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**GORE® Carotid Stent Clinical Study for the treatment of carotid artery  
stenosis in patients at increased risk for adverse events from carotid  
endarterectomy**

**The Gore SCAFFOLD Clinical Study**

Protocol Number: GCS 10-08

Amendment 3:	22 OCT 2014
Amendment 2:	10 JUL 2013
Amendment 1:	04 FEB 2013
Original Protocol:	10 FEB 2012

W. L. Gore & Associates, Inc.  
Medical Products Division



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MD133246 Protocol Template  
Revision#: 1  
Doc Type: GC

### Protocol Modification Summary

List of Changes in: GORE® Carotid Stent Clinical Study for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy – The Gore SCAFFOLD Clinical Study GCS 10-08

The following clarification changes have been made to the protocol:

Changes from Amendment 2: 10 JUL 2013 to **Amendment 3: 22 OCT 2014**

Section	Changes to Protocol	Rationale
Throughout the document	Header changed: <u>Current Version:</u> GORE® Carotid Stent MD134865 GCS 10-08 PROT Revision#:1 Doc Type SP  <u>Previous Version:</u> GCS 10-08 13-07-10 GORE® Carotid Stent	Update to current protocol date and updated template
Throughout the document	Footer changed: <u>Current Version:</u> MD133246 Protocol Template Revision#1 Doc Type: GC  <u>Previous Version:</u> TMPLT 11-05-27 Protocol APP.doc PROT 14-10-XX GCS 10-08 APP.doc	Update to current protocol date and updated template
Cover Page	Addition of Amendment 3: 22 OCT 2014	Update to current protocol date
Protocol Summary	Addition of Amendment 3: 22 OCT 2014	Update to current protocol date
Protocol Summary	Removed Europe and Japan from “Number of Clinical Investigative Sites”	Update to reflect study will be in the U.S. only.
List of Abbreviations	<u>Removed European Union and Pharmaceuticals and Medical Devices Agency (Japan)</u>	Update to reflect study will be in the U.S. only.
Section 3.1 Description of Study Design	<u>Removed reference of Europe and Japan from second paragraph and reference of</u>	Update to reflect study will be in the U.S. only.



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MD133246 Protocol Template  
Revision#: 1  
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	<u>“PMDA” and “Shonin” approval</u>	
Section 4.1 Description of Population	<u>Addition of:</u> The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the study or the interpretation of results.	Updated to reflect the current protocol template wording.
Section 4.3 Exclusion Criteria – Angiographic Exclusion Criteria	<p><u>Current version:</u> Patient has a previously placed arterial stent distal to or including the origin of the ipsilateral great vessel (includes a stent anywhere in the ICA, CCA, or brachiocephalic artery).</p> <p><u>Previous version:</u> Patient has previously placed stent in the ipsilateral carotid artery.</p>	Subjects who have a stent in the ipsilateral side to target lesion will be excluded. This includes internal and common carotid arteries as well as the innominate artery if applicable.
Section 4.3 Exclusion Criteria – Angiographic Exclusion Criteria	<p><u>Current version:</u> Patient has known mobile plaque, thrombus, or excessive calcification in the aortic arch.</p> <p><u>Previous version:</u> Patient has known mobile plaque or thrombus in the aortic arch.</p>	Subjects who have excessive calcification in the arch will be excluded
Section 4.3 Exclusion Criteria – Angiographic Exclusion Criteria	<u>Addition of Exclusion Criteria #9:</u> Patient has aneurysmal carotid bifurcation on the ipsilateral side.	Additional criteria included to exclude subjects with aneurysmal carotid bifurcation on the treatment side.
Section 4.3 Exclusion Criteria – Angiographic Exclusion Criteria	<u>Addition of Exclusion Criteria #10:</u> Patient has tortuous anatomy or disease morphology which would prohibit the safe placement of guide catheter, sheaths, embolic protection systems or stent systems within the access or target vessel	Additional criteria included to exclude subjects with tortuous anatomy that will prevent safe introduction of interventional equipment.



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Section 5.1 Study Procedures and Evaluation Schema	<u>Addition of</u> : “Obtain review by Screening Committee”	Update to reflect current process for Screening Committee review.
Section 5.2 Schedule of Events	Multiple changes to reflect new screening process.	Update to reflect current process for Screening Committee review.
Section 5.3 Informed Consent Process	<p><u>Current version</u>: All patients must provide written informed consent prior to submission of pre-procedure imaging and medical history to the Screening Committee for review (refer to Section 5.5 for details) and prior to and study related procedures being performed.</p> <p><u>Previous version</u>: All patients must provide written informed consent prior to any study related procedure being performed.</p>	Update to reflect current process for Screening Committee review.
Section 5.5 Pre-Screening/Screening	<p><u>Current version</u>: Inclusion and exclusion criteria assessed: confirmation is required by Screening Committee</p> <p><u>Previous version</u>: Inclusion and exclusion criteria assessed.</p>	Update to reflect current process for Screening Committee review.
Section 5.5 Pre-Screening/Screening	<u>Addition of</u> : “Angiography and/or CTA” as a requirement for the Pre-Screening/Screening visit	Update to reflect current process for Screening Committee review.
Section 5.5 Pre-Screening/Screening	<p><u>Addition of</u>:</p> <p><b>Pre-screening Assessment</b></p> <p>A Screening Committee will review pre-operative angiography and/or CTA, along with patient medical history, for assessment of entry criteria, and approval prior to the study procedure.</p> <p>The Screening Committee will be comprised of an interdisciplinary team of study investigators with pertinent</p>	Update to reflect current process for Screening Committee review.



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	<p>knowledge in carotid stenting. The members will not review potential cases from their own sites. The members will be compensated for their involvement in the Screening Committee, including reimbursement for reasonable travel expenses to attend meetings.</p> <p>This committee will operate under pre-specified procedures as outlined in the Screening Committee Charter.</p> <p>Prior to a patient being enrolled in the study, the investigational site must receive confirmation from the Screening Committee that the subject is eligible to be enrolled. Although patient may be deemed eligible to be enrolled, it is still the responsibility of the investigator to assess all inclusion and exclusion criteria prior to enrollment.</p> <p><b>Screening Angiogram and/or CTA</b></p> <p>In addition to review of medical history, patients will be screened by the Screening Committee based on the results of an angiogram or CTA. These images must include at a minimum the aortic arch, ipsilateral carotid artery, target lesion, and intracranial and extracranial views. A complete diagnostic study will be needed in order to evaluate fully the patient against entry criteria. Submission of complete case images is strongly encouraged.</p>	
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Section 5.6 Pre-Procedure Assessments	<p><u>Current version</u>: Baseline Cardiac Enzyme -Troponin (may be obtained once arterial access is gained but not after any interventional wires enter the subject's vasculature)</p> <p><u>Previous version</u>: Baseline Cardiac Enzyme (Troponin)</p>	Added additional clarification as to when cardiac Troponin may be drawn.
Section 5.6 Pre-Procedure Assessments	<p><u>Current version</u> : Concomitant Medications (antiplatelet and anticoagulant therapy)</p> <p><u>Previous version</u>:</p> <ul style="list-style-type: none"> <li>• Concomitant medications</li> <li>• Assess Antiplatelet Therapy</li> </ul>	Clarify which medications are being collected
Section 5.7 Procedure	<p><u>Current version</u> : Concomitant Medications (antiplatelet and anticoagulant therapy)</p> <p><u>Previous version</u>: Concomitant medications</p>	Clarify which medications are being collected
Section 5.10 Post-Procedure	<p><u>Current version</u> : Concomitant Medications (antiplatelet and anticoagulant therapy) assessment</p> <p><u>Previous version</u>: Concomitant medications</p>	Clarify which medications are being collected
Section 5.11 Follow-Up	<p><u>Current version</u> : Concomitant Medications (antiplatelet and anticoagulant therapy) assessment</p> <p><u>Previous version</u>: Concomitant medications assessment</p>	Clarify which medications are being collected
Section 6.4 Core Labs	<p><u>Current Version</u>:</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	Update to reflect change in address for [REDACTED].



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	<p>[REDACTED]</p> <p><u>Previous Version:</u></p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	
Section 6.5 Protocol Deviations	<p><u>Current Version:</u> A Protocol Deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly reporting Protocol Deviations to their reviewing IRB per IRB policy and the Sponsor.</p> <p><u>Previous Version:</u> A protocol deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol that is under the Investigator's control and that has not been approved by the IRB/EC. The Investigator is responsible for promptly reporting protocol deviations to their IRB/EC per IRB/EC policy and the Sponsor.</p>	Update to reflect the current protocol template wording
Sections 6.5, 6.6, 6.8, and 6.9	<u>Removed all 'EC' from IRB/EC regulatory references</u>	Update to reflect study will be in the U.S. only.
Section 6.9	<p><u>Current version:</u></p> <p>Records will be maintained during the clinical study and for a minimum of two years after the latter of the date on which the study is terminated or completed, or the date the records are no longer required to support regulatory approval of the device.</p>	Update to reflect the current protocol template wording.



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	<p><u>Previous version:</u> Records will be maintained during the clinical study and three years after the day on which marketing authorization of the investigational device is obtained or three years after the date of discontinuation or completion of the clinical trial, whichever comes later.</p>	
Section 9.1.1 Adverse Event Relationship	<p><u>Addition of:</u> Only one primary relationship will be assigned to each reported AE. Study Device-related Current version: The functioning or characteristics of the device caused or contributed to the Adverse Event.</p> <p><u>Previous version:</u> If the functioning or characteristics of the stent caused or contributed significantly to the adverse event, the adverse event would be suspected as primarily related to the stent.</p> <p>Embolic Protection System (EPD)-related <u>Current version:</u> The functioning or characteristics of the EPD caused or contributed to the Adverse Event.</p> <p><u>Previous version:</u> If the functioning or characteristics of the EPD caused or contributed significantly to the adverse event, the adverse event would be suspected as primarily related to the EPD.</p>	<p>Update to reflect the current protocol template wording.</p> <p>Update to reflect the current protocol template wording.</p> <p>Update to reflect the current protocol template wording.</p>



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	<p><u>Study Procedure-related</u> <u>Current version:</u> The study index procedure (and not the device or EPD) caused or significantly contributed to the Adverse Event.</p> <p><u>Previous version:</u> If the procedure (and not the device) caused or significantly contributed to the adverse event, the adverse event would be suspected as primarily related to the procedure.</p> <p><u>Medication-related</u> <u>Current version:</u> The Adverse Event was a result of medical therapy prescribed by the study protocol and not the device, EPD, or procedure.</p> <p><u>Previous version:</u> If the adverse event was a result of a medication taken as part of the study/procedure, the adverse event would be suspected as primarily related to the medication.</p> <p><u>Disease-related</u> <u>Current version:</u> The Adverse Event was a result of the underlying disease progression for which the study procedure is being performed, and not the device, EPD or procedure.</p> <p><u>Previous version:</u> If the adverse event was a</p>	<p>Update to reflect the current protocol template wording.</p> <p>Update to reflect the current protocol template wording.</p> <p>Update to reflect the current protocol template wording.</p>
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	<p>result of the underlying disease progression for which the study procedure is being performed, and not the device or procedure, the adverse event would be suspected as primarily related to the disease.</p> <p>Not related <u>Current version:</u> An Adverse Event which cannot be attributed to the device, EPD, procedure, medication or disease.</p> <p><u>Previous version:</u> If an adverse event cannot be attributed to the device, procedure, medication, or disease, it will be reported as “Not related”.</p> <p>Unknown relationship <u>Current version:</u> The relationship of the Adverse Event to the device, EPD, procedure, medication or disease cannot be determined.</p> <p><u>Previous version:</u> If the relationship of the adverse event to the device, procedure, medication, or disease cannot be determined, it will be coded as “Unknown”.</p>	<p>Update to reflect the current protocol template wording.</p> <p>Update to reflect the current protocol template wording.</p>
Section 9.2 Unanticipated Adverse Device Effect (UADE)	<p><u>Removed ‘EC’ from IRB/EC regulatory references</u></p> <p><u>Addition of:</u> A report from the Sponsor will be submitted to the FDA and to all reviewing IRBs and participating Investigators within 10 working days after the Sponsor first receives notice of the effect.</p>	<p>Update to reflect study will be in the U.S. only.</p> <p>Update to reflect the current protocol template wording.</p>



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Section 10.4.3 Analysis Sets	<p><u>Current Version:</u> The primary analysis set for testing of the primary endpoint is the per-protocol analysis set.</p> <p><u>Previous Version:</u> The primary analysis set for testing of the primary endpoint is the intent-to-treat, or full, analysis set.</p>	Because subjects with technical failure are followed only to 30 days, they will not be evaluable for the primary endpoint. The ITT set includes technical failures; the per-protocol set does not.
Section 10.4.3 Intent-To-Treat Analysis Set	<p><u>Current Version:</u> The ITT analysis set is defined as all enrolled subjects with adequate informed consent, regardless of whether the study stent was implanted. Because technical failures (test device attempted but not implanted) are followed only to 30 days, this set will be used in the analysis of safety endpoints (major, serious, and nonserious adverse events) to 30 days and secondary endpoints evaluated at procedure, discharge, and 30 days.</p> <p><u>Previous Version:</u> The ITT analysis set is defined as all enrolled subjects with adequate informed consent, regardless of whether or not the study stent was implanted. This set will be used in the analysis of the primary and all secondary endpoints evaluated at procedure, 30 days and one year, as well as supplemental analyses of the primary endpoint (for example, Kaplan-Meier survival analysis).</p>	Same as above.
Section 10.4.3 Per-Protocol Analysis Set (Primary Analysis Set)	<u>Current Version:</u> For per-protocol analysis, only subjects who had the study stent implanted in the target vessel and had no major protocol deviations will be included in the analysis. Major protocol deviations are defined as protocol deviations with a level	Same as above, plus clarification to definition of major protocol deviation.



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	<p>of seriousness such that inclusion of the subject(s) would unacceptably bias the primary endpoint analysis. An example of a major protocol deviation might be failure to satisfy eligibility criteria to a degree where the subject does not fit the underlying scientific model for the treatment.</p> <p>The per-protocol set will be used for the primary analyses of the primary endpoint. Ideally, this analysis set will consist of all subjects from the ITT set with technical success (test device implanted).</p> <p>Per-Protocol Analysis Set (Primary Analysis Set)</p> <p><u>Previous Version:</u> For per-protocol analysis, only subjects who had the study stent implanted in the target vessel and had no major protocol deviations will be included in the analysis. Anticipated major protocol deviations are defined as any of the following:</p> <ul style="list-style-type: none"> <li>• Subject does not satisfy inclusion/exclusion criteria</li> <li>• Inadequate informed consent</li> </ul> <p>Per-Protocol Analysis Set</p>	
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11.1 Statement of Compliance	<p><u>Removed reference “so that global data can be used for submission in the U.S. and Japan”</u></p> <p><u>Removed the following local regulatory requirements:</u></p> <table><tr><td>2005 Ministry of Health, Labor and Welfare Ordinance No.36</td><td>Ministerial Ordinance on Good Clinical Practice for Medical Devices</td></tr><tr><td>Medical Device Directive (93/42/EEC) Article 15 Annex X</td><td>Council Directive 93/42/EEC of 14 June 1992</td></tr><tr><td>Amendment to the MDD (2007/47/EC) Article 15 Annex X</td><td>Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007</td></tr></table> <p><u>Removed the following sentence:</u> The Sponsor will obtain clinical trials insurance as required by the laws of each country in which the study is conducted.</p>	2005 Ministry of Health, Labor and Welfare Ordinance No.36	Ministerial Ordinance on Good Clinical Practice for Medical Devices	Medical Device Directive (93/42/EEC) Article 15 Annex X	Council Directive 93/42/EEC of 14 June 1992	Amendment to the MDD (2007/47/EC) Article 15 Annex X	Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007	<p>Update to reflect study will be in the U.S. only.</p> <p>Update to reflect study will be in the U.S. only.</p> <p>Update to reflect study will be in the U.S. only.</p>
2005 Ministry of Health, Labor and Welfare Ordinance No.36	Ministerial Ordinance on Good Clinical Practice for Medical Devices							
Medical Device Directive (93/42/EEC) Article 15 Annex X	Council Directive 93/42/EEC of 14 June 1992							
Amendment to the MDD (2007/47/EC) Article 15 Annex X	Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007							
Section 11.2 Compliance Responsibilities	<p><u>Removed all ‘EC’ from IRB/EC regulatory references</u></p> <p><u>Removed Caretaker office location in Japan</u></p>	<p>Update to reflect study will be in the U.S. only.</p> <p>Update to reflect study will be in the U.S. only.</p>						
Sections 11.3, 11.4 and 11.6	<p><u>Removed all ‘EC’ from IRB/EC regulatory references</u></p>	<p>Update to reflect study will be in the U.S. only.</p>						



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### PROTOCOL SUMMARY

Study Title	GORE® Carotid Stent Clinical Study for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy
Protocol Number	GCS 10-08
Amendment 3	22 OCT 2014
Amendment 2	10 JUL 2013
Amendment 1	04 FEB 2013
IDE Number	G110127
Sponsor	W. L. Gore & Associates, Inc. Medical Products Division 4250 West Kiltie Lane Flagstaff, AZ 86001 Telephone: 800-437-8181
Study Design	Multicenter, single-arm, prospective study comparing the GORE® Carotid Stent to a performance goal developed from carotid endarterectomy (CEA) outcomes
Study Objective	To evaluate the safety and effectiveness of the GORE® Carotid Stent for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy.
Study Endpoints	Primary Endpoint: Major Adverse Event (MAE) rate defined as a composite of: <ul style="list-style-type: none"> <li>• Death, stroke, or MI through 30 days post-index procedure, and</li> <li>• Ipsilateral stroke from Day 31 through 1 year</li> </ul> Secondary Endpoints: <ul style="list-style-type: none"> <li>• Stent Technical Success</li> <li>• Embolic Protection Technical Success</li> <li>• Procedure Success</li> <li>• In-Stent Restenosis</li> <li>• Target Lesion Revascularization</li> </ul>
Subject Population	Patients at least 18 years of age who have either de novo atherosclerotic or postendarterectomy restenotic lesions in the internal carotid arteries or at the carotid bifurcation, with either ≥50% (by angiography) stenosis if symptomatic (stroke, TIA, TMB within 180 days of procedure), or ≥80% (by angiography) stenosis if asymptomatic. Patients must have either anatomic or medical co-morbidities that place them at high perioperative risk for CEA.
Number of Subjects	312
Number of Clinical Investigative Sites	Up to 50 sites in the U.S.
Study Duration	Time to Complete Enrollment: 18-24 months Follow-up Time: 36 months Total Study Duration: 54-60 months



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Follow-up Schedule	Screening, Pre-procedure, Procedure, Post-Procedure, 30 days, 6 months, 1 year, 2 years, and 3 years
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MD133246 Protocol Template

Revision#: 1

Doc Type: GC

### LIST OF ABBREVIATIONS

ACT	Activated Clotting Time
AE	Adverse Event
BUN	Blood Urea Nitrogen
CAS	Carotid Artery Stenting
CBC	Complete Blood Count
CCA	Common Carotid Artery
CDUS	Carotid Duplex Ultrasound
CDMS	Clinical Data Management System
CEA	Carotid Endarterectomy
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
Cm	Centimeters
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CT	Computed Tomography
CTA	Computed Tomographic Angiography
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
ECA	External Carotid Artery
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ePTFE	Expanded Polytetrafluoroethylene
FDA	Food and Drug Administration (United States)
Fr	French (sizing)
GCP	Good Clinical Practice
HIT	Heparin-Induced Thrombocytopenia
ICA	Internal Carotid Artery
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board (U.S.)
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
mm	Millimeters
MRA	Magnetic Resonance Angiography
MRI	Magnetic Resonance Imaging
NASCET	North American Symptomatic Carotid Endarterectomy Trial



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MD133246 Protocol Template  
Revision#: 1  
Doc Type: GC



NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PFO	Patent Foramen Ovale
PG	Performance Goal
PMA	Premarket Approval
SAE	Serious Adverse Event
TIA	Transient Ischemic Attack
TLR	Target Lesion Revascularization
UADE	Unanticipated Adverse Device Effect



**CONFIDENTIAL INFORMATION**

1.	INTRODUCTION .....	20
1.1.	DISEASE .....	20
1.2.	HISTORICAL TREATMENTS .....	20
1.3.	STUDY DEVICE DESCRIPTION .....	21
1.4.	GORE EMBOLIC PROTECTION SYSTEMS .....	23
2.	STUDY OBJECTIVES .....	23
2.1.	PRIMARY OBJECTIVE(S) .....	23
3.	STUDY DESIGN .....	23
3.1.	DESCRIPTION OF STUDY DESIGN .....	23
3.2.	STUDY ENDPOINTS .....	24
3.2.1.	<i>Definitions</i> .....	24
3.2.2.	<i>Primary Endpoint</i> .....	25
3.2.3.	<i>Secondary Endpoints</i> .....	25
4.	STUDY POPULATION .....	26
4.1.	DESCRIPTION OF POPULATION .....	26
4.2.	INCLUSION CRITERIA .....	26
4.3.	EXCLUSION CRITERIA .....	27
5.	STUDY PROCEDURES/EVALUATIONS .....	29
5.1.	STUDY PROCEDURES AND EVALUATION SCHEMA .....	29
5.2.	SCHEDULE OF EVENTS .....	30
5.3.	INFORMED CONSENT PROCESS .....	31
5.4.	GENERAL STUDY EVALUATION GUIDELINES .....	31
5.5.	PRE-SCREENING/SCREENING .....	31
5.6.	PRE-PROCEDURE ASSESSMENTS .....	33
5.7.	PROCEDURE .....	34
5.8.	ENROLLMENT .....	34
5.9.	REPEAT INTERVENTIONS .....	37
5.10.	POST-PROCEDURE .....	37
5.11.	FOLLOW-UP .....	37
5.12.	SUBJECT WITHDRAWAL FROM THE CLINICAL STUDY .....	38
5.13.	SUBJECT LOST TO FOLLOW-UP .....	38
5.14.	SUBJECT STUDY COMPLETION .....	39
5.15.	EXPLANT PROCEDURES .....	39
6.	CLINICAL STUDY ADMINISTRATION .....	39
6.1.	DEVICE TRAINING .....	39
6.2.	MONITORING .....	39
6.3.	DEVICE ACCOUNTABILITY AND STORAGE .....	40
6.4.	CORE LABS .....	40
6.5.	PROTOCOL DEVIATIONS .....	41
6.6.	PROTOCOL AMENDMENTS .....	41
6.7.	SPONSOR REPRESENTATIVES .....	41
6.8.	ACCESS TO SOURCE DATA/DOCUMENTS .....	42
6.9.	STUDY RECORDS RETENTION .....	42
7.	DATA COLLECTION AND SUBMISSION .....	43
7.1.	DATA COLLECTION METHODS .....	43
7.2.	DATA CLARIFICATION AND CORRECTION .....	43
7.3.	CRF COMPLETION SCHEDULE .....	43



CONFIDENTIAL INFORMATION

<b>8.</b>	<b>RISK ASSESSMENT .....</b>	<b>44</b>
8.1.	POTENTIAL RISKS .....	44
8.2.	MINIMIZATION OF RISKS .....	46
8.3.	SUMMARY OF EXPECTED BENEFITS.....	46
<b>9.</b>	<b>ADVERSE EVENTS AND SAFETY MONITORING .....</b>	<b>47</b>
9.1.	ANTICIPATED ADVERSE EVENTS .....	47
9.1.1.	<i>Adverse Event Relationship</i> .....	47
9.1.2.	<i>Adverse Event Classification</i> .....	48
9.1.3.	<i>Adverse Event Reporting and Coding</i> .....	48
9.1.4.	<i>Subject Death</i> .....	49
9.2.	UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE) .....	49
9.3.	DATA AND SAFETY MONITORING BOARD .....	50
9.4.	CLINICAL EVENTS COMMITTEE.....	50
<b>10.</b>	<b>STATISTICAL ANALYSIS.....</b>	<b>51</b>
10.1.	STUDY HYPOTHESES .....	51
10.2.	SAMPLE SIZE ASSUMPTIONS .....	51
10.3.	SAMPLE SIZE DETERMINATION .....	53
10.4.	DATA ANALYSIS.....	55
10.4.1.	<i>Timing of Analyses</i> .....	55
10.4.2.	<i>Analysis Populations</i> .....	55
10.4.3.	<i>Pooling of Data</i> .....	56
10.4.4.	<i>Statistical Analysis of Primary Endpoint(s)</i> .....	56
10.4.5.	<i>Sensitivity Analyses</i> .....	56
10.4.6.	<i>Statistical Analysis of Secondary Endpoint(s)</i> .....	56
10.5.	PUBLICATION PLAN.....	56
<b>11.</b>	<b>ETHICAL AND REGULATORY CONSIDERATIONS .....</b>	<b>57</b>
11.1.	STATEMENT OF COMPLIANCE .....	57
11.2.	COMPLIANCE RESPONSIBILITIES.....	57
11.3.	INFORMED CONSENT .....	58
11.4.	INDEPENDENT ETHICAL REVIEW .....	58
11.5.	CONFLICT OF INTEREST .....	58
11.6.	CONFIDENTIALITY.....	58
<b>12.</b>	<b>REFERENCES.....</b>	<b>59</b>
<b>13.</b>	<b>STUDY-SPECIFIC APPENDICES .....</b>	<b>61</b>
	APPENDIX A NIH STROKE SCALE .....	61
	APPENDIX B MODIFIED RANKIN SCALE .....	61



CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

## 1. Introduction

### 1.1. Disease

It has been estimated that carotid artery disease accounts for 20-30% of the greater than 500,000 new strokes that occur annually in the United States<sup>1</sup>. As stroke is the leading cause of serious, long-term disability in the United States, treatment of carotid artery disease may diminish part of the \$53.6 billion yearly health care costs associated with the treatment of stroke<sup>2</sup>.

### 1.2. Historical Treatments

Treatment options for carotid artery disease include the current standard of care, carotid endarterectomy (CEA), medical therapy, and the continuously evolving procedure of carotid artery stenting (CAS).

CEA remains the gold standard as an effective technique for the treatment of chronic carotid artery stenosis associated with stroke. The technique is endorsed by the American Heart Association (AHA) as a first-line therapy for symptomatic subjects with recent cerebral ischemia and carotid artery diameter stenosis exceeding 70% and for carotid stenosis exceeding 60% in asymptomatic subjects with surgical risk less than 3% and a life expectancy of at least 5 years<sup>1,3</sup>. However, for CEA to provide a greater benefit than medical therapy, the combined morbidity and mortality rate should be under 3% for asymptomatic subjects and less than 6% for symptomatic subjects<sup>4</sup>.

In patients at high risk for complications during CEA, such as those with anatomic or physiologic co-morbidities, outcomes with surgery are less well defined and in some cases documented to be worse than the standard surgical risk patient<sup>5</sup>. In these cases CAS has been shown to be a potentially safer and equally effective stroke reduction therapy<sup>6</sup>. Furthermore, high surgical risk registry data have demonstrated a continued reduction in stroke/MI/death rates over the last several years suggesting that as technique, patient selection, and technology improves, so do outcomes<sup>7,8</sup>. In the standard risk patient, the recently released results of the Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) study found equivalence between the two strategies in terms of the primary endpoint of death, stroke, and myocardial infarction to 30 days plus ipsilateral stroke to 4 years<sup>9</sup>.

## Advantages and Disadvantages with Current Carotid Stents

### Closed Cell vs Open Cell

Currently, the stents available for CAS are divided into two types; Closed-Cell and Open-Cell. Locally approved Closed-Cell stents, such as the Xact® Carotid Stent System (Abbott Vascular, Santa Clara, CA) or the Wallstent® Monorail® System (Boston Scientific Corporation Natick, MA) are characterized by individual apices of the stent frame being connected by a strut to the apices in the adjacent row and is further characterized by each of the individual apices having a smaller cell size. The obvious benefit from such a design is that the stent provides a higher degree of plaque stabilization, thus minimizing plaque protrusion through the stent struts and maintaining greater contact with the vessel wall. However, such a design is typically considered to be more rigid and not able to conform to the native anatomy with clinical reports of kinks forming in the vasculature at the distal end of the device<sup>10</sup>.



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In contrast, Open Cell stents, such as the PRECISE® Carotid Stent System (Cordis, Miami, FL), are characterized as having fewer connections between adjacent apices and thus having larger cell sizes. The benefit of such a design allows for a higher degree of flexibility, which conforms to the native anatomy, however the design has less of a scaffolding effect and does not cover the plaque as efficiently as do Closed Cell stents. An additional issue reported is the so called “fish-scaling” of the stent struts where when deployed in tortuous anatomy, the stent struts come out of alignment and appear as individual scales protruding from the stent<sup>11</sup>.

As carotid artery stenting devices and techniques continue to evolve, many clinicians have described the optimal design. Consistent with these statements from the podium at scientific presentations, Stefan Müller-Hülsbeck describes the ideal carotid stent as having features which include *“scaffolding that is adequate enough to control plaque prolapse but has acceptable levels of flexibility, conformability, and radial strength to track to the lesion, appose the vessel wall, and control recoil”*.<sup>12</sup>

### 1.3. Study Device Description

#### **GORE® Carotid Stent System**

The GORE® Carotid Stent is designed as a true “hybrid” stent in that it incorporates the flexibility and conformability of an Open Cell stent as well as the plaque stabilization of the Closed Cell Stent. Additionally, the device is coated with a covalently bonded Carmeda® Bioactive surface heparin to create an anti-thrombogenic surface. Ease of use of the system is designed into the delivery system which not only offers a single-handed deployment handle, but allows complete closure of the hemostatic valve to aid in stabilization of the delivery system and minimized blood loss.

The GORE® Carotid Stent System consists of a self expanding nitinol stent frame with a 500µ pore size lattice on the exterior of the stent frame. Additionally the stent frame and lattice are coated with a permanently bound anti-thrombogenic surface in the form of CBAS® Heparin. The stent is mounted on a 5Fr or 6Fr introducer sheath compatible delivery system with a working length of 135 cm and a single-handed delivery handle.

The GORE® Carotid Stent, used with the GORE® Embolic Filter, is indicated for the treatment of carotid artery stenosis in patients deemed at high surgical risk for CEA.

- Patients with symptomatic carotid artery stenosis,  $\geq 50\%$ , as confirmed by ultrasound or angiography.
- Patients with asymptomatic carotid artery stenosis,  $\geq 80\%$ , as confirmed by ultrasound or angiography.
- Patients must have a Reference Vessel Diameter of 3.7 mm – 9.0 mm.



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[REDACTED]

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CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

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#### 1.4. Gore Embolic Protection System

##### **GORE® Embolic Filter**

The GORE® Embolic Filter consists of a device, a delivery catheter, and a retrieval catheter, and is compatible with guiding catheters and sheaths having a minimum inner diameter of 0.066". The GORE® Embolic Filter is indicated for general use as a guide wire and embolic protection system during angioplasty and stenting procedures in carotid arteries with reference vessel diameters of 2.5 to 5.5mm.

## 2. Study Objectives

### 2.1. Primary Objective(s)

The primary objective of this study is to evaluate the safety and efficacy of the GORE® Carotid Stent for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy.

## 3. Study Design

### 3.1. Description of Study Design

This study is a prospective, multicenter, multinational, single-arm clinical study to evaluate the safety and efficacy of the GORE® Carotid Stent for the treatment of carotid artery stenosis in patients at increased risk for adverse events from carotid endarterectomy. The primary endpoint is a composite of Major Adverse Events through 1 year post-index procedure and will be compared to a performance goal developed from published carotid endarterectomy outcomes in a high-risk population.



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A maximum of 50 investigative sites in the U.S will participate in this study. Three hundred twelve (312) subjects will be enrolled in this study with a limit of 40 subjects enrolled per site. The anticipated accrual rate is approximately 15-20 subjects per month for a total accrual period of approximately 18-24 months.

Patients may be enrolled into the clinical study provided all inclusion and no exclusion criteria are met. Subjects will be evaluated through hospital discharge and return for follow-up visits at 30 days, 6 months, and 1, 2, and 3 years post-procedure.

The total study duration from start-up to close-out is expected to be 60 months. A primary endpoint analysis will be submitted to the FDA for PMA approval upon completion of the 1-year follow-up.

### **3.2. Study Endpoints**

#### **3.2.1. Definitions**

Stroke: An acute neurologic event with focal symptoms and signs, lasting for 24 hours or more.

Minor Stroke: A stroke that resolves completely within 7 days or increases the NIHSS by < 4 points.

Major Stroke: A stroke that persists after 7 days and increases the NIHSS by  $\geq 4$  points.

Ipsilateral Stroke: A stroke affecting the cerebral hemisphere supplied by the carotid artery that is being treated.

Myocardial Infarction: A troponin level that is twice the upper limit of the normal range or higher according to the center's laboratory, accompanied by either chest pain/symptoms consistent with ischemia or ECG evidence of ischemia.



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### 3.2.2. Primary Endpoint

The primary study endpoint is a composite of Major Adverse Events (MAE) defined as death, any stroke, or myocardial infarction (MI) through 30 days post-index procedure, and ipsilateral stroke between 31 days and 1 year. All primary endpoint events will be adjudicated and determined by the study Clinical Events Committee.

### 3.2.3. Secondary Endpoints

Stent Technical Success: Successful deployment of a GORE® Carotid Stent

EPD Technical Success: Technical success for the GORE® Embolic Filter is defined as: Device delivered, placed, and retrieved without requiring assisting interventional methods.

Procedure Success: Successful GORE® Carotid Stent deployment, <30% residual angiographic stenosis by visual assessment post-procedure in the target lesion and no in-hospital (pre-discharge) Major Adverse Event

30-Day Major Adverse Events: Composite of death, any stroke, or myocardial infarction through 30 days post-index procedure

In-stent Restenosis: Measured as percent stenosis at follow-up evaluation within the stented lesion or within 5 mm proximal or distal to the stent. Additionally will assess percent of subjects with stenosis  $\geq 50\%$  by ultrasound and  $\geq 80\%$  by angiographic evaluation

Target Lesion Revascularization (TLR): any clinically driven revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis, performed to open or increase the luminal diameter inside or within 5 mm of the previously treated lesion.



CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

## 4. Study Population

### 4.1. Description of Population

The study has been designed with standard eligibility criteria to address any known or foreseeable factors that may compromise the outcome of the study or the interpretation of results.

The following sections outline the specific inclusion and exclusion criteria for the study according to clinical, angiographic, and neurologic components. Patients who meet all of the General Inclusion Criteria, at least one of the High-Risk Inclusion Criteria, and none of the General and Angiographic Exclusion Criteria will be eligible for study participation. All potential patients considered for this study should have been diagnosed with carotid stenosis and be considered a high perioperative risk for carotid endarterectomy.

### 4.2. Inclusion Criteria

For inclusion in the study, a patient must meet all general inclusion criteria, as shown below:

#### **General Inclusion Criteria:**

1. Patient is at least 18 years old at informed consent
2. Patient is willing and capable of complying with all study protocol requirements, including specified follow-up period and can be contacted by telephone.
3. Patient is willing to provide written informed consent prior to enrollment in study.
4. Patient has no childbearing potential, or is a non-lactating female of childbearing potential practicing an acceptable method of birth control with a negative pregnancy test within 10 days of study procedure.
5. Patient is either:
  - *Symptomatic* with carotid stenosis  $\geq 50\%$  as determined by angiography using NASCET methodology<sup>13</sup>. Symptomatic is defined as amaurosis fugax ipsilateral to the carotid lesion; TIA or non-disabling stroke within 180 days of the procedure within the hemisphere supplied by the target vessel; or
  - *Asymptomatic* with carotid stenosis  $\geq 80\%$  as determined by angiography using NASCET methodology.
6. Patient has a target lesion located at the carotid bifurcation and/or proximal ICA.
7. Patient has a single de novo or restenotic (post CEA) target lesion that can be covered by a single 40mm stent.
8. Patient has a stent landing zone diameter between 3.7 mm and 9.0 mm

#### **High Risk Inclusion Criteria:**

For inclusion in the study, a patient must qualify in **at least one** High-Risk condition, as shown below:



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### **Anatomic Conditions**

1. Patient has surgically inaccessible lesions at or above the level of C2 or below the clavicle.
2. Patient is status/post radical head or neck surgery or radiation therapy.
3. Patient has spinal immobility of the neck.
4. Patient has the presence of tracheostomy stoma.
5. Patient has laryngeal palsy or laryngectomy.
6. Patient has contralateral laryngeal nerve paralysis.
7. Patient has restenosis after a previous CEA.

### **Co-morbid Conditions**

1. Patient is  $\geq 75$  years of age at time of enrollment.
2. Patient has NYHA Class III or IV congestive heart failure (CHF).
3. Patient has chronic obstructive pulmonary disease (COPD) with FEV  $< 30\%$ .
4. Patient has a left ventricular ejection fraction (LVEF)  $< 30\%$ .
5. Patient has documented uncontrolled diabetes.
6. Patient has unstable angina with ECG changes.
7. Patient has had a recent myocardial infarction ( $\geq 72$  hours,  $< 30$  days).
8. Patient has coronary artery disease with two or more vessels with  $\geq 70\%$  stenosis.
9. Patient has planned CABG or valve replacement surgery between 31-60 days after the CAS procedure.
10. Patient has contralateral total occlusion of the ICA.

## **4.3. Exclusion Criteria**

### **General Exclusion Criteria:**

A patient is not eligible for enrollment in the study if he/she meets any of the following general exclusion criteria:

1. Patient has life expectancy of less than one year.
2. Patient is experiencing (or has experienced) an evolving, acute, or recent disabling stroke.
3. Patient has anticipated or potential sources of emboli (e.g. atrial fibrillation, known previously symptomatic patent foramen ovale (PFO), mechanical heart valve, or DVT treated within 6 months).
4. Patient has had an acute myocardial infarction within 72 hours prior to index procedure.
5. Patient has had any major surgical procedure (i.e. intraabdominal or intrathoracic surgery or any surgery/interventional procedure involving cardiac or vascular system) within 30 days of the index procedure.
6. Patient plans to have a major surgical procedure (i.e. intraabdominal or intrathoracic surgery or any surgery/interventional procedure involving cardiac or vascular system) within 30 days after index procedure.
7. Patient has a history of major, disabling ipsilateral stroke with residual deficit that may confound the neurological subject assessments.



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8. Patient has known severe carotid stenosis contralateral to the target lesion requiring treatment within 30 days following the index procedure.
9. Patient has a modified Rankin Scale of >3 or has another neurological deficit not due to stroke that may confound the neurological subject assessments.
10. Patient has chronic renal insufficiency (serum creatinine  $\geq 2.5$  mg/dL).
11. Patient has platelet count  $< 100,000/\mu\text{L}$ .
12. Patient has known sensitivity to heparin or previous incidence of Heparin-Induced Thrombocytopenia (HIT) type II.
13. Patient has contraindication to standard of care study medications, including antiplatelet therapy.
14. Patient has known sensitivity to contrast media that cannot be adequately controlled with pre-medication.
15. Patient has known bleeding diathesis or hypercoagulable state or refuses blood transfusions.
16. Patient has intracranial pathology that, in the opinion of the investigator, makes the patient inappropriate for study participation (e.g. brain tumor, AVM, cerebral aneurysm, etc) or would confound neurological evaluation.
17. Patient had intracranial hemorrhage within the last 90 days.
18. Patient is contraindicated for the GORE® Embolic Filter per the criteria outlined in the IFU.
19. Patient is currently enrolled in another investigational study protocol and has not completed its primary endpoint or that will confound the current study endpoints. Patients who are involved in the long-term surveillance of a clinical study are eligible.

**Angiographic Exclusion Criteria:**

A patient is not eligible for enrollment in the study if he/she meets any of the following angiographic exclusion criteria:

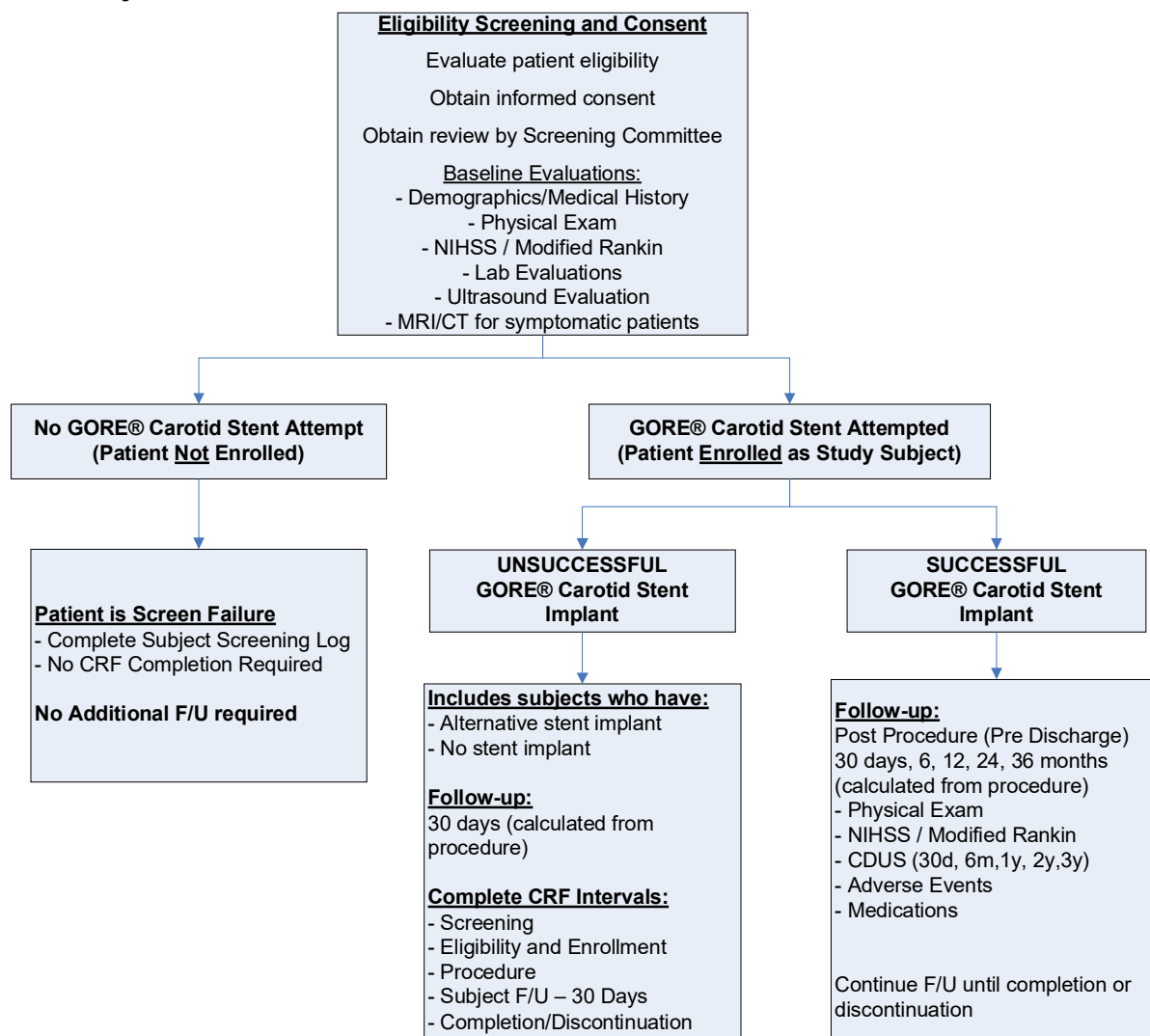
1. Patient has a total occlusion of the target carotid arteries (i.e., CCA or ICA).
2. Patient has a previously placed arterial stent distal to or including the origin of the ipsilateral great vessel (includes a stent anywhere in the ICA, CCA or brachiocephalic artery).
3. Patient has severe lesion calcification that may restrict the full deployment of the carotid stent.
4. Patient has the presence of filling defect or thrombus in target vessel.
5. Patient has occlusion or presence of “string sign” of the target vessel.
6. Patient has carotid (intracranial) stenosis located distal to target stenosis that is more severe than target stenosis.
7. Patient has  $\geq 50\%$  stenosis of the CCA proximal to the target lesion.
8. Patient has known mobile plaque, thrombus, or excessive calcification in the aortic arch.
9. Patient has aneurysmal carotid bifurcation on the ipsilateral side.
10. Patient has tortuous anatomy or disease morphology which would prohibit the safe placement of guide catheter, sheaths, embolic protection systems or stent systems within the access or target vessel.



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## 5. Study Procedures/Evaluations

### 5.1. Study Procedures and Evaluation Schema



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MD133246 Protocol Template

Revision#: 1

Doc Type: GC

## 5.2. Schedule of Events

The table below presents the procedures and evaluations for each protocol interval.

Procedure or Evaluation	Screening	Pre-procedure	Procedure/ Enrollment	Post-Procedure (prior to hospital discharge)	30 days (±7 days)	6 months (±14 days)	1 Year (±30 days)	2 & 3 Years (±45 days)	Unscheduled	Early Withdrawal
Informed Consent	X									
Demographics & Medical History	X									
Exam & Vital Signs <sup>7</sup>	X <sup>6</sup>			X	X	X	X	X	X <sup>5</sup>	X
NIH Stroke Scale <sup>1</sup>		X		X	X	X	X	X	X <sup>5</sup>	X
Modified Rankin Scale <sup>6</sup>	X				X	X	X	X	X <sup>5</sup>	X
CT Scan or MRI	X <sup>2</sup>									
Carotid Duplex Ultrasound	X <sup>3</sup>				X	X	X	X	X <sup>5</sup>	X
Cerebral Angiography			X						X <sup>5</sup>	
Screening angiogram or CTA	X									
Screening Committee review	X									
12-lead ECG <sup>6</sup>	X			X					X <sup>5</sup>	
Chemistry <sup>6</sup> (BUN, Creatinine)	X								X <sup>5</sup>	
Hematology <sup>6</sup> (CBC with Platelets)	X			X					X <sup>5</sup>	
Cardiac Enzymes (Troponin)		X		X					X <sup>5</sup>	
Pregnancy Test <sup>4</sup>		X								
Assess Concomitant Medications(antiplatelet or anticoagulant therapy)	X	X	X	X	X	X	X	X	X	X
Assess Adverse Events			X	X	X	X	X	X	X	X

- 1 Neurological assessments by a physician certified in the administration of NIHSS or research personnel certified in the administration of NIHSS
- 2 Required for symptomatic patients only within 180 days prior to index procedure
- 3 Obtained within the 60 days preceding the index procedure
- 4 Obtained within the 10 days preceding the index procedure. Pregnancy test (via urine or blood) required for females of childbearing potential
- 5 To be done when clinically indicated



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- 6 May be obtained at either screening or pre-procedure visit  
7 Vital Signs include: Blood Pressure, Pulse, and respirations. Collection of height and weight will be done at screening. Temperature should be collected pre- and post- procedure at a minimum

### 5.3. Informed Consent Process

All patients must provide written informed consent prior to submission of pre-procedure imaging and medical history to the Screening Committee for review (refer to Section 5.5 for details) and prior to any study related procedures being performed. The case history (i.e. source documents/subject chart) for each subject shall document that such informed consent was obtained. The IRB approved consent form will be signed and personally dated by the subject, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the subject records. A copy of the informed consent document will be given to the subject for their records.

### 5.4. General Study Evaluation Guidelines

For the purposes of the study the following are required:

National Institutes of Health Stroke Scale (NIHSS) may only be performed by an individual certified to perform the NIHSS even if others may be qualified per state or local regulation. Any potential endpoint neurological symptoms will be assessed by the NIHSS. All NIHSS certifications must be kept up to date.

Electrocardiograms (ECG) will not be sent to a core lab and should be reviewed per site's standard processes.

Screening and follow-up carotid duplex ultrasounds will be sent to the ultrasound core lab. Any unscheduled ultrasounds performed due to an Adverse Event will also be sent to the core lab. Please refer to section 6.4 for details.

All applicable angiograms as well as any re-intervention angiograms will be sent to the Angiographic core lab. Please refer to sections 5.7 and 6.4 for details.

Other tasks may be performed by those individuals who are qualified by training and who have been designated by the site's Principle Investigator to perform those tasks

### 5.5. Pre-Screening/Screening

All patients who sign an ICF will be considered entered into the screening phase of the study. A subject screening log will be maintained at each site to document select information about the patients who sign informed consent. For patients who did not meet eligibility criteria **after** signing informed consent, the reasons for exclusion will be documented on the subject screening log.

The following evaluations will be conducted at the **screening visit** or must have been completed no more than 30 days prior to enrollment (except as noted):

- Informed consent (prior to any study related procedures being performed)



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- Inclusion and exclusion criteria assessed; confirmation is required by Screening Committee
- Assess medical history, demographics, and concomitant medications
- Modified Rankin Scale
- 12-lead ECG
- Examination and vital signs
- Chemistry (BUN & Creatinine)
- Hematology (CBC including platelets)
- Bilateral Carotid Duplex Ultrasound (within the 60 days preceding the index procedure)
- Angiography (within 30 days) and/or CTA (within 60 days)
- CT or MRI Brain Imaging for symptomatic patients only (Within 180 days of the index procedure)

### **Pre-screening Assessment**

A Screening Committee will review pre-operative angiography and/or CTA, along with patient medical history, for assessment of entry criteria, and approval prior to the study procedure. The Screening Committee will be comprised of an interdisciplinary team of study investigators with pertinent knowledge in carotid stenting. The members will not review potential cases from their own sites. The members will be compensated for their involvement in the Screening Committee, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under pre-specified procedures as outlined in the Screening Committee Charter.

Prior to a patient being enrolled in the study, the investigational site must receive confirmation from the Screening Committee that the subject is eligible to be enrolled. Although patient may be deemed eligible to be enrolled, it is still the responsibility of the investigator to assess all inclusion and exclusion criteria prior to enrollment.

### **Screening Angiogram and/or CTA**

In addition to review of medical history, patients will be screened by the Screening Committee based on the results of an angiogram or CTA. These images must include at a minimum the aortic arch, ipsilateral carotid artery (origin and bifurcation), target lesion and intracranial and extracranial views. A complete diagnostic study will be needed in order to evaluate fully the patient against entry criteria. Submission of complete case images is strongly encouraged.

### **Carotid Duplex Ultrasound**

Patients will be screened using a bilateral carotid duplex ultrasound within 60 days of enrollment to verify that baseline percent stenosis values are consistent with entry criteria and justify proceeding with angiography and stent placement.

The diagnostic angiography results prior to the stenting procedure will be the definitive measure of compliance with vessel stenosis criteria.



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If a bilateral carotid duplex ultrasound was completed prior to the patient's consent to participate in the clinical trial but is within 60 days preceding the study procedure, the results may be used in lieu of repeating the ultrasound for the clinical trial.

### **MRI / CT for Symptomatic Patients**

CT or MRI brain imaging is required for symptomatic patients in order to rule out non-carotid pathology. Additional assessment of the carotid arteries and the morphology of the aortic arch may be achieved through CTA or MRA but the results of these studies may not be used as a substitute for a carotid ultrasound or carotid angiography. If CT or MRI brain imaging was completed at the time of the "symptomatic" event (within 180 days) and is prior to the patient's informed consent to participate in the clinical trial, the CT or MRI results obtained following that event may be used in lieu of repeating the imaging for the clinical trial.

## **5.6. Pre-Procedure Assessments**

The following must be completed within 24 hours preceding the index procedure:

- Exam and vital signs (if not done at screening)
- NIHSS
- Modified Rankin Scale (if not done at screening)
- 12-lead ECG (if not done at screening)
- Baseline Cardiac Enzyme -Troponin (may be obtained once arterial access is gained but not after any interventional wires enter the subject's vasculature)
- Pregnancy test if applicable (within the 10 days preceding the index procedure)
- Blood work not completed at screening visit

Concomitant medications (antiplatelet or anticoagulant therapy)

### **Pre Procedure Antiplatelet Therapy**

Preparation of patients receiving the GORE® Carotid Stent should include initiation of an appropriate dosage of oral antiplatelet medication prior to and following the procedure. Effective anticoagulation therapy should be maintained throughout the procedure and continued into the postoperative period as deemed appropriate by the treating physician.

Prior to the index procedure, patients must be on a form of antiplatelet therapy. Patients who are on antiplatelet therapy prior to consenting for the trial may continue their current regimen. However, if a patient is not on any antiplatelet regimen, the following dosages are recommended:

- Aspirin 75-325 mg by mouth beginning 3 days prior to procedure
- Clopidogrel 75 mg by mouth beginning 3 days prior to procedure

If the above is not possible the following may be administered 4-6 hours prior to procedure:

- Aspirin 325 mg by mouth



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- Clopidogrel 75-600 mg by mouth (in accordance with local standard of practice)

### 5.7. Procedure

The following will be collected during the procedure and enrollment time points:

- Cerebral angiography to confirm Angiographic entry criteria
- Concomitant medications (antiplatelet or anticoagulant therapy)
- Adverse events assessment

Only physicians who have received appropriate training and are familiar with the principles, clinical applications, complications, side effects and hazards commonly associated with carotid interventional procedures should use this device.

The index procedure begins at time of vascular access and is considered completed at the time of vascular closure, sheath removal, or when all wires, catheters and devices are removed and the sheath is secured for removal outside the cath lab; whichever comes first. This information will be collected on the procedure case report form.

The procedure is performed under local anesthesia with minimal sedation to facilitate continuous neurological evaluation. The need for continuous monitoring of the subject's baseline level of awareness during the procedure, with techniques that can consist of a rubber squeeze toy or verbal verification, should be utilized and explained to the subject. If it is believed that a neurological status change has occurred, the NIHSS will be repeated.

An initial arch and carotid angiogram must be performed prior to cannulation of the arch vessels or the carotid artery. Cerebral angiograms (extracranial and intracranial images) must also be completed showing the tip of the catheter, or other form of calibration, and the carotid bifurcation. This complete diagnostic study is required to fully evaluate the subject against angiographic exclusion criteria. If subjects have undergone the above diagnostic imaging within 30 days preceding the index procedure, these films may be substituted for performance of repeat diagnostic angiography. These films must be made available to the investigator prior to the procedure and be submitted to the angiographic core lab per their specifications following the index procedure.

Once it is determined that the subject meets all entry requirements for the study, systemic anticoagulation should be given. Administer heparin (bivalirudin may be substituted in local regions where approved) to achieve and maintain an activated clotting time (ACT) of  $\geq 250$  seconds prior to deployment of the embolic protection device. Periodic testing of the ACT level should be done to ensure that the ACT level is maintained during the intervention. The use of IIb/IIIa inhibitors is prohibited during the procedure.

### 5.8. Enrollment



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The patient will be considered enrolled in the study when the investigational device enters the patient's vasculature. All patients enrolled in the study should be followed until completion of the study, or withdrawal from study follow-up.

If the decision is made not to attempt the GORE® Carotid Stent and therefore not enroll the patient, the patient will be considered a screen failure and the status and reason for not enrolling noted on the subject screening log.

A patient may only be enrolled into the study once. A patient with carotid artery disease contralateral to the target lesion in which both sides require treatment may be enrolled into the study; however, only one side may be treated at the index procedure.

### **Embolic Protection System**

The investigator must select the GORE® Embolic Filter for embolic protection during the procedure and should pay specific attention to the device IFU for specific patient selection criteria.

After an unsuccessful documented attempt with the GORE® Embolic Filter, an alternative locally approved embolic protection device may be used to complete the procedure.

Unprotected pre-dilation is strongly discouraged. Embolic protection with the GORE® Embolic Filter should be in place prior to stenting.

### **GORE® Carotid Stent**

Selection of the correct size GORE® Carotid Stent should be done using the sizing instructions in the table below and/or the IFU for the device. Oversizing of the stent to the vessel diameter is not recommended.



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	<b><u>GORE® Carotid Stent Part Number</u></b>	<b><u>Unconstrained Stent Dimensions</u></b>	<b><u>Reference Vessel Diameter</u></b>	<b><u>Minimum Introducer or Guiding Sheath Catheter I.D.</u></b>
5F	GCS5530	5 x 30 mm	3.7-4.5 mm	074" (1.88 mm)
	GCS5540	5 x 40 mm		
	GCS6630	6 x 30 mm	4.5-5.4 mm	
	GCS6640	6 x 40 mm		
	GCS7730	7 x 30 mm	5.4-6.3 mm	
	GCS7740	7 x 40 mm		
	GCS8830	8 x 30 mm	6.3-7.2 mm	
	GCS8840	8 x 40 mm		
	GCS6830	6-8 x 30 mm taper	4.5-5.4 mm x 6.3-7.2 mm	
GCS6840	6-8 x 40 mm taper			
6F	GCS9930	9 x 30 mm	7.2-8.1 mm	080" (2.03 mm)
	GCS9940	9 x 40 mm		
	GCS0030	10 x 30 mm	8.1-9.0 mm	
	GCS0040	10 x 40 mm		
	GCS7930	7-9 x 30 mm taper	5.4-6.3 mm x 7.2-8.1 mm	
	GCS7940	7-9 x 40 mm taper		
	GCS8030	8-10 x 30 mm taper	6.3-7.2 mm x 8.1-9.0 mm	
	GCS8040	8-10 x 40 mm taper		

Post-procedural extracranial and intracranial angiograms should be performed in accordance with the angiographic core laboratory specifications.

#### **GORE® Carotid Stent Technical Failure**

If a GORE® Carotid Stent is not implanted due to technical reasons, another locally approved carotid stent may be used to complete the procedure. Subjects who do not have a successful GORE® Carotid Stent implant during the index procedure will be considered technical failures. Technical failure subjects only require follow-up through 30 days post-procedure and will then have completed the study.

Device failures and malfunctions will be documented on the Stent Assessment case report form and the study device will be returned to W. L. Gore and Associates, Inc. for analysis. Instructions for returning the study device will be provided in the study binder supplied by W. L. Gore and Associates, Inc.

Examples of when to return device malfunctions include (but are not limited to):

- Device fails to perform as intended
- Device physically deforms or breaks, even if due to user error
- Packaging is defective

Any opened but unused device will need to be returned to W. L. Gore and Associates, Inc.



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

### 5.9. Repeat Interventions

Any clinically driven revascularization procedure of the original treatment site, including angioplasty, stenting, endarterectomy, or thrombolysis performed to open or increase the luminal diameter inside, or within 5 mm, of the previously treated lesion may be performed.

Only devices or therapies that are commercially available at the time of the revascularization may be used. All angiograms in relation to the re-intervention must be sent to the Angiographic core lab. Please refer to section 6.4.

### 5.10. Post-Procedure

The following will be completed between 4-48 hours post procedure or prior to discharge, whichever comes first (unless otherwise indicated):

- Exam and vital signs
- NIHSS
- 12-lead ECG
- Hematology blood work (CBC including platelets)
- Cardiac Enzymes (Troponin) – to be completed within 8-16 hours post-procedure. If the subject experiences cardiac related chest pain lasting longer than 15 minutes, a change in baseline ECG, or the value has increased to 2 (two) times the upper limit of normal, serial cardiac enzymes will also be completed at 18-24 hours post procedure.
- Adverse events assessment
- Concomitant medications (antiplatelet or anticoagulant therapy) assessment

#### Post Procedure Antiplatelet Therapy

Subjects will receive post-procedure antiplatelet medication per the institution's standard of care, or using the following recommended regimen:

- Aspirin 75-325 mg by mouth once a day for the duration of the study
- Clopidogrel 75 mg by mouth once a day for 30 days; then per physician discretion

### 5.11. Follow-Up

Subjects with successful GORE® Carotid Stent implant will return for follow-up at 30 days, 6 months, 1, 2 and 3 years. Subjects considered Technical Failures (no GORE® Carotid Stent implant) are only required to complete a 30 day follow-up and will have then completed the study.

The following assessments are required for each follow-up visit (unless indicated otherwise):

- Exam and vital signs
- NIHSS
- Modified Rankin Scale
- Carotid Duplex Ultrasound of target vessel
- Concomitant medications (antiplatelet or anticoagulant therapy) assessment
- Adverse events assessment



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### Follow-up Visit Windows

The follow-up visits should be completed within an acceptable time frame and in accordance with the protocol defined visit windows. All intervals are to be calculated from the index procedure. The 6-Month visit target is 180 days. The yearly visits are calculated on a calendar year from index procedure.

30 Days	6 Months (180 Days)	1 Year	2 & 3 Years
± 7 days	± 14 days	± 30 days	± 45 days

If the visit is not able to be completed during these windows the visit should be completed as soon as possible; however, it will be considered a protocol deviation and should be reported per local IRB policy.

### 5.12. Subject Withdrawal from the Clinical Study

A subject may withdraw from the clinical study at any time and should notify the Investigator in this event. The Investigator may also withdraw the subject from the clinical study at any time based on his/her medical judgment. The Investigator will encourage subjects to return for all required follow-up visits.

All subjects who withdraw from the study should complete an end of study visit. No further visits are required by the subject once the end of study visit is complete.

### 5.13. Subject Lost to Follow-Up

The Investigator should encourage subjects to return for the required follow-up visits. These measures are important as the clinical study objectives may not be realized if a large number of subjects are lost to follow-up (LTF).

A subject may withdraw from the clinical study at any time and should notify the Investigator in this event. If a subject refuses to return for the follow-up visits, the Investigator will attempt to obtain at least vital status and whether or not the subject has experienced a stroke or TIA. In the event of subject death, a death certificate or autopsy report should be obtained to confirm cause of death and reported on the Subject Completion / Discontinuation Form.

A subject will be considered LTF and discontinued from the study once they have missed two required follow-up visits and three documented attempts for each pending study related visit have been made by the Investigator to contact the subject.

One of the three documented attempts must include a certified (traceable) letter. The Investigator must complete the appropriate CRF (CRF Study Completion / Discontinuation Form) documenting the subject's withdrawal or discontinuation from the clinical study. The subject will be considered withdrawn once the Sponsor receives the respective CRFs.



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The Investigator may also withdraw the subject from the clinical study at any time based on the Investigator's medical judgment.

The study Monitor will ensure that subject withdrawals are documented properly, discussed with the Investigator, and reported to the Sponsor

#### **5.14. Subject Study Completion**

A subject has completed the study when he/she has completed the 3-year follow-up evaluations. Any subject that does not complete these requirements due to voluntary withdrawal, physician withdrawal, death, or any other reason will be considered as an early withdrawal. In the event of a Technical Failure (no GORE® Carotid Stent implanted), the subject will be followed through the 30-day visit and will be considered to have completed the study.

#### **5.15. Explant Procedures**

The GORE® Carotid Stent may be explanted during a surgical procedure or as part of an autopsy. Sites are requested to return explanted device to the Sponsor for gross and histological evaluation. Prior to planned or potential device retrieval, contact the Gore associate managing the study to communicate that a specimen is being retrieved from a study subject. A specimen shipping kit will be immediately sent to the Site. The specimen kit provides specific packaging and handling instructions for the specimen and contains a shipping container.

### **6. Clinical Study Administration**

#### **6.1. Device Training**

Physician device training will be provided by a qualified Gore Associate. The minimum requirements for physician device training include:

1. Didactic training for each investigator at site
2. First case for each investigator is supported by a qualified Gore Associate.

#### **6.2. Monitoring**

Site monitoring for this study will be provided by:

[REDACTED]

The Site monitors are qualified by training and experience to oversee the progress of the study at the Site and will ensure that the Investigators and their staff understand and adhere to both the applicable regulatory requirements and the study protocol. In addition, they may assist in resolution of any problems that may arise during the study.



**CONFIDENTIAL INFORMATION**

#### Site Initiation

Site initiation will be performed to ensure that each Investigator and his/her staff understands the protocol, applicable regulations, human subject protection requirements, and the Investigator's obligations. This visit will ensure that required documentation with the appropriate approval is in place prior to subject enrollment.

Training on the study EDC System and data gathering requirements may also be done at this time.

#### Periodic Site Monitoring

Periodic Site monitoring will occur as necessary to ensure continuing adequacy of facilities and adherence to the clinical study protocol, GCP, and applicable regulations and laws that pertain to the conduct of the clinical study. These activities will also review the CRFs and source documentation, the timely submission of accurate records to the Sponsor, and the maintenance of proper records. A report will be written following each Site visit and a follow up letter will be provided to the Site with a summary of findings.

### **6.3. Device Accountability and Storage**

The GORE® Carotid Stent may only be used under the supervision of the Investigator and in strict accordance with this protocol and applicable laws and regulations. The device may only be implanted in subjects who meet the inclusion/exclusion criteria set forth in this protocol and used only as described in this protocol. The Investigator will maintain accurate, detailed records of all devices received from the Sponsor and the disposition of each device. The Investigator will record each device used on the corresponding CRF. The Investigator will notify the Sponsor immediately if any devices are damaged or unaccounted for. The devices must be accessible only to the personnel involved in the study and stored in a secure location.

Upon completion or termination of the clinical study or the Investigator's participation in the clinical study, or at the Sponsor's request, the Investigator will return any remaining supply of the device to the Sponsor.

### **6.4. Core Labs**

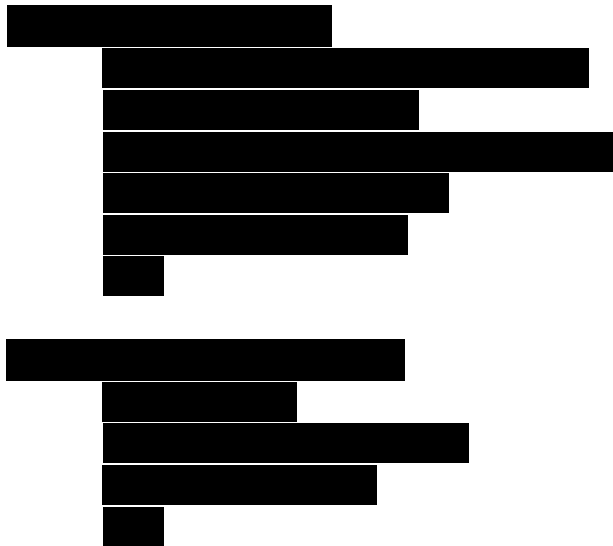
Core Lab services for this study will be provided by:

[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]  
[REDACTED]



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Please refer to the Imaging Guidelines for each specific core lab for instructions on submission of images and specific requirements for the images.

#### **6.5. Protocol Deviations**

A Protocol Deviation is defined as any change, divergence, or departure from the study design or procedures of a research protocol. The Investigator is responsible for promptly reporting Protocol Deviations to their reviewing IRB per IRB policy and the Sponsor. The Sponsor will determine the effect of the protocol deviation on the scientific soundness of the clinical study and subject safety and determine if additional reports or actions are required. Additional action may include Site retraining, removal of devices from the Site, and/or Site termination.

The Investigator will not implement any changes to the protocol without first obtaining written agreement from the Sponsor and documented approval from the IRB, except in the event of an immediate hazard(s) to a subject. The Investigator will report the deviation in accordance with the applicable regulations.

#### **6.6. Protocol Amendments**

The Investigator will obtain IRB approval on all amendments in a timely manner. The Sponsor will ensure proper training of Investigator and Site staff on all protocol amendments.

#### **6.7. Sponsor Representatives**

Sponsor representatives may be present during study procedures to provide technical assistance to the Investigator in the use of the device. The activities of these Sponsor representatives will be supervised by the Investigator.



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## 6.8. Access to Source Data/Documents

Source data are defined as all information necessary for the reconstruction and evaluation of the clinical investigation.

The Investigator will keep all study records, source data and investigational devices available for inspection by the Sponsor, Sponsor's monitors, IRB, and regulatory authorities.

## 6.9. Study Records Retention

The Investigator will maintain complete, accurate and current study records as required by applicable regulatory requirements. Records will be maintained during the clinical study and for a minimum of two years after the latter of the date on which the study is terminated or completed, or the date the records are no longer required to support regulatory approval of the device. In any event, clinical study records will not be disposed of, nor custody of the records transferred, without prior written Sponsor approval.

Investigator records will include, but not be limited to:

- All correspondence with another investigator, an IRB, the Sponsor, a monitor, or Regulatory Authority, including required reports.
- Records of receipt, use or disposition of a device that relate to:
  - The type and quantity of device(s) received, the date(s) of its receipt, and lot or batch number or code mark.
  - The names of all persons who received, used, or disposed of each device.
- Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records, including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
  - Documents evidencing informed consent and, for any use of a device without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain the informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.
  - All relevant observations, including records concerning adverse device effects (anticipated and unanticipated), the information and date and condition of each subject upon entering, and information about relevant previous medical history and the results of all diagnostic tests;
  - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, any amendments, and documentation of any deviations from the protocol, including the dates and the reasons for such deviations.
- Any other records that Regulatory Authority requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.
- A certification stating that the US IRB is in compliance with FDA regulations
- A signed Investigator Agreement.
- Any other records as required by the Regulatory Authority, the IRB and the Sponsor.



**CONFIDENTIAL INFORMATION**

The Investigator will prepare and submit the following reports:

- Withdrawal of IRB approval: The Investigator will report any withdrawal of approval within 5 working days after the Investigator has been notified of the withdrawal.
- Progress reports: Progress reports documenting the procedure, AEs and follow-up data concerning individual subjects will be submitted to the Sponsor on standardized CRFs. The Investigator may also be required to submit progress reports and final reports to the IRB and to the Sponsor summarizing the Investigator's experience during the study.
- UADE Reports: UADEs shall be reported as described in Section 9.
- Protocol Deviations shall be reported as described in Section 6.
- Other: Any other reports as reasonably requested by the Sponsor or required by Regulatory Authority.

## 7. Data Collection and Submission

The Clinical Data Management System (CDMS) for this study will be provided by:



### 7.1. Data Collection Methods

This study will report clinical data using the [REDACTED] CDMS web-based application. The CDMS will be the database of record for the protocol and subject to regulatory inspections. All users will be trained to use the CDMS and will comply with study specific guidelines/instructions as well as applicable regulatory requirements.

Subject data will be collected using protocol-specific electronic case report forms (eCRF). The approved annotated case report forms will be used to create the electronic screens in the CDMS application. Site staff will enter data into the eCRF for transmission to the Sponsor. The Sites will be notified of any amendments to the eCRFs.

### 7.2. Data Clarification and Correction

All eCRFs will be evaluated upon receipt by the Sponsor. Corrections to missing, incomplete or inconsistent data will be requested from the Site personnel and made through the CDMS. The changes, reason for changes, and person making the change will be documented in the CDMS.

### 7.3. CRF Completion Schedule

All CRFs should be completed within 14 days of each visit.



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## 8. Risk Assessment

### 8.1. Potential Risks

The risks associated with the GORE® Carotid Stent for use in carotid arteries are expected to be similar to the risks associated with the use of other commercially available standard of care devices.

Such risks associated with these devices, including the GORE® Carotid Stent include, but are not limited to:

- Deployment and retrieval failure
- Detachment and / or implantation of a component of the system
- Stent deformation
- Stent embolization
- Stent / filter entanglement / damage / dislodgement
- Stent malposition
- Stent migration
- Stent thrombosis / occlusion

Risks associated with these devices including the GORE® Carotid Stent or the interventional procedures include, but are not limited to:

- Allergic reactions to anti-platelet agents / contrast medium
- Aneurysm
- Angina / coronary ischemia
- Arrhythmia
- Arterial occlusion / thrombosis at puncture site or remote site
- Arteriovenous fistula
- Bacteremia or septicemia
- Balloon burst or rupture
- Balloon associated thrombosis
- Bleeding from anticoagulant or antiplatelet medications
- Bradycardia / arrhythmia and other conduction disturbances
- Cerebral edema
- Cerebral hemorrhage
- Cerebral ischemia / transient ischemic attack (TIA)
- Congestive heart failure
- Death
- Drug reactions
- Emboli, distal (air, tissue or thrombotic emboli)



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- Emergent or urgent endarterectomy surgery (CEA)
- Fever
- Filter fracture
- Filter thrombosis / occlusion
- Fluid overload
- Groin hematoma, with or without surgical repair
- Headache
- Hemorrhage, with or without transfusion
- Hemorrhagic stroke
- Heparin induced thrombocytopenia (HIT)
- Hyperