WEAVE™ Trial

Wingspan® StEnt System Post MArket SurVEillance Study

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Study Centers:	Up to 50 (US and International)
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Investigator's Signature Page

STUDY TITLE: WEAVE™ Trial: Wingspan® Stent System Post Market Surveillance Study

STUDY CENTER: _____

(Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

Principal Investigator	Date
Print name:	
Co Principal Investigator (if applicable)	Date
Print name:	
Co Principal Investigator (if applicable)	Date
Print name:	

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Protocol Synopsis

WEAVE™ Trial

Wingspan® StEnt System Post MArket SurVEillance Study

Study Objective	
Primary Objective	The primary objective of this study is to evaluate the rate of stroke and death in patients treated with the Wingspan Stent System, according to the Indications for Use, within 72 hours post procedure.
Study Device	The Wingspan Stent System includes: • A self-expanding, nitinol stent with four radiopaque markerbands on each end (distal and proximal). • A flexible over-the-wire stent delivery system (Inner Body and Outer Body) with pre-loaded stent. • The Wingspan Stent System is intended to be used in conjunction with the Gateway® PTA Balloon Catheter.
Device Sizes	Wingspan Stent Sizes: Diameters: 2.5, 3.0, 3.5, 4.0, 4.5 mm Lengths: 9, 15, 20 mm
Study Design	
Study Design	Prospective, single-arm, consecutive enrollment, post market surveillance study
Planned Number of Patients	Approximately 389 patients will be required to obtain 350 patients eligible for the primary analysis. Enrollment rate is expected to be between 75 and 250 patients per year.
Planned Number of Sites	Maximum number of US or International sites: 50 sites Minimum number of Total US or International sites: 30 sites Minimum number of US sites: 25 sites
Primary Endpoint	Stroke or Death within 72 hours of the procedure
Secondary Endpoints	• Hemorrhagic stroke within 72 hours post procedure • Ischemic stroke within72 hours post procedure • Neurological death within 72 hours post procedure • Stroke recovery at 90 days post procedure • Stroke in the territory of the stented artery within 72 hours post procedure
Follow-Up Schedule	All patients treated with a stent will be assessed at 72 hours post procedure.

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	Any patient treated with a stent who experiences a stroke within 72 hours post procedure will be required to complete a Day 30 telephone assessment and a Day 90 clinic visit.
Required Medication Therapy	Standard of care for procedure and pre/post operative medication management is to be followed. Specific care and attention must be given to achieve therapeutic levels of antiplatelet and anticoagulation prior to the procedure without inadvertently subjecting the patient to an increased risk of intracerebral hemorrhage.
Key Inclusion / Exclusion Criteria	All patients who have a Wingspan stent procedure attempted will be considered enrolled in the study.
Statistical Methods	
Primary Statistical Hypothesis	The study aims to evaluate the event rates in the stent group with regard to the study endpoints based on the data collected. The study will use data available from eligible patients to provide reasonable precision in the event rate estimation.
Statistical Test Method	All patients who have a Wingspan Stent implanted in accordance with the Indications for Use will be considered evaluable and analyzed as the primary analysis group (Per Protocol cohort (PP)). Descriptive statistical analyses will be used for the primary endpoint. Logistic regression models will be used to determine if there is a relationship between the 72 hour post procedure stroke or death rate and baseline factors. Periodic interim analyses will be performed to assess the stroke and death rate within 72 hours among patients implanted with the Wingspan stent. Study reports will be submitted to the FDA every six months for the first two years and annually thereafter. The reports will include U.S. and international sales figures for each six or twelve month period related to the reports. Interim analyses for the purpose of stopping this study early will be performed after 150, 225, and 300 primary analysis group (Per Protocol Cohort (PP)) subjects have been enrolled and have completed their 72-hour post procedure follow-up. If at an interim analysis, there is at least a 95% predictive probability of observing no more than 23 events among 350 PP subjects, this trial will stop early for statistical success. Alternatively, if at those times the entire two-sided 95% exact confidence interval of the 72 hour death or stroke rate is above the 9.7% rate specified in the protocol, then the study will be stopped early for safety.
Sample Size Parameters	The 72 hour stroke and death rate is expected to be approximately 6.6%. Using the Clopper-Pearson exact method with a 95% CI as (0.042, 0.097), with a width of 0.055 (±0.0275), 350 evaluable patients will be required. Enrollment of 389 patients is planned for an adequate sample size in the Per Protocol analysis group allowing for a 10% attrition rate.

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Table of Contents

STRYKER CONFIDENTIAL - THIS DOCUMENT CONTAINS CONFIDENTIAL AND PROPRIETARY INFORMATION THAT IS THE PROPERTY OF STRYKER CORPORATION. NEITHER THIS DOCUMENT NOR THE INFORMATION HEREIN MAY BE REPRODUCED, USED, OR DISCLOSED TO ANY THIRD PARTY WITHOUT THE PRIOR WRITTEN CONSENT OF STRYKER CORPORATION.

List of Tables

List of Figures

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1 Background and Purpose

The Wingspan® Stent System with Gateway® Percutaneous Transluminal Angioplasty (PTA) Balloon Catheter was approved in the United States (US) under a Humanitarian Device Exemption (HDE) and received CE Mark in 2005.

This study is being conducted to fulfill Food and Drug Administration (FDA) post market safety surveillance requirements.

2 Device Description

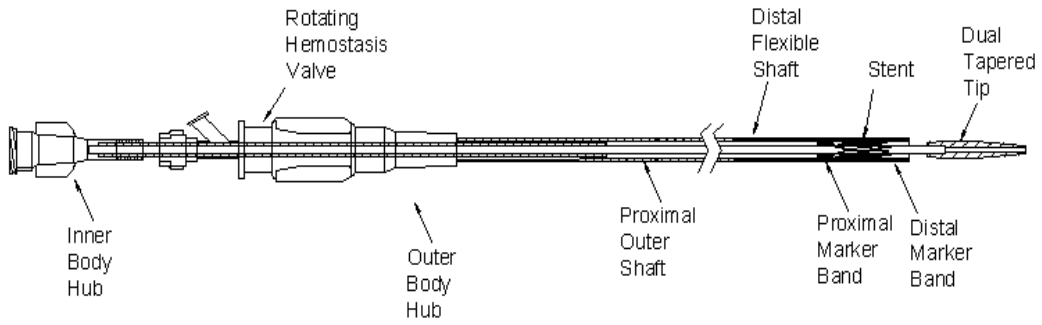
2.1 Overview

The Wingspan Stent System is a self-expanding, Nitinol stent and delivery system intended for use in the treatment of intracranial atherosclerotic disease. The Gateway PTA Balloon Catheter is an over-the-wire balloon catheter used to pre-dilate the lesion prior to insertion and deployment of the Wingspan Stent System.

The Wingspan Stent System includes:

- A self-expanding, Nitinol stent with four radiopaque markerbands on each end (distal and proximal).
- A flexible over-the-wire stent delivery system (Inner Body and Outer Body) with pre-loaded stent.
- The Wingspan Stent System is intended to be used in conjunction with the Gateway PTA Balloon Catheter.

Wingspan Stent System



2.2 Indication for Use

The Wingspan® Stent System with Gateway® PTA Balloon Catheter is Authorized by Federal law for use in improving cerebral artery lumen diameter in patients 22 to 80 years old with recurrent (2 or more) strokes refractory to a comprehensive regimen of medical therapy and due to atherosclerotic disease of intracranial vessels with 70-99% stenosis that are accessible to the system. The most recent stroke must have occurred more than 7 days prior to

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treatment with the Wingspan Stent System. Patients are eligible for treatment with the Wingspan Stent System if their modified Rankin Scale score is 3 or less at the time of treatment.

The Gateway PTA Balloon Catheter is indicated for balloon dilation of the stenotic portion of intracranial arteries prior to stenting for the purpose of improving intracranial perfusion.

The Wingspan Stent System is contraindicated for the following:

- Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
- Lesions that are highly calcified or otherwise could prevent access or appropriate expansion of the stent
- For the treatment of stroke within 7 days or less from the onset of symptoms
- For the treatment of transient ischemic attacks

3 Study Design

3.1 Overview

This is a prospective, single-arm, study of the Wingspan® Stent System and Gateway® PTA Balloon Catheter. Enrollment of approximately 389 patients at a maximum of 50 sites (US or International) is planned. Subject enrollment may stop early for statistical success or safety after 150, 225, and 300 primary analysis group subjects have been enrolled and have completed their 72-hour post procedure follow-up. Enrollment rate is expected to be between 75 and 250 patients per year.

3.2 Study Objective

3.2.1 Primary Objective

The primary objective is to evaluate the rate of stroke and death within 72 hours in patients treated with the Wingspan Stent System in accordance with the Indications for Use.

- Ischemic stroke is defined as a neurological deficit that is thought to have an ischemic cause and is detectable on examination at least 24 hours after onset of symptoms.
- Hemorrhagic stroke is defined as a symptomatic intracerebral, subarachnoid, or primary intraventricular hemorrhage. To be considered a hemorrhagic stroke, the patient must experience new symptoms (e.g., new severe headache) that last for at least 24 hours (symptoms do not need to be associated with a new neurological deficit).
- Stroke type (ischemic or hemorrhagic) must be confirmed by imaging.

3.2.2 Secondary Objectives

The secondary objectives are:

1. To determine the following for any stented patient experiencing a stroke within 72 hours following the procedure.
   - Required interventions
   - Type of stroke (ischemic or hemorrhagic)
   - Timing of event resolution

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2. To determine the cause of death for any stented patient that dies within 72 hours following the procedure.
3. To determine if there is a relationship between the post procedure stroke or death rate within 72 hours and baseline factors including but not limited to the following:
    - Level of operator experience at the time of treating their first study patient
    - Baseline characteristics (demographics and clinical characteristics)
    - Procedural characteristics
    - Post procedure patient management
    - Operator specialty

3.3 Study Endpoints

3.3.1 Primary Endpoint

The primary endpoint is the rate of stroke or death within 72 hours of the procedure.

3.3.2 Secondary Endpoints

Secondary endpoints include the following:

- Hemorrhagic stroke within 72 hours post procedure
- Ischemic stroke within 72 hours post procedure
- Neurological death within 72 hours post procedure
- Stroke recovery at 90 days post procedure
- Stroke in the territory of the stented artery within 72 hours post procedure

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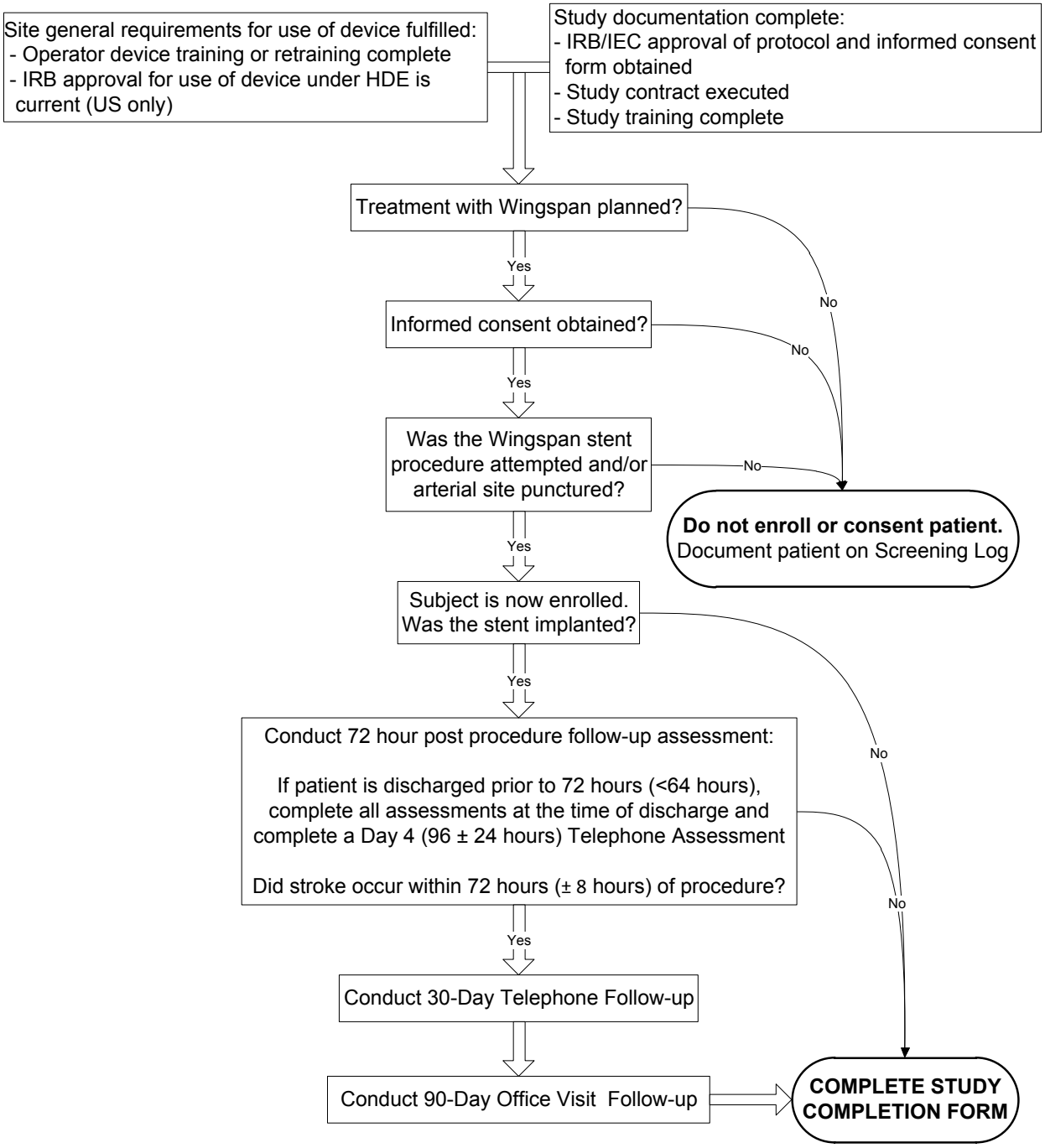
Figure 1. Schematic of Study Design



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4 Study Population

4.1 Selection Criteria

All patients for whom treatment with the Wingspan Stent System is considered are eligible for enrollment in the study.

4.2 Withdrawal and Replacement of Patients

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn patients will not undergo any additional follow-up, nor will they be replaced.

5 Study Procedures

The schedule of required observations and assessments are summarized in Tables 1 and 2 below.

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Table 1. Study Event Schedule

Assessment	Baseline	Procedure	Day 3 Office[1] Visit (72 ± 8 hours from procedure) (or at Discharge whichever comes first)	Day 4 Telephone Assessment[2] (96 ± 24 hours from procedure) (see footnote below)
Pre-Treatment (Informed Consent)	X			
Demographics	X			
Medical History	X			
Qualifying Events	X			
Neurological Exam	X		X	
Vital signs	X			
Target Lesion Assessment	X	X		
Medications	X	X	X	X
NIHSS	X			
Modified Rankin Scale (mRS)	X		X	X
Procedure		X		
Balloon Use		X		
Stent Use		X		
Adverse Events (AE)[3]		X	X	
Stroke Symptom Assessment				X

NIHSS: National Institutes of Health Stroke Scale

1. For patients who complete the 64 to 80 hour Office Visit (72 ± 8 hours), the Day 4 Telephone Assessment is *not required.*
2. The Day 4 Telephone Assessment is required for any patient discharged prior to 64 hours post procedure.
3. Only Neurological AEs, Bleeding/Hemorrhagic AEs (including non-neurological events), groin puncture AEs and AEs that resulted in death experienced by the study subject after enrollment are required to be recorded in the CRF.

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5.1 Written Informed Consent

Written Informed Consent must be obtained for all patients. Patients will be asked to sign the Informed Consent form before any study-specific tests or procedures are performed. The Informed Consent form is study-specific and must be approved by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

All patients who sign an informed consent form and have a stenting procedure attempted will be considered enrolled in the study at the time of arterial puncture. A Screening/Enrollment Log will be maintained to document selection information about candidates for whom treatment with the device is planned.

5.2 Baseline

The following Baseline data must be collected within 2 weeks prior to the index procedure (unless otherwise specified) for all patients and documented in the case report form (CRF):

- Demographics and medical history
- Medications

  Physicians will be required to assess and document failed attempts to achieve a comprehensive regimen of medical therapy and risk factor management.

  Only antiplatelets, anticoagulants, and medications or supplements taken to control blood pressure, lipids, or glucose will be documented in the CRF.
- Vital signs
- Neurological exam
- National Institutes of Health Stroke Scale (NIHSS) score
- Modified Rankin Scale score
- Target lesion characteristics (including imaging findings associated with the lesion).

In addition, information for an alternate contact person(s) will be requested from the patient during the consent process to facilitate patient follow up if discharged prior to 64 hours post procedure. This information will be provided to the Independent Study Neurologist to enable follow up of any patient discharged prior to 64 hours post procedure. Additional details on post procedure follow-up can be found in Section 5.4.

5.3 Procedure

The following procedural data must be collected for all patients and documented on the CRF:

- Name of primary operator
- Target lesion characteristics
- Specific devices used
- Procedure start time: Time of access site puncture
- Procedure end time: Time guide catheter removed from access site

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- Medications (including pre-operative medication)

  All medications administered in conjunction with the procedure will be documented.

Specific medications used for the stenting procedure (including pre-procedure antiplatelets, anesthesia, etc.) and post operative management will be determined by the standard of care for patients undergoing neurointerventional procedures at each institution. Specific care and attention must be given to achieve therapeutic levels of antiplatelet and anticoagulation prior to the procedure without inadvertently subjecting the patient to an increased risk of intracerebral hemorrhage.

For sites that conduct platelet-resistance testing as a pre-operative standard of care, details on specific testing and results will be documented.

- Activated Clotting Time
- Adverse events
- Device malfunctions

5.4 Post Procedure Follow Up

5.4.1 72 hours Post Procedure

The following assessments will be performed on all patients with a stent at 72 hours (± 8 hours) post procedure or at the time of discharge, whichever comes first:

- Neurological exam
- Modified Rankin Scale
- Medications

All medications administered from procedure end to 72 hours or discharge will be recorded. Specific medications for subsequent management of risk factors will be at the discretion of the treating physician and will be recorded.

- Adverse events

The subject may be discharged from the hospital when clinically stable, at the Investigator's discretion. If a patient who received a stent is discharged before 64 hours post procedure, the study site must immediately notify the Independent Stroke Neurologist (ISN) by email of the need to contact the patient for additional telephone follow-up on Day 4 (see 5.4.2). Details of the patient's discharge assessment including neurological exam, modified Rankin Scale and medications must also be provided to the ISN.

The designated staff at the clinical site will review the study requirements with the subject to maximize compliance with the follow-up schedule and any prescribed medications. **It is imperative that patients understand the need to complete the post procedure telephone contact if discharged early.**

Patients who are enrolled but do not receive a stent will not be required to have study follow up assessments.

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5.4.2 Day 4 Post Procedure

Patients who receive a stent and are discharged prior to 64 hours post procedure will be contacted by the ISN on Day 4 (96 ± 24 hours post procedure) by telephone to ensure that any potential strokes that occurred post discharge are systematically identified and documented. The following assessments will be conducted.

- Stroke symptom assessment
- Modified Rankin Scale
- Medications

  All medications the patient has taken since discharge will be assessed and recorded.

If the patient has experienced any new or worsening symptoms or there is a worsening of the modified Rankin score since discharge, the study site will be notified by the ISN and the patient will be instructed to contact the study site immediately for follow-up. If the study site determines that the patient experienced a stroke within 72 hours of the procedure, the patient must be followed for an additional 90 days per Table 2 below.

If a patient or alternative contact are unable be contacted on Day 4, the ISN will make two additional attempts to contact the patient and/or alternate contact up to 90 days. Attempts to contact the patient should be documented.

The completed Telephone Assessment Form and/or documentation of attempts to contact the patient will be provided to the study site. The ISN or the study site will perform entry of the data into the CRF and the site will retain documentation with the study files.

5.5 Post Stroke Follow-Up

Patients who receive a stent and have a stroke within 72 hours post procedure will be followed for 90 days to assess functional outcomes per Table 2 below. If a patient has had a stroke within 72 hours and was treated at an outside facility, every attempt should be made to obtain medical records and information on the etiology and treatment of the stroke. Post stroke follow up assessments are not required as part of the study protocol for patients who have a stroke within 72 hours but did not receive a stent.

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Table 2. Study Event Schedule for Patients who experience stroke within 72 hours1

Assessment	Stroke onset	Day 30 (±7) (Telephone)	Day 90 (±7) (Office)
NIHSS	X		X
Imaging[2]	X		
Stroke management[3]	X		
Modified Rankin Scale	X	X	X
Medications		X	X
Adverse Events[4]		X	X

1 Only required for patients who had a stent implanted
2 Required for any stroke that occurs within 72 hours post procedure to determine whether stroke was ischemic or hemorrhagic.
3 Documentation of interventions and treatment (including medications, devices, etc.) administered for acute management and recovery of the stroke.
4 Only Neurological AEs, Bleeding/Hemorrhagic AEs (including non-neurological events), groin puncture AEs and AEs that resulted in death experienced by the study subject after enrollment are required to be recorded in the CRF.

5.6 Sample Size Estimate and Justification

This study aims to evaluate the rate of stroke or death within 72 hours post procedure using data available from eligible patients treated according to the Indications for Use (PP cohort) which is expected to be approximately 6.6%. Using the Clopper-Pearson exact method with a 95% confidence interval (CI) as (0.042, 0.097), with a width of 0.055 (±0.0275), 350 evaluable patients will be required. Enrollment of 389 patients is planned to allow for a 10% attrition rate.

5.7 Analysis Populations

Only patients who had a Wingspan Stent implanted in accordance with the Indications for Use will be considered evaluable as the primary analysis (PP) group. The Per Protocol cohort will be analyzed for the primary and secondary endpoints. Patients who meet the following criteria at the time of treatment will be considered to have been treated according to the Indications for Use.

- Age 22 to 80 years old, inclusive
- 70-99% stenosis of an intracranial vessel due to atherosclerotic disease
- Experienced recurrent stroke (2 or more) on a comprehensive regimen of medical therapy
- The most recent stroke occurred more than 7 days prior to treatment with the Wingspan system.
- Modified Rankin Scale score of 3 or less

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5.7.1 Subgroup Analysis

The primary and secondary endpoints will also be analyzed for the following subgroups:

- Patients who have evidence of hemodynamic compromise in the territory of the stenotic artery prior to the procedure.
- Patients who present with stroke only in the territory of a perforator artery prior to the procedure.
- Patients who are treated not in accordance with the Indications for Use.

  Patients who meet any of the following contraindications will also be considered to have been treated not in accordance with the Indications for Use and will be included in the sub group analysis:

  - Patients in whom antiplatelet and/or anticoagulation therapy is contraindicated
  - Lesions that are highly calcified or otherwise could prevent access or appropriate expansion of the stent
  - Patients with an onset of symptoms within 7 days prior to the procedure
  - Patients who have only experienced transient ischemic attacks (TIAs)

5.8 Statistical Analysis

Only patients who have a Wingspan Stent implanted in accordance with the Indications for Use will be considered evaluable and analyzed as the primary analysis (PP) group. Descriptive statistical analyses will be used for the primary endpoint. The percentage rate as well as exact Clopper-Pearson 95% CI will be calculated for the rate of stroke or death within 72 hours post procedure for the evaluable patients in the study. For all binary variables, the rate and 95% CI will be consistently reported. For all continuous variables, the standard descriptive statistics will be reported, including but not limited to the number of the events or patients with non-missing data (N), mean and standard deviation, median and interquartiles, and minimum and maximum values.

5.8.1 Statistical Software

Primary statistical analyses will be performed, using the SAS System software, version 9.2 or above (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved). Some interim analysis and figures may be done with R 3.2.3 or above.

5.8.2 Interim Analyses

Interim analyses are planned after 150, 225, and 300 primary analysis group (Per Protocol Cohort (PP)) subjects have been enrolled and have completed their 72-hour follow-up. At the maximum sample size of 350 PP subjects, if the proportion of subjects experiencing stroke or death within 72 hours is 6.6%, the upper limit of the exact two-sided 95% Clopper-Pearson CI will be 9.7%.

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This trial may stop early for safety or statistical success.

For safety, if, at a pre-specified interim analysis, the entire two-sided 95% exact confidence interval of the 72 hour death or stroke rate is above the 9.7% rate specified in the protocol, then the study will be stopped early for safety.

For success, if, at a pre-specified interim analysis, there is at least a 95% predictive probability of achieving a 95% Clopper-Pearson CI that lies entirely below 9.7% with 350 PP subjects. This translates directly into a 95% predictive probability of observing no more than 23 events among 350 PP subjects.

It is assumed the probability of an event, p, has a Beta prior distribution

$$[p] \sim \text{Beta}(0.5, 0.5).$$

At each interim analysis, the total study sample size, Nmax is the sum of the current sample size, Nc, and the number of patients who remain to be enrolled, the future sample size, Nf. The number of observed events among the currently enrolled patients, Xc, follows a binomial distribution

$$[X_C] \sim \text{Binomial}(N_C, p).$$

The prior distribution is updated with the currently observed data (Xc, Nc) and the resulting posterior distribution is

$$[p \mid X_C, N_C] \sim \text{Beta}(0.5 + X_C, 0.5 + N_C - X_C).$$

The number of future events, Xf, among the future patients, Nf, has a beta-binomial distribution

$$[X_f \mid a, b, X_C] \sim \text{Beta-Binomial}(N_f, 0.5 + X_C, 0.5 + N_C - X_C).$$

To calculate the predictive probability of achieving a 95% confidence interval that lies entirely below 9.7%, or early study statistical success, the probability of observing Xf = y events is calculated from 0 to Nf, among the future subjects, where y additional events would result in an early study statistical success or

$$\text{Pr(Study Success)} = \sum_{y=0}^{y=N_f} \Pr(X_f = y) I_y$$

$$I_y = \begin{cases} 1 & y + X_C <= 23 \text{ events} \\ 0 & y + X_C > 23 \text{ events} \end{cases}$$

5.8.3 Operating Characteristics

The performance of these interim analyses were evaluated via simulation across a variety of scenarios to evaluate the Type I error and power of this study. Results are based on 5000 simulations per scenario. Under the null hypothesis, where the true rate of stroke or death within 72 hours post procedure is 9.7%, the total probability of statistical success, either early at an interim analysis or at the final analysis with all 350 PP subjects is 3.4%. This is the overall one-sided Type I error

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rate of this trial. The probability of declaring a success early at one of the interim analyses in this scenario is 1.8%.

This trial is highly likely to stop early for statistical success in the event that rate of stroke or death within 72 hours is lower than anticipated. For example, if the rate of stroke or death within 72 hours is 5.5%, there is a 66% probability of declaring success early at an interim analysis. The total probability of success in this scenario is 86%. This is the power of this trial under this alternative hypothesis.

5.8.4 Additional Analysis Methods

Logistic regression models will be used to determine if there is a relationship between the 72 hour post procedure stroke or death rate and baseline factors including but not limited to the following:

- Level of operator experience at the time of first patient enrollment
- Baseline characteristics (demographics and clinical characteristics)
- Procedural characteristics
- Post procedure patient management
- Operator specialty

Sufficient baseline information will be collected to assess composite risk of stroke.

6 Data Management

Subject data will be collected in a secure electronic data capture (EDC) system. The Principal Investigator or Sub-investigator must ensure the accuracy and completeness of the recorded data and then provide his/her electronic signature on the appropriate electronic CRFs. Changes to data previously submitted will require a new electronic signature by the investigator to acknowledge/approve the changes.

Visual and/or computer data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. The site staff will be responsible for resolving all queries in the database.

7 Monitoring Procedures

7.1 Monitoring

Periodic site monitoring visits will be conducted during which original source documentation will be reviewed for verification of data entered in the electronic database for all patients who have experienced a stroke or death within 72 hours. The Investigator/institution guarantees direct access to original source documents by Stryker personnel, its designees, and/or appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a subject that is seen by a non-study physician at a non-study institution, photocopies of the original source documents should be made available for review.

It is important that the Investigator and relevant study personnel are available during monitoring visits and that sufficient time is devoted to the process.

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7.2 Auditing

The study may also be subject to a quality assurance audit by Stryker or its designees, as well as inspection by applicable regulatory authorities. It is important that the Investigator and relevant study personnel are available during any audits and that sufficient time is devoted to the process.

7.3 Device Accountability

This is a post market surveillance study and sites will use devices from their commercially obtained supply of Wingspan Stents and Gateway Balloons. Sites will document details of the devices used in the CRF. No additional study-specific device accountability procedures are required.

8 Adverse Events

8.1 Adverse Event Definitions and Classification

The following definitions are used in this study:

Adverse Event (AE): Any untoward medical occurrence in a subject. This definition does not imply that there is a relationship between the adverse event and the device under investigation.

Serious adverse event (SAE): An adverse event that:

- led to death
- led to a serious deterioration in the health of the subject that:
  - resulted in a life-threatening illness or injury
  - resulted in a permanent impairment of a body structure or a body function
  - required in-subject hospitalization or prolongation of existing hospitalization
- resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with the study device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of patients.

Only the following AEs experienced by the study subject are required to be recorded in the CRF:

- Neurological AEs
- Bleeding/Hemorrhagic AEs (including non-neurological events)
- Groin puncture AEs
- AEs resulting in Death (including non-neurological AEs)

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Death should not be recorded as an adverse event, but should only be reflected as an outcome of an AE. The cause of all deaths that occur during the study should be recorded as the AE term with "death" noted as the outcome. In addition, time of death should be recorded, if known.

The Investigator will assess the relationship of the adverse event to the study devices (i.e., Wingspan and Gateway) as well as the relationship of the event to other aspects of the index procedure.

8.2 Reporting Requirements

The communication requirements for Adverse Events reporting to Stryker are as follows:

Adverse Event Classification	Communication Method to Stryker	Communication Timeline to Stryker
UADE	Complete AE eCRF with available information	Within 24 hours of first becoming aware of the event.
SAE	Complete AE eCRF with available information	Within 24 hours of first becoming aware of the event.
AE	Complete AE eCRF page	As soon as possible
Device Failures, Malfunctions, and Product Nonconformities	Complete applicable Device eCRF	Within 24 hours of first becoming aware of the event.

8.3 Device Failures, Malfunctions, and Product Nonconformities

All device failures, malfunctions, and product nonconformities (i.e., Wingspan and Gateway) will be documented on the appropriate CRF and the devices should be returned to Stryker for analysis. Device failures and malfunctions should also be documented in the subject's medical record.

Device failures, malfunctions, and product nonconformities are not to be reported as adverse events however, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded and reported as per the requirements in section 8.2.

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8.4 Known and Anticipated Risks

Potential adverse events associated with the use of the Wingspan Stent System or with the procedure are noted in the DFU. These include but are not limited to the following.

- Aneurysm
- Cerebral ischemia
- Coagulopathy
- Death
- Drug reaction to contrast or antiplatelet medication
- Emboli (air, tissue, or thrombotic tissue)
- Hemorrhagic event
- Hypotension
- Infection
- Intimal dissection
- Ischemia/infarct
- Neurological symptoms
- Restenosis
- Pseudoaneurysm
- Stent migration
- Stent misplacement
- Stent occlusion
- Stent embolization
- Stent thrombosis
- Stroke
- Transient Ischemic Event
- Thromboembolic event
- Vasospasm
- Vessel dissection
- Vessel occlusion
- Vessel perforation
- Vessel rupture
- Vessel spasm
- Vessel thrombosis
- Vessel trauma requiring surgical repair or intervention

8.5 Reporting to Regulatory Authorities / IRBs / IECs / Investigators

Stryker is responsible for reporting adverse event information to all participating investigators and regulatory authorities, as applicable.

The Site Principal Investigator is responsible for informing the IRB/IEC of UADE, SAE, and/or adverse events as required by local procedure. A copy of this report should be provided to Stryker.

Study reports, which will include the stroke or death rate within 72 hours post procedure, will be provided to the Food and Drug Administration (FDA) every six months and will include U.S. and international sales figures for each six month period related to the report.

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9 Ethical Considerations

9.1 Compliance with Good Clinical Practices (GCP)

The Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory (local) requirements; whichever affords the greater protection to the patient.

9.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed Informed Consent form, other written subject information, and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written IRB/IEC approval of the protocol and Informed Consent form must be received by Stryker before recruitment of patients into the study.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC for all subsequent protocol amendments and changes to the Informed Consent form. The Investigator must notify the IRB/IEC of deviations from the protocol or SAEs/UADEs occurring at the site and other SAE/UADE reports received from Stryker in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC approval and renewal for the study. In the U.S., the Investigator is also responsible for IRB approval for use of the devices under the HDE throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Stryker.

9.3 Written Informed Consent Form

Stryker will provide a sample study Informed Consent Form to the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential subject population.

Stryker and the reviewing IRB/IEC must first approve the study Informed Consent Form(s) before use. The Informed Consent form(s) must be in agreement with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki, and the International Conference on Harmonization (ICH). Before participating in the clinical trial, each subject must give written Informed Consent after the context of the study has been fully explained to the subject in language that is easily understood by the subject. The subject also must be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

Written Informed Consent must be recorded appropriately by means of the subject's, or his/her legal representative's dated signature. The consent process must be documented in the subject's medical chart.

9.4 Protocol Adherence

Prior to beginning the study, the Investigator must sign the Investigator Agreement and Signature page documenting his/her agreement to conduct the study in

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accordance with the protocol. An Investigator must not make any changes or deviate from this protocol except to protect the life and physical well-being of a subject in an emergency. Each deviation from the protocol must be documented with the reason for the deviation and reported to the sponsor. Sites are responsible for reporting protocol deviations to their local IRB/IEC in accordance with local guidelines.

10 Study Administration

Sites will make every effort to ensure that this study is conducted in compliance with GCP and all applicable regulatory requirements.

10.1 Site Selection

It is expected that each primary operator shall be able to treat at least 5 patients per year with the study device in accordance with the Indications for Use. Site selection will attempt to ensure that approximately ⅓ to ½ of participating sites conduct platelet-resistance testing as part of standard hospital care to assess any impact of testing and subsequent changes in medical therapy can be analyzed.

10.2 Pre-Study Documentation Requirements

Prior to screening and enrolling patients in the study, the following requirements must be fulfilled:

10.2.1 General

Device Training: In accordance with training requirements for the use of the Wingspan® Stent System and Gateway® PTA Balloon Catheter as Humanitarian Use Devices, all study operators must complete Stryker's device training program on the proper use of the device, proper patient selection and care and consideration of intra- and post procedure medications prior to participation in the study.

IRB approval: All US sites must have current IRB approval for use of the Wingspan® Stent System with Gateway® PTA Balloon Catheter under the HDE and approval must be maintained for continued participation in the study.

10.2.2 Study-specific

IRB/IEC approval: All sites must have IRB/IEC approval of the study protocol and study consent form.

Training: All sites must complete training on the protocol and EDC system.

Clinical Study Agreement: All sites must have a fully executed agreement in place.

10.3 Record Retention

The Investigator will maintain all essential trial documents and source documentation, in original format, in compliance with the ICH/GCP guidelines. Documents must be retained for at least 2 years after FDA acceptance of the final report. These documents may be retained for a longer period of time per agreement with Stryker or in compliance with other regulatory requirements. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these documents, custody must be transferred to an individual who

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will assume responsibility. Stryker must receive written notification of this custodial change.

10.4 Criteria for Terminating Study

Stryker reserves the right to terminate the study and intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of patients. Investigators and associated IRB/IECs will be notified in writing in the event of termination.

10.5 Criteria for Suspending/Terminating a Study Center

Stryker reserves the right to stop the enrollment of patients at a study center if no patients have been enrolled in 6 consecutive months or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Stryker also reserves the right to investigate any single occurrence or multiple occurrences of procedure related serious adverse events or technical difficulties. Outcomes of these investigations may range from no action to re-training/proctoring, suspension or termination of the operator or site.

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11 Appendices

A. Abbreviations

AE	Adverse Event
CRF	Case Report Form
DFU	Directions for Use
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDE	Humanitarian Device Exemption
ICAD	Intracranial Atherosclerotic Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
ISN	Independent Stroke Neurologist
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PTA	Percutaneous Transluminal Angioplasty
PTAS	Percutaneous Angioplasty And Stenting
SAE	Serious Adverse Event
TIA	Transient Ischemic Attack
UADE	Unanticipated Adverse Device Effect
US	United States

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