Procedure and Product Out of Service (where applicable) eCRFs.

6. Study Procedures

This study will be conducted in accordance with the clinical protocol and IFU. All persons participating in the conduct of the study will be qualified by education, training, or experience to perform study-related tasks.

The study will not commence at each selected site until Abbott receives written approval from the IRB/EC and relevant regulatory authorities, and all required documents have been collected from the participating sites.

Figure 3 below describes the study flowchart for subject screening, consent, enrollment and follow-up through the 2-year follow-up visit. **Table 2** outlines the testing and assessments required per study visit interval for subjects who are implanted with an AMPLATZER LAA Occluder.

Figure 3: Study flowchart for subject screening, consent, enrollment and follow-up

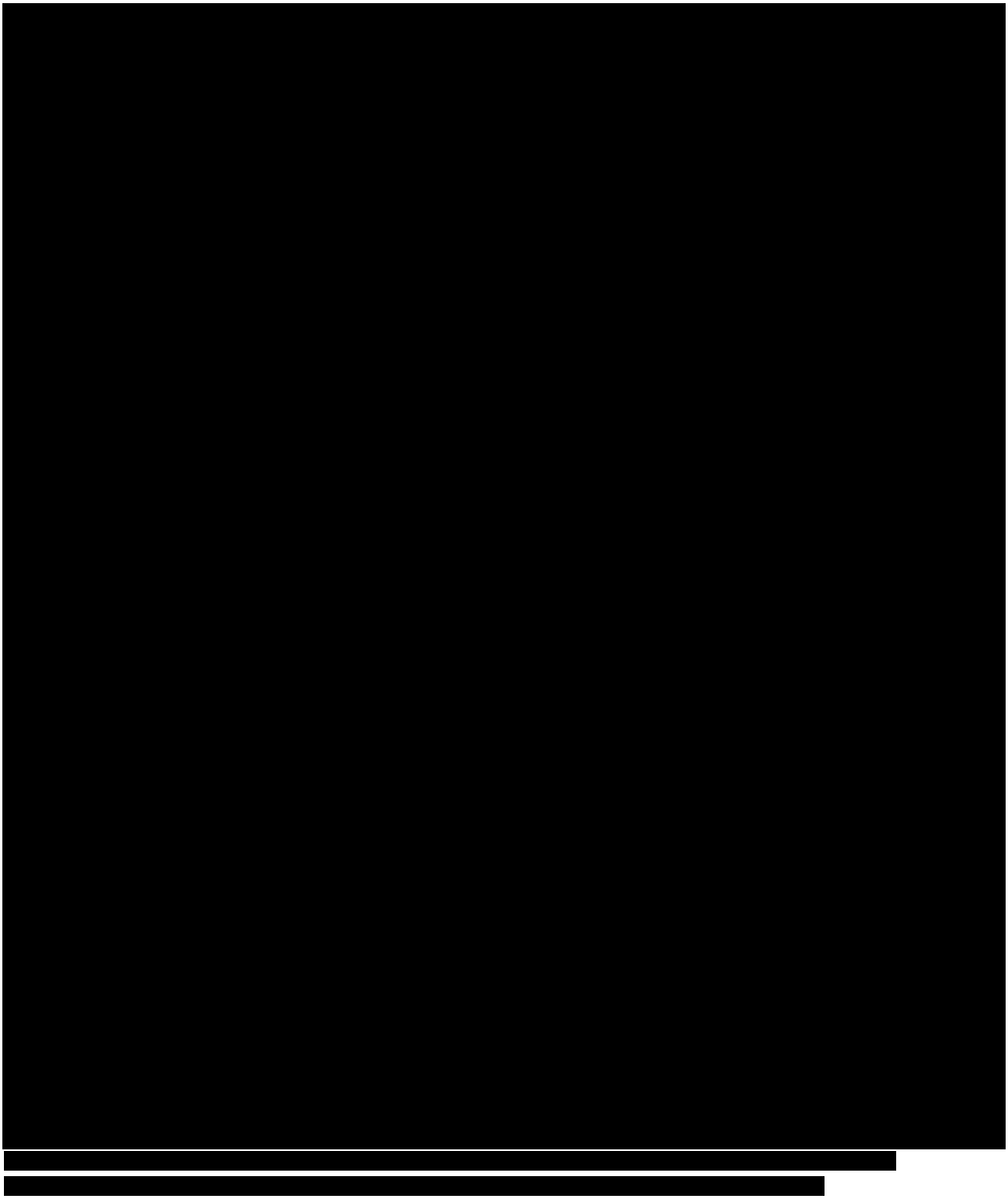

Table 2: Study visits and assessments (subjects who are implanted with an AMPLATZER LAA Occluder)

[redacted]

Follow up visit timing begins from the date of the procedure for both prospective and retrospective enrollments.

The electronic Case Report Forms (eCRFs) to be completed for enrolled subjects per the study visit intervals are:

- Baseline – Baseline, Enrollment, Modified Rankin Scale, Medication, and Echo
- Procedure – Procedure, Echo, Medication
- Discharge, 2M, 6M, 12M and 24M – Follow-up, Echo (as required), Medication
- Unscheduled visit - Follow-up, Medication, Echo (as required)

[redacted]

For retrospective enrollments, the applicable Baseline, echo, and adverse events CRFs should be retrospectively completed based on information from the subject's medical records. Retrospective data should include any adverse events from the date of implant or attempted implant. Protocol required follow up visits will begin after the subject's trial enrollment date.

Additional eCRFs, reports and assessment noted below should be completed upon occurrence, and/or as applicable:

- Withdrawal eCRF
- Adverse Event eCRF
- Protocol Deviation eCRF
- Death eCRF
- Stroke/TIA Assessment eCRF
- Echo eCRF
- Modified Rankin Scale (**Appendix G**: Modified Rankin Scale (mRS) (complete 90 days after confirmed stroke)

Suspected stroke or TIA

- Prospective enrollment: If a stroke or TIA is suspected, the subject should be seen by a neurologist or neurosurgeon for evaluation and appropriate neurological testing (CTA (computed tomography angiography) or MRA (magnetic resonance angiography). If a stroke is confirmed, a TOE is required as soon as possible, but no later than 7 days to confirm device placement, LAA flow parameters and presence/absence of device-related thrombus. See **Section 8.1** for further details.
- Retrospective enrollment: If a previous stroke or TIA was suspected, any neurologic evaluation data including neurological testing and echo imaging should be submitted through the Stroke/TIA Assessment eCRF and any previous AEs due to the suspected stroke or TIA should be submitted according to **Section 8.1**.

6.1 Screening/Enrollment/Baseline

The following baseline and enrollment activities are performed as part of the screening process:

- Informed consent process
- History and physical
- Cardiovascular and medical exam
- Pregnancy testing for women of childbearing age
- TOE (optional if a TOE is performed on the day of procedure)
- Modified Rankin Scale
- Medication assessment
- CHA_2DS_2-VASc score:

Table 3: CHA_2DS_2-VASc score

CHA_2DS_2-VASc	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/TE	2
Vascular disease [prior myocardial infarction, peripheral artery disease or aortic plaque]	1
Age 65-74	1
Sex category [i.e. female gender]	1

- HAS-BLED score:

Table 4: HAS-BLED score

HAS-BLED	Score
Hypertension history (uncontrolled, > 160 mmHg systolic)	1
Abnormal renal function/renal disease (dialysis transplant, creatinine > 2.6 mg/dL or > 200µmol/L)	1
Liver disease (cirrhosis, bilirubin > 2x normal AST/ALT/AP > 3x normal)	1
Stroke history	1
Bleeding, anemia, or predisposition to bleeding	1
Labile INR (Unstable/high INR's, or poor time (< 60% time in therapeutic range)	1
Elderly - Age ≥ 65 years	1
Drugs - Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)	1
Alcohol usage history (> 8 drinks/week)	1

The principal investigator or delegated study personnel is responsible for screening potential subjects to determine subject eligibility for the study. Enrollment information (date of consent, enrollment criteria, etc.) will be recorded in the subject's hospital records and on the Baseline eCRF. For prospective subjects, the Baseline eCRF should be submitted within one week of signing the informed consent form. Baseline eCRFs for retrospectively enrolled subjects will capture data before attempted implant, collected from their medical history.

For prospective subjects, if a subject does not meet criteria for AMPLATZER LAA Occluder implant, the subject cannot participate in the study. The Baseline eCRF (consented screen failure), as applicable, must be completed and the subject should be withdrawn. If the subject was enrolled (i.e. consented and vascular access initiated), but does not get a device implanted due to anatomy or other reason, the Baseline, Procedure, and Withdrawal eCRFs should be completed.

Serious adverse events will be reported from the time vascular access was initiated to the time the subject concludes the study. Adverse Event eCRFs should be completed, as applicable.

6.2 Implant/Procedure/Post-Procedure

Refer to the IFU for procedural and post-procedural instructions.

6.3 Attempt to treat

Subjects who are consented, in whom vascular access for the AMPLATZER LAA Occluder was initiated, but the device was not implanted, will be considered “Attempt to Treat”. The subject will be followed for 7 days or until discharge, whichever is later. Retrospectively enrolled subjects will include “Attempt to Treat” subjects; AEs that occurred within 7 days following the implant attempt or by discharge, whichever was later, will be captured.

6.4 Scheduled Follow-ups

Required follow-up visits for subjects who are prospectively implanted with an AMPLATZER LAA Occluder will be at 2 months, followed by a 6-month telephone follow-up, and 12 and 24-month follow-up visits. For retrospective subjects, follow-up visits after enrollment will be conducted per protocol, and will be based on the date of implant. However, all AEs from the time of the implant procedure will be collected. Refer to **Table 2** for required follow-up testing and assessments. Subjects in whom vascular access is initiated for an AMPLATZER LAA Occluder, but the device is not implanted, will be considered “Attempt to Treat” and will be followed for 7 days until discharge, whichever is later.

6.5 Unscheduled Visits

If an unscheduled visit occurs, a Follow-up eCRF should be completed to capture data collected at the visit as well as pertinent additional eCRFs (medication, echo, and adverse event assessments as applicable).

In the event of a confirmed stroke, a TOE is required as soon as possible, but no later than 7 days after the stroke. The Stroke/TIA assessment, modified Rankin Scale, and Echo eCRFs should be completed and applicable imaging submitted to the Sponsor. Ninety (90) days after the event, the Stroke/TIA assessment and mRS should be repeated and applicable eCRFs submitted to the sponsor.

6.6 Sponsor Representatives

Trained Sponsor personnel may perform certain study activities to ensure compliance to the clinical protocol and may provide technical expertise. Monitoring may be performed by Abbott and/or authorized designees according to the International Organization for Standardization (ISO) 14155 for post market studies, and applicable Abbott standard operating procedures and work instructions. Qualified monitors will ensure investigators comply with this clinical protocol and ISO 14155 post market requirements.

Sponsor representatives will periodically request source documents, resolution of discrepancies, submission of echocardiography imaging etc. for data cleaning and reporting purposes.

6.7 Subject Study Completion

Subjects will complete their participation in the study at the 2-year follow-up visits and will return to receiving medical care per their physician’s recommendations.

6.8 Subject Withdrawal

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the

investigator. Subjects will be asked to specify the reason for their termination, but have the right not to answer.

All reasonable efforts should be made to retain the subject in the study until completion of the study.

Reasons for subject withdrawal include, but are not limited to:

- Subject withdraws consent
- Subject dies (adverse events leading to death must be documented on an Adverse Event eCRF)
- Subject did not have a successful implant and does not have a study device implanted (subjects who had an unsuccessful implant, the withdrawal date should be at 7 days post-implant attempt)
- Subject is 'lost to follow up' (a subject will be considered "lost to follow-up" after a minimum of 2 attempted phone calls and a letter to the subject from study site personnel. Attempts to contact subject must be documented in the subject's study chart and/or medical record. If phone attempts are unsuccessful, a letter should be sent to the subjects last known address)

If a subject withdraws from the study, the site will record the subject's reasons for withdrawal on the Withdrawal eCRF.

7. Compliance Statements

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki (**Appendix C**), ISO 14155, and any regional and/or national regulations and will be compliant to these International Standards and any regional and national regulations, as appropriate.

The investigator will not enroll subjects or obtain informed consent from any subject prior to obtaining EC approval and authorization from the Sponsor in writing for the study. For prospective enrollments, the subject must sign the study informed consent form prior to implant procedure.

If additional requirements are imposed by the EC, those requirements will be followed, if appropriate. If any action is taken by an EC, and regulatory requirements with respect to the study, that information will be forwarded to the Sponsor.

As the Sponsor, Abbott has taken general liability insurance in accordance with the requirements of applicable local laws. Appropriate Abbott country representatives will be utilized to interpret the requirements regarding the type of insurance that will be provided to subjects, and such information will be incorporated into the informed consent form, as applicable. If required, additional subject coverage or study specific insurance may also be provided by the Sponsor.

8. Serious Adverse Events, Serious Adverse Device Effects, Deaths and Device Deficiencies

Only serious adverse events (SAEs) will be collected for this study. Serious adverse events are classified as serious adverse events or serious adverse device effects (SADEs). A planned hospitalization for a pre-existing condition is not considered a serious adverse event.

8.1 Serious Adverse Events

A serious adverse event is an adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:

- A life-threatening illness or injury OR
- A permanent impairment to a body structure or a body function OR
- An in-patient or prolonged hospitalization OR
- A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body OR
- A malignant tumor OR
- Fetal distress, fetal death or a congenital abnormality or birth defect

8.1.1 Serious Adverse Device Effect

A serious adverse device effect is a serious adverse event related to the device or procedure which resulted in any of the consequences characteristic of a serious adverse event, or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

8.1.2 Assessing, recording and reporting serious adverse events, serious adverse device effects, and device deficiencies/complaints

Safety surveillance within this study and the safety reporting performed both by the investigator and Sponsor starts as soon as vascular access has been initiated. The safety surveillance and the safety reporting will continue until the last visit has been performed, the subject is deceased, or the subject withdraws from the study.

All serious adverse events (including deaths), serious adverse device effects, and device deficiency information (if applicable) will be collected throughout the clinical study and reported to the Sponsor. Investigators will record all serious adverse events, serious adverse device effects, and deaths on the appropriate eCRF. Device deficiencies/complaints will be reported per country reporting timeline requirements using the standard process per country regulations.

For any serious adverse event (including deaths) and any serious adverse device effect, the investigator shall notify the Sponsor within 3 calendar days of the investigator's awareness of the event and provide the Sponsor with all necessary documentation needed.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Additional information may be requested, when required, by the Sponsor in order to support the reporting of serious adverse events to the CEC, regulatory authorities and/or other authorities.

Serious adverse events and serious adverse device effects should be monitored by the investigator until resolved. The status of the subject's condition should be documented at each follow-up visit.

Events reportable to the Sponsor, EC, CAs and regulatory authorities (as applicable) include:

- All serious adverse device effects
- All serious adverse events (including deaths and whether or not the event is considered device or procedure related)

The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities per country specific regulations.

8.1.3 Subject death

All subject deaths with all necessary documentation needed are to be reported to the Sponsor within 3 calendar days upon the investigator's awareness of the event. The Sponsor must report the death (classified as a serious adverse event) to the National Competent Authorities (NCAs) where the study has commenced no later than 2 calendar days after awareness of the event. An Adverse Event eCRF should be completed and include additional detail surrounding the death and cause of death. The principal investigator should also record observed device deficiencies and assessment, if applicable.

8.2 Device Deficiency/Complaint Handling

During the trial, the investigator will be responsible for reporting all device deficiencies per country reporting timeline requirements. A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance and includes malfunctions, and inadequate labeling.

Abbott will manage all device deficiencies related to the identity, quality, durability, reliability, safety or performance of the marketed study device and reporting to the appropriate regulatory bodies.

9. Data Management

Overall, the Sponsor will be responsible for data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Canada, Europe and/or any other worldwide regulatory authority in support of a market-approval application.

Abbott respects and protects personally identifiable information that is collected or maintained. As part of its commitment, Abbott is certified to the U.S. - European Union Framework and PIPEDA-Canada privacy act. Agreements regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

Electronic CRFs will be used in this study, as noted below and in the data management plan. Informed consent documents will be translated to each country's language, as applicable. If additional documentation is required for any reason (e.g. procedural notes for an adverse event), it is to be appropriately redacted/de-identified prior to being sent to Abbott. Source documents will be collected and translated, as needed, for CEC meetings, reporting, etc.

The principal investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and regulatory authority inspections.

9.1 Data Management Plan

A detailed data management plan (DMP) will be established to ensure consistency of the collected data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

Electronic CRF data will be captured in a validated electronic database management Oracle Clinical system hosted by Abbott. Only authorized site personnel will be permitted to enter the data through the electronic data capture (EDC) system deployed by Abbott. An electronic audit trail will be used to track any subsequent changes of the entered data.

9.2 Document and Data Control

9.2.1 Document and data traceability

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the eCRFs and in all required reports.

9.2.2 Recording data

Source documents will be created and maintained by the investigational site throughout the duration of the clinical study. Data reported on the eCRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

The eCRFs will be signed and dated (validated eCRF) by the authorized site personnel, as specified in the Data Management Plan.

10. Risks and Benefits

10.1 Anticipated Clinical Benefits

Patients suitable to receive the AMPLATZER LAA Occluder should be deemed by their physician to have an appropriate rationale to seek an alternative to pharmocologic therapy such as the inabilty to tolerate long term anticoagulants. The AMPLATZER LAA Occluder is intended to be an alternative long term stroke prophylaxis when long term anticoagulation therapy is unacceptable. The potential benefit of participating in this clinical study are close follow-up of the subejct by their treating physicians.

10.2 Anticipated Adverse Events and Adverse Device Effects

Anticipated adverse events and adverse device effects may occur during and after the AMPLATZER LAA Occluder implant procedure. Serious adverse event definitions are provided in **Section 8**. Refer to IFU for a complete list of potential anticipated serious adverse events.

10.3 Risks

The risks associated with the AMPLATZER LAA Occluder are no different from the risks associated with undergoing implant of an LAA Occluder with other commercially available transcatheter devices.

10.4 Risk to Benefit Rationale

Risks associated with participating in this clinical study are no different from risks associated with undergoing LAAO implant with a commercially available transcatheter device. A potential benefit of participation in this clinical study may be close follow-up of the subject by their treating physicians.

10.5 Residual Risks Associated with the Device

The AMPLATZER Left Atrial Appendage Occluder device is market approved in all the countries where the study will be conducted. The risk profile of the LAA Occluder device implant procedure is described in the IFU, and **Section 8** of this protocol. Risks associated with participating in this clinical study are no different from risks associated with undergoing LAAO implant with a commercially available transcatheter device.

10.6 Steps to Control or Mitigate Risks

The Sponsor will select investigators qualified by training and experience to participate in this study. Participating sites will be selected based upon qualifications of the principal investigator. During the study, sites may be subject to quality assurance audits by the Sponsor (or designee), as well as monitoring visits to assess data integrity and study compliance. Any additional risk is mitigated with vigilance reporting for a licensed product.

11. Clinical Events Committee (CEC)

A CEC will be responsible for providing an independent adjudication of study endpoints as outlined in the CEC Charter.

12. Monitoring

It is the responsibility of Abbott as the Sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring will be conducted according to the study-specific monitoring plan.

Prior to beginning the clinical investigation, the Sponsor will contact the investigator or designee to discuss the clinical investigation and data requirements. A designated 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.

Additionally, centralized monitoring may occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance.

13. Regulatory Inspections

The investigator and/or delegate should contact SJM as soon as possible upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

14. Statistical Methods

[redacted]

14.1 Primary Endpoints

There are three primary endpoints, two effectiveness endpoints and one safety endpoint.

14.1.1 Primary Effectiveness Endpoint 1:

Primary effectiveness endpoint 1 is the occurrence of the composite of stroke (including ischemic or hemorrhagic), systemic embolism, or cardiovascular or unexplained death at 24 months.

Hypothesis:

Ho: $\lambda_1 \geq 9.6\%$

[redacted]

Ha: $\lambda_1 < 9.6\%$,
where λ_1 is the rate of primary composite endpoint 1 at 24 months.

Analysis Methods:

Kaplan-Meier analysis will be used to estimate the event rate of at 24 months (731 days post implant). The 97.5% upper confidence bound for the event rate must be less than 9.6% in order to declare success. [redacted]

Analysis Population:

Subjects in this study who receive an implant of the AMPLATZER LAA Occluder will be included in the analysis.

14.1.2 Primary Effectiveness Endpoint 2:

Primary effectiveness endpoint 2 is the occurrence of the composite of ischemic stroke or systemic embolism at 24 months.

Hypothesis:

Ho: $\lambda_2 \geq 6.6\%$
Ha: $\lambda_2 < 6.6\%$,
where λ_2 is the rate of primary composite endpoint 2 at 24 months.

Analysis Methods:

Kaplan-Meier analysis will be used to estimate the rate of event at 24 months (731 days post implant). The 97.5% upper confidence bound for the event rate must be less than 6.6% in order to declare success. [redacted]

Analysis Population:

Subjects in this study who receive an implant of the AMPLATZER LAA Occluder will be included in the analysis.

14.1.3 Primary Safety Endpoint:

The primary safety endpoint is the occurrence of one of the following events between the time of implant and within 7 days of the procedure or by hospital discharge, whichever is later: All-cause death, ischemic stroke, systemic embolism, or device or procedure related events requiring open cardiac surgery or major endovascular repair (percutaneous catheter drainage of pericardial effusion, snaring of an embolized device, thrombin injection to treat femoral pseudoaneurysm, and nonsurgical treatments of access site complication will not be included in the assessment of the third primary endpoint).

Hypothesis:

Ho: $P \geq 2.66\%$
Ha: $P < 2.66\%$,
where P is the proportion of subjects experiencing a primary safety event within 7 days of the procedure or by hospital discharge, whichever is later.

Analysis Methods:

The proportion of subjects experiencing a primary safety endpoint will be estimated. The 97.5% upper confidence bound for the proportion of subjects experiencing a safety event will be calculated using the exact binomial method. The 97.5% upper confidence bound for the

proportion must be less than 2.66% in order to declare success. [redacted]

Analysis Population:

Subjects who undergo an implant attempt with the AMPLATZER LAA Occluder will be included. An attempt is defined as a subject in whom vascular access has been initiated.

14.2 Secondary Endpoint

The secondary endpoint is a comparison of the observed rate of ischemic stroke at 24 months with the CHA_2DS_2-VASc predicted rate.

14.2.1 Analysis method

[redacted]

14.2.2 Analysis population

The analysis will include subjects who receive an implant of an AMPLATZER LAA Occluder.

14.3 Descriptive Endpoints/Outcomes Measures

The following endpoints will be summarized using descriptive statistics.

Oral anticoagulant use over time:

The count and proportion of subjects using oral anticoagulants will be summarized at scheduled follow-up visit. Subjects who are implanted with the AMPLATZER LAA Occluder will be included in this analysis.

Device closure:

The number and proportion of subjects in whom device closure is achieved at the 2-month visit will be summarized. Device closure is defined as residual jet around the device ≤ 5mm at the 2-month visit documented by transesophageal echocardiogram (TOE). Subjects who are implanted with the AMPLATZER LAA Occluder and in whom device closure is assessed will be included in this analysis.

Procedure duration:

Procedure duration will be summarized using descriptive statistics including mean, standard deviation, median and range. Procedure duration is defined as the time from the device delivery/device sheath is inserted into the vasculature until delivery sheath removed. Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder, or have been retrospectively enrolled will be included in this analysis.

Procedure success:

The count and proportion of subjects with a successful implant will be summarized. A successful implant procedure is defined as implantation of the AMPLATZER LAA Occluder during the procedure with no serious adverse device effect prior to hospital discharge. Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder will be included in this analysis.

Technical success:

The count and proportion of subjects with a successful implant will be summarized. Technical success is defined as delivery and release of the AMPLATZER LAA Occluder. Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder (introduction of the delivery/device sheath into the vasculature) will be included in this analysis.

[redacted]

Device Thrombosis:

The count and proportion of subjects with a device thrombus will be summarized. Subjects implanted with an AMPLATZER LAA Occluder will be included in this analysis.

Transient Ischemic Attack:

Kaplan-Meier analysis will be used to estimate the rate of transient ischemic attack (TIA). Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder, or have been retrospectively enrolled will be included in this analysis.

All Cause Death:

Kaplan-Meier analysis will be used to estimate the rate of death. Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder, or have been retrospectively enrolled will be included in this analysis.

Major Bleeding:

Kaplan-Meier analysis will be used to estimate the rate of major bleeding events. Major bleeding is defined as Type 3 or greater based on BARC. Subjects who are attempted to be implanted with the AMPLATZER LAA Occluder, or have been retrospectively enrolled will be included in this analysis.

Reporting:

The following data will be summarized and reported annually to Health Canada.

- Investigator sites and enrollment status
- Demographic and baseline characteristics
- Serious Adverse Events
- Procedural results (procedure success, implanted device size, procedure duration)
- Device closure rates
- Oral anticoagulant use

14.4 Compromising Factors

This is an observational post approval study evaluating real-world outcomes in subjects undergoing implant with an AMPLATZER LAA Occluder. The study endpoints and analysis populations will appropriately characterize safety of the procedure and long-term effectiveness of the device. There are no known or foreseeable factors that may compromise the outcome of the clinical investigation or the interpretation of results.

15. Document Retention

After the termination of the study, the principal investigator will maintain all clinical study documents on file at the site for the minimum number of years required per local laws, or 2 years following study completion, whichever is longer duration.

16. Amendments to the Clinical Protocol

Study related documents such as, protocol, eCRFs (

Appendix F: Case Report Forms) informed consent form (**Appendix E**: Sample Informed Consent) and other subject information, or other clinical study documents will be amended as needed throughout the clinical study, and a justification statement will be included with each amended section of a document. Proposed amendments to the protocol will be agreed upon between the Sponsor and the coordinating investigator (if applicable).

The protocol, the subject's informed consent form and amendment notification will be submitted for review and approval by the local IRB/EC and regulatory authorities (as applicable). The version number and date of amendments will be documented (**Appendix B**: Protocol Revision History).

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment. Any amendment affecting the subject requires that the subject be informed of the changes, and a new consent be signed and dated at the subject's next follow up.

17. Outsourcing of Sponsor Duties and Functions

The Sponsor does not anticipate transferring any duties and functions related to the clinical study, including monitoring, to an external organization (such as a contract research organization or individual contractor). If outsourcing does occur, the ultimate responsibility for the quality and integrity of the clinical study will reside with the Sponsor. All requirements applying to the Sponsor will also apply to the external organization inasmuch as this organization assumes the clinical study related duties and functions of the Sponsor.

18. Investigation Suspension or Termination

18.1 Premature Termination

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.

Possible reasons for early termination of the study by the Sponsor, either at local, national or international level, may include, but are not limited to:

- Sponsor's decision
- Request from regulatory authorities
- Request of EC(s)
- Concern for subject safety and welfare
- Failure to secure subject informed consent prior to any protocol activity
- Failure to report unanticipated adverse device effects within 72 hours to SJM and the EC
- Repeated non-compliance with this clinical protocol or the clinical trial agreement
- Inability to successfully implement this clinical protocol
- Violation of the Declaration of Helsinki (refer to **Appendix C**)
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles

In such events, the study will be terminated according to applicable regulations. The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor. Should either of these events occur, the investigator should provide a written statement as to why the premature termination has taken place, and notify the EC and/or the CA (if applicable). Follow-up for all enrolled subjects will be per center standard of care.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

18.2 Study Conclusion

The study will be concluded when:

- All sites are closed AND
- The final report generated by Abbott has been provided to sites or Abbott has provided formal documentation of study closure

19. Publication Policy

The results of the clinical study are planned to be submitted for publication. If a principal investigator will be involved in publishing the data, a publication agreement will be signed between the PI and Sponsor either as a separate publication agreement or within the clinical trial agreement.

The investigator or site may not publish any information that the Sponsor believes to be confidential information. The publication of the initial results of the AMPLATZER LAA Occluder Post Approval Study shall be subject to review and release of the Sponsor's publication committee, which shall confer with the site regarding such publication.

Publication guidelines will be followed according to the International Committee of Medical Journal Editors (ICMJE). This study will also be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

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34. Figure 17 from Sponsor's Executive Summary/ Circulatory System Devices Panel Meeting: 2014 Boston Scientific WATCHMAN™ Left Atrial Appendage Closure Technology for Patients with Non-Valvular Atrial Fibrillation.

Appendix A: Abbreviations

Abbreviation	Term
ACP	Amplatzer Cardiac Plug
AE	Adverse Event
AF	Atrial Fibrillation
AP	Asia-Pacific
ANZ	Australia-New Zealand
CA	Competent Authority
CE	Conformité Européenne
CEC	Clinical Events Committee
CP	Clinical Protocol
CRF	Case Report Form
CNS	Central Nervous System
CT	Computed Tomography
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
EP	Electrophysiologist
IB	Investigator's Brochure
IC	Interventional Cardiologist
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions For Use
INR	International Normalized Ratio
ISO	International Organization for Standardization
LAA	Left Atrial Appendage
LAAO	Left Atrial Appendage Occlusion
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NCA	National Competent Authority
NVAF	Non-Valvular Atrial Fibrillation
OAC	Oral Anticoagulant
PI	Principal Investigator
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical, Inc.
TIA	Transient Ischemic Attack
TOE	Transoesophageal Echocardiography
WMA	World Medical Association

Appendix B: Protocol Revision History

[redacted]

Appendix C: Declaration of Helsinki

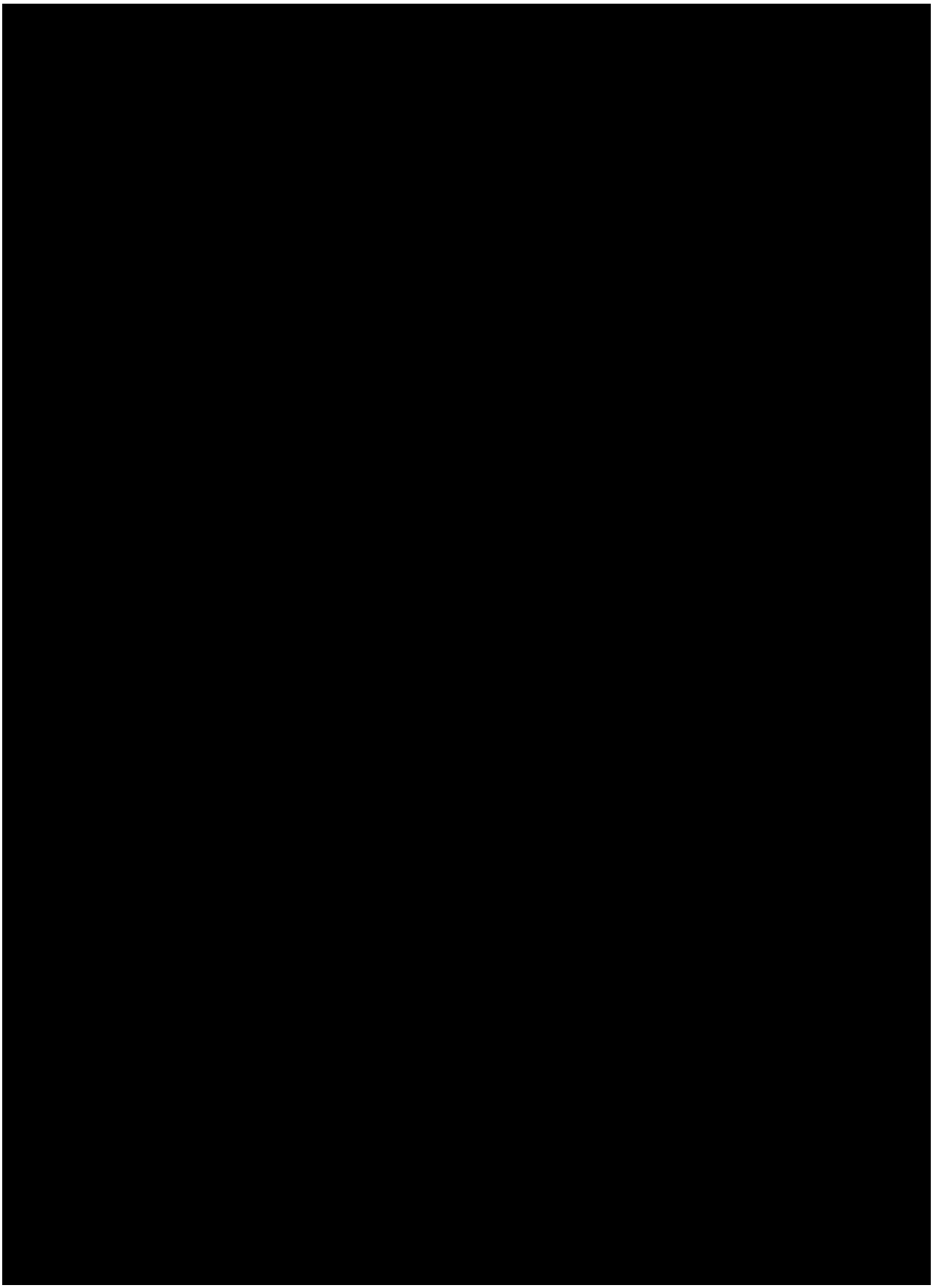
The 2013 version of the Declaration of Helsinki is available at: http://www.wma.net/en/20activities/10ethics/10helsinki/. Please check the website during the course of the study for updated revisions.

Appendix D: List of Clinical Investigation Sites and Ethics Committees

[redacted]

Appendix E: Sample Informed Consent

[redacted]



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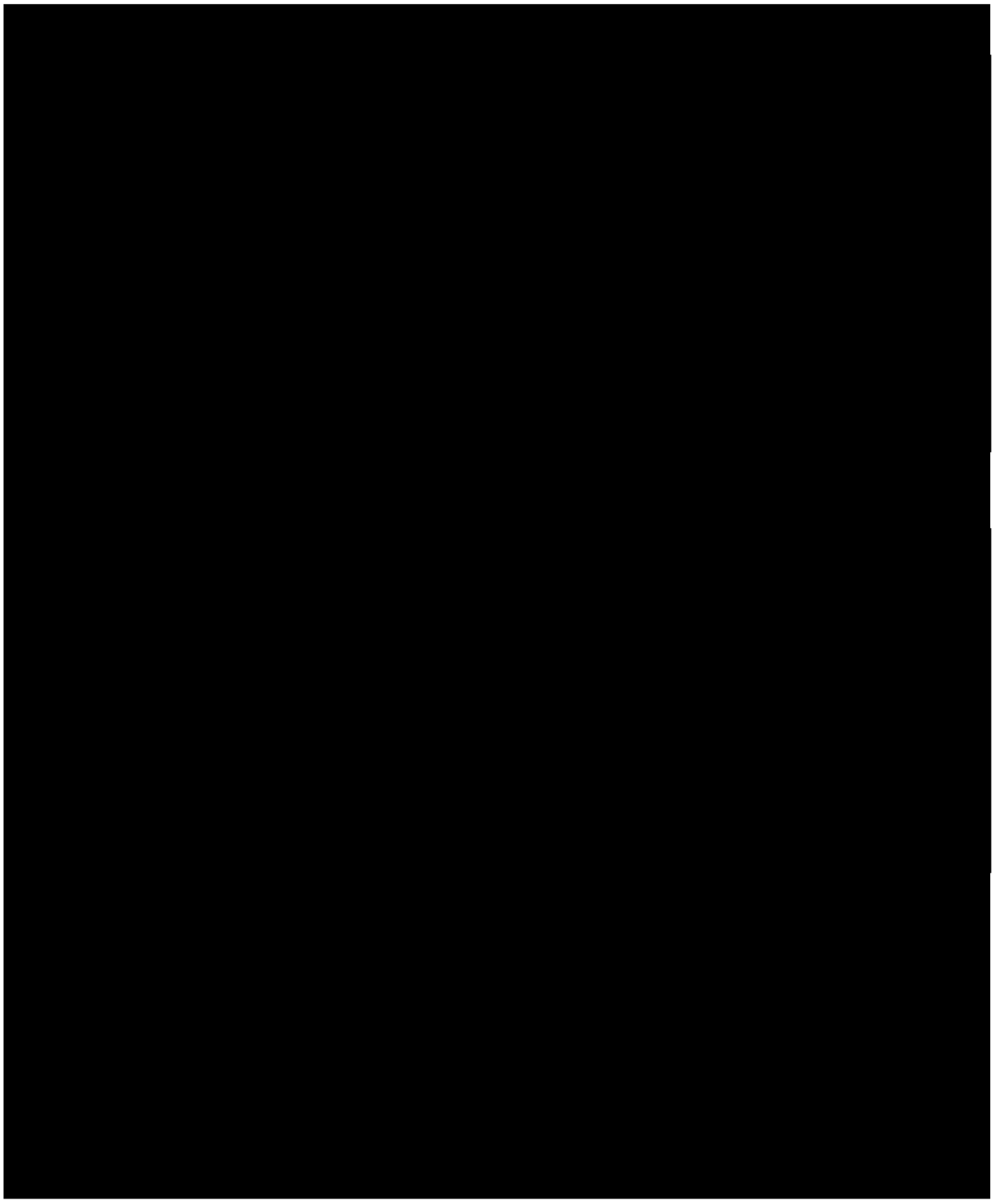

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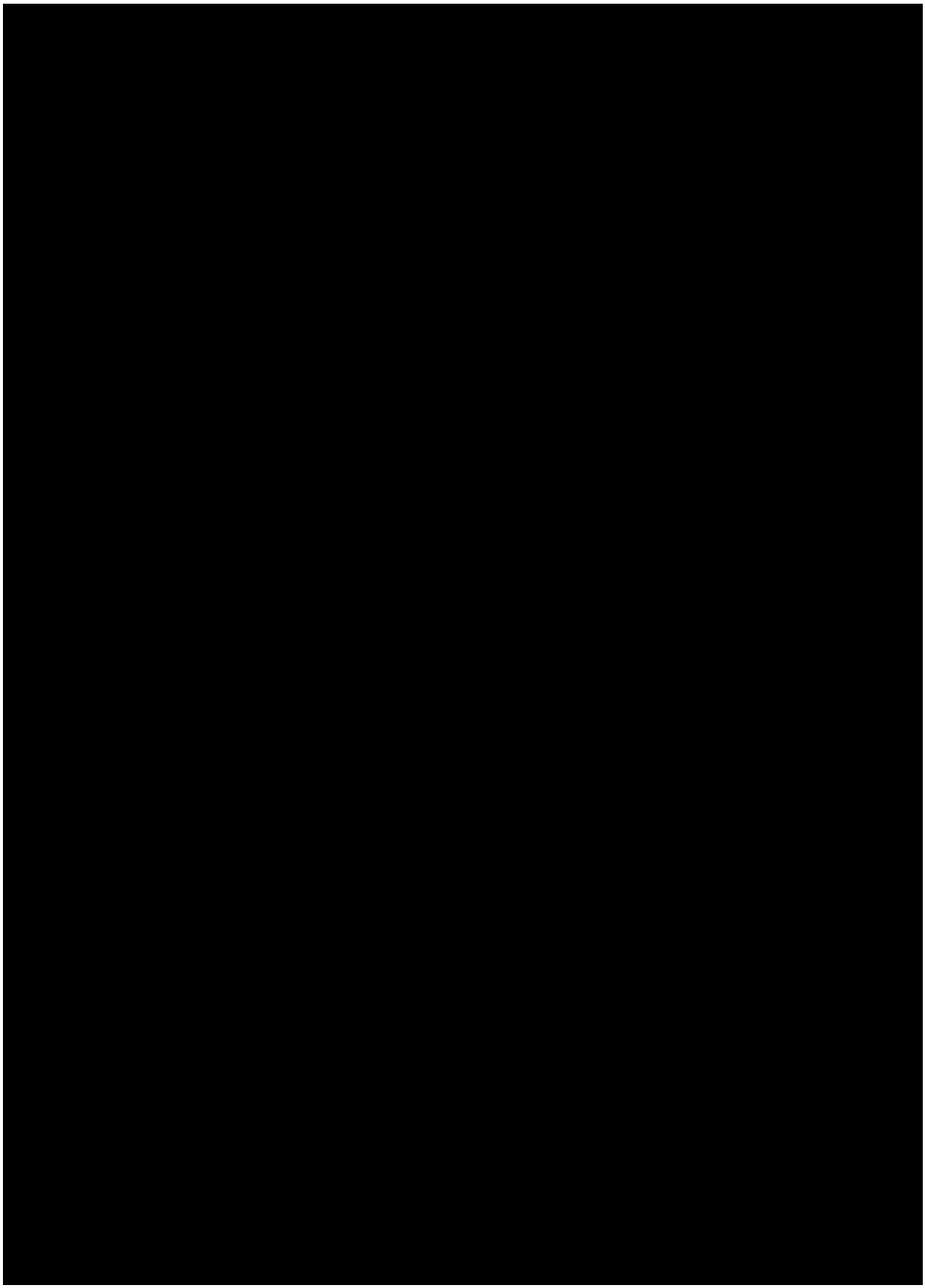

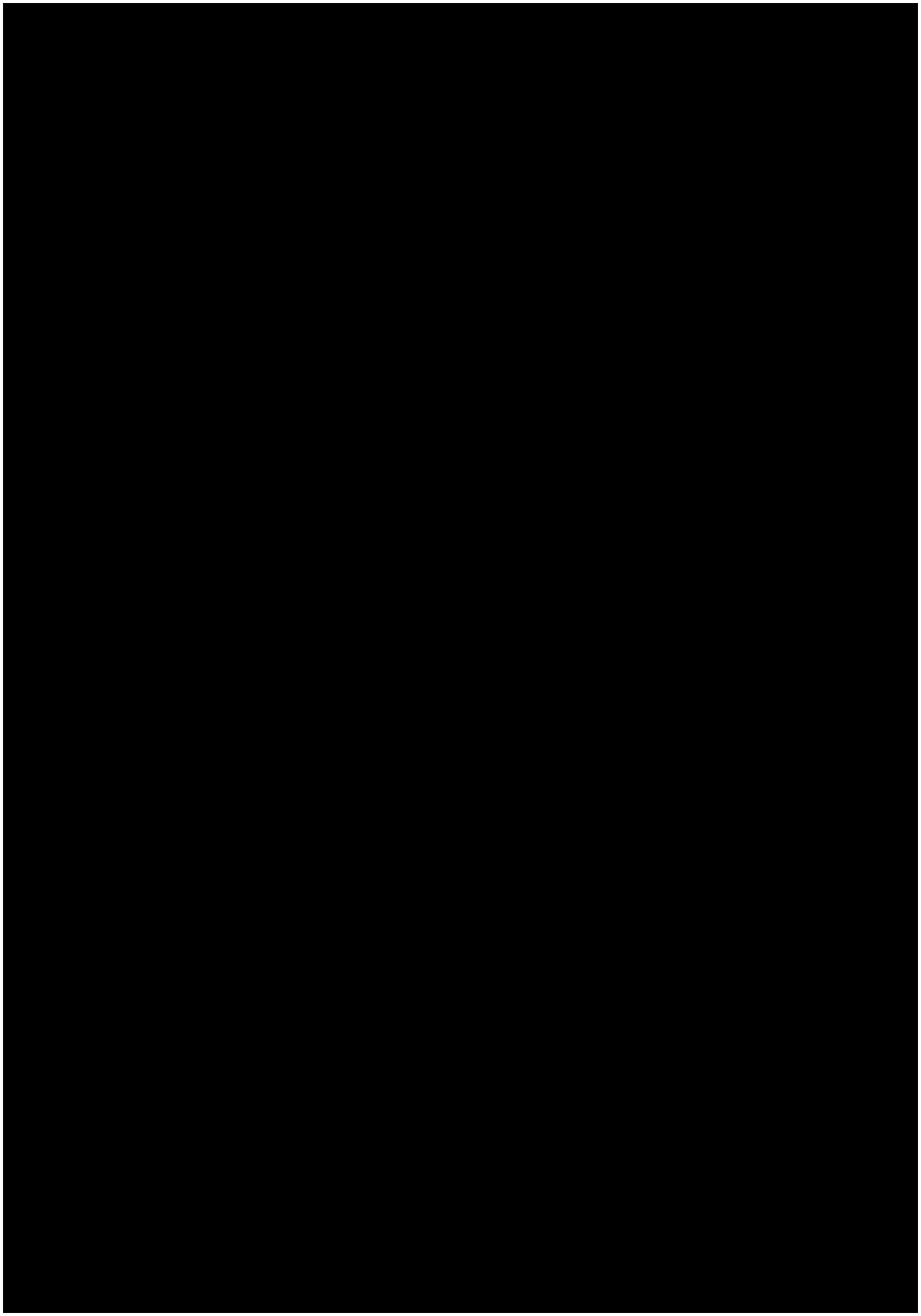

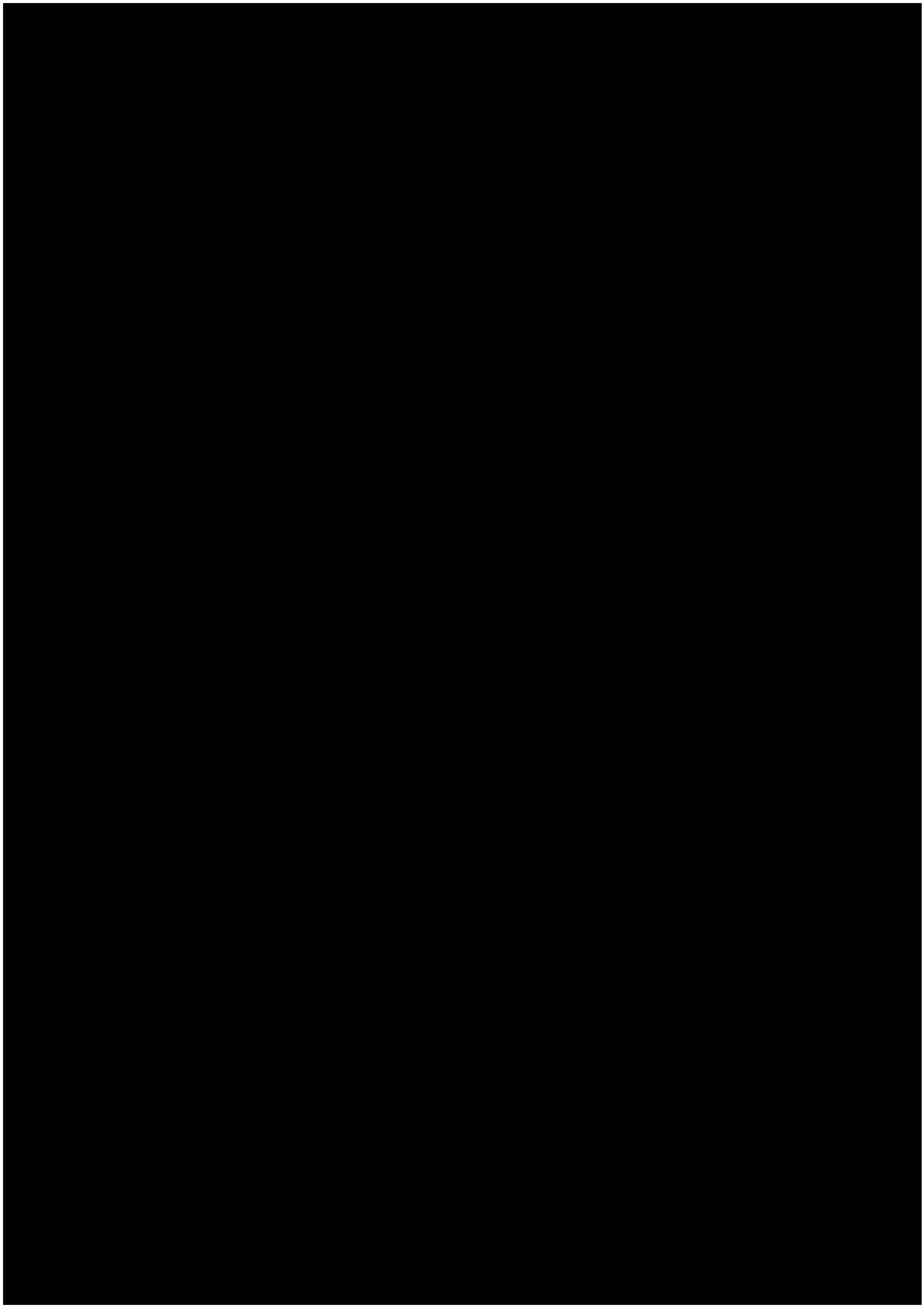

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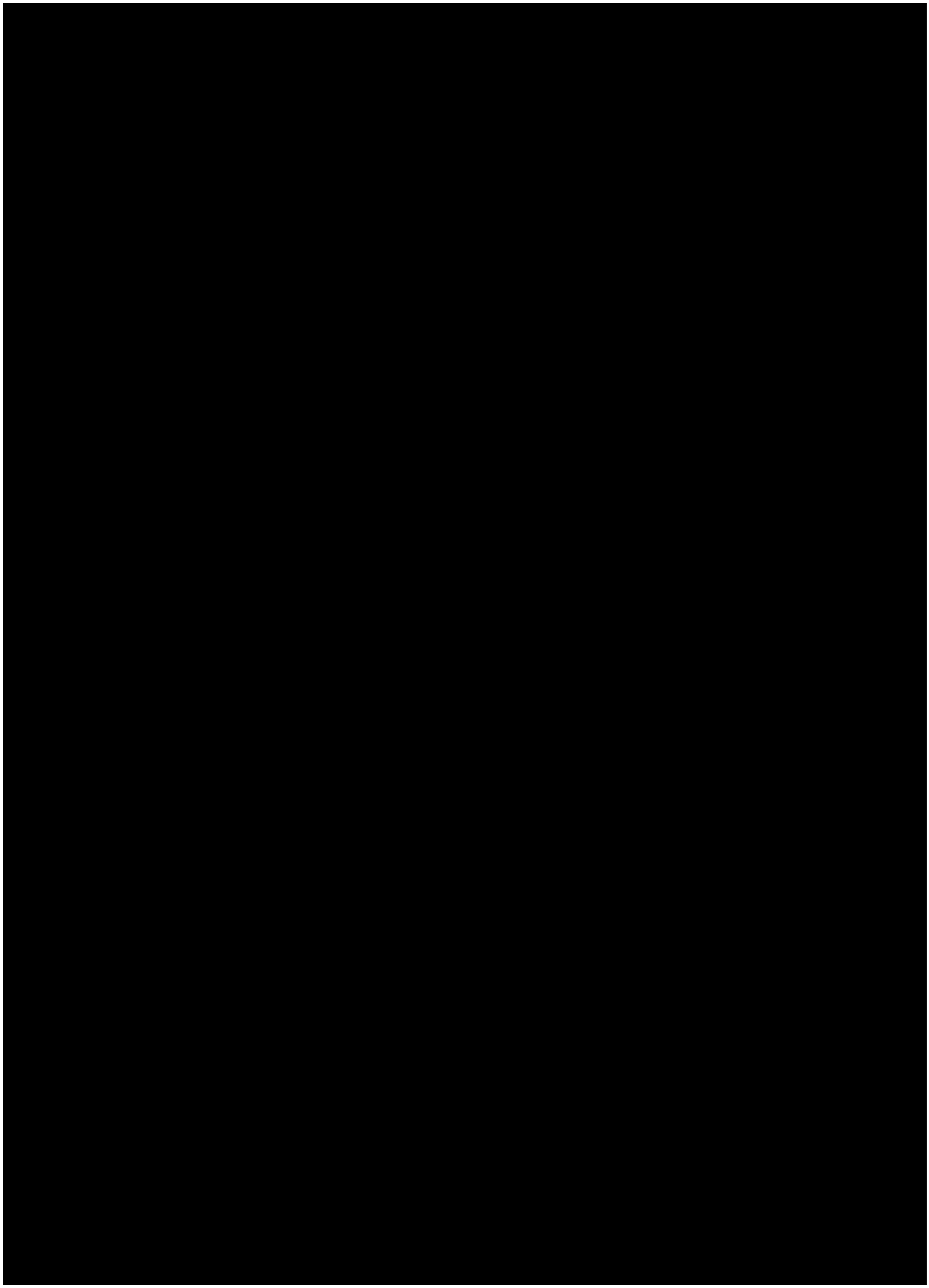

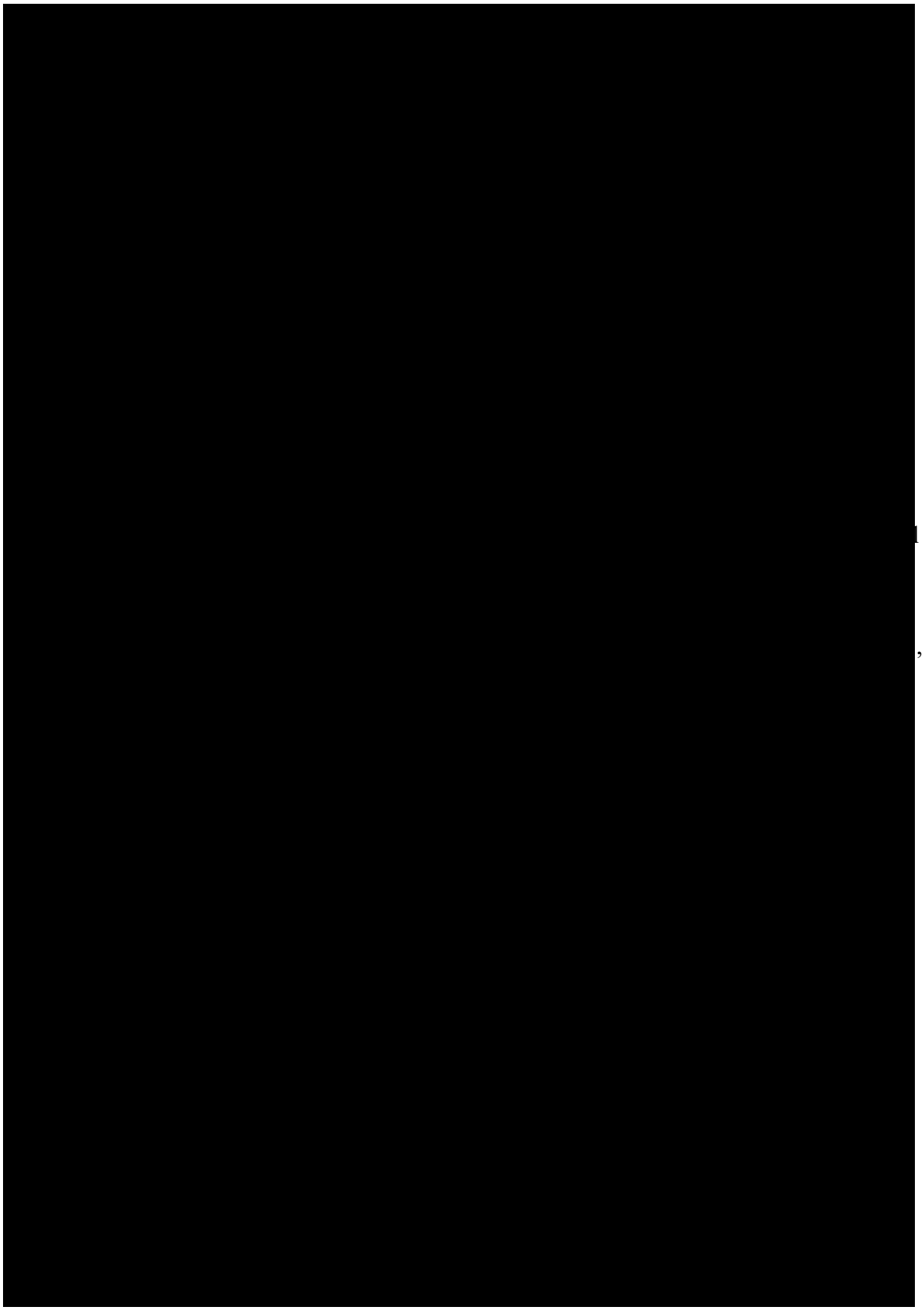

Appendix F: Case Report Forms

[redacted]

Appendix G: Modified Rankin Scale (mRS)

Subject Identifier: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0-6): _____

Comments:

_____

_____

_____

_____

Appendix H: Major Bleed classification/definition

***Bleeding**
Classified as Type 0 – 5 according to the following BARC definitions[36]:

Type 0: No bleeding

Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional

Type 2 (minor): Any overt, actionable sign of hemorrhage (e.g. more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation

Type 3 (major):
Type 3a:

- Any transfusion with overt bleeding
- Overt bleeding plus a hemoglobin drop of ≥ 3 to < 5 g/dL (provided hemoglobin drop is related to bleeding)

Type 3b:

- Overt bleeding plus hemoglobin drop ≥ 5 g/dL (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/ hemorrhoid)
- Bleeding requiring intravenous vasoactive drugs

Type 3c:

- Intracranial hemorrhage including subdural hemorrhages (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: Coronary artery bypass graft (CABG)–related bleeding:

- Perioperative intracranial bleeding within 48 hours
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥ 5 units whole blood or packed red blood cells within a 48-hour period (only allogenic transfusions are considered transfusions for CABG-related bleeds)
- Chest tube output ≥ 2 L within a 24-hour period

Notes: If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will not be classified as a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (i.e. within a 48-hour timeframe) but does not meet type 4 severity criteria, it will not be classified as a bleeding event.

Type 5: Fatal bleeding
Fatal bleeding is bleeding that directly causes death with no other explainable cause.

BARC fatal bleeding is categorized as either definite or probable as follows:

Type 5a:
Probably fatal bleeding: bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging

Type 5b:
Definite fatal bleeding: bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc.] or imaging) or confirmed on autopsy

The site of fatal bleeding is specified as intracranial, gastrointestinal, retroperitoneal, pulmonary, pericardial, genitourinary, or other.

Bleeding Academic Research Consortium (BARC) indicates fatal bleeding is meant to capture deaths that are directly due to bleeding with no other cause. The time interval from the bleeding event to the death should be considered with respect to likely causality, but there is no specific time limit proposed. Bleeding that is contributory but not directly causal to death is not classified as fatal bleeding but may be categorized as other forms of bleeding. Bleeding that leads to cessation of antithrombotic or other therapies may be contributory but again would not be classified as fatal bleeding.

Appendix I: Cardiovascular Mortality Definition

Cardiovascular Mortality	▪ Death resulting from an acute myocardial infarction (MI), sudden cardiac death, death due to heart failure (HF), death due to stroke, death due to cardiovascular (CV) procedures, death due to CV hemorrhage, and death due to other CV causes.

Appendix J: Definitions of Potential Adverse Event

- **Air Embolus** – symptomatic event resulting from the introduction of air into the circulatory system
- **Allergic reaction** – idiosyncratic reaction to the device implanted or to nickel
- **Anesthesia reaction** – undesired reaction to anesthetic agent
- **Arrhythmia** – cardiac rhythm disturbance
- **Bleeding** –see **Appendix I**
- **Cardiac arrest** – failure of the heart to contract
- **Cardiac tamponade** – constriction of the heart causing inefficient contraction resulting from accumulation of excess fluid in the pericardium
- **Death** – permanent cessation of all vital bodily functions
- **Device embolization** – movement of the device from its intended location
- **Device migration** – movement of the device within its intended location
- **Embolic event** – acute vascular insufficiency or occlusion of the extremities or any non-central nervous system organ associated with clinical, imaging, surgical/autopsy evidence of arterial occlusion in the absence of other likely mechanism (e.g., trauma, atherosclerosis, or instrumentation). When there is presence of prior peripheral artery disease, angiographic or surgical or autopsy evidence is required to show abrupt arterial occlusion
- **Fever** – defined as a body temperature > 37.5 or 38.3 °C (99.5 or 100.9 °F)
- **Foreign body embolization** – movement of device material, delivery system material, or other material from its intended location
- **Hypotension** – sustained systolic blood pressure < 90 mmHg
- **Hypertension** – systolic blood pressure of > 160 mmHg
- **Infection** – invasion and growth of a pathogenic organism within the body
- **Multi-Organ Failure –** the failure of two or more systems, such as the cardiovascular and renal systems, and is a common consequence of sepsis (the presence of bacteria in the blood) and of shock (very low blood pressure)
- **Myocardial infarction (heart attack)** – the death of heart muscle from the sudden blockage of a coronary artery by a blood clot
- **Perforation** – physical penetration of a vessel or the myocardium
- **Pericardial effusion** – abnormal fluid collection around the heart without hemodynamic compromise
- **Renal failure/dysfunction** – inability of kidneys to perform normal functions
- **Respiratory failure** – inability of the lungs to perform normal functions
- **Seizure** – uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances, or a combination of symptoms
- **Significant Residual Flow –** flow > 3 mm jet into the LAA
- **Stroke** – an acute episode (lasting > 24 hours) of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Strokes are characterized as follows[35]:
    - **Ischemic Stroke**: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

  - **Hemorrhagic Stroke**: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
  - **Undetermined Stroke**: an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as ischemic or hemorrhagic stroke
- **Thrombus Formation** – a blood clot
- **Transient Ischemic Attack** (TIA)– a transient episode (lasting ≤ 24 hours) of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, *without* acute infarction on brain imaging
- **Valvular regurgitation/insufficiency** – backflow of blood during contraction of the heart; caused by a defective heart valve
- **Vascular access site injury** – damage at vascular access site (e.g., AV fistula, hematoma, and aneurysm)
- **Vessel Trauma/Injury** – traumatic injuries that damage an artery or vein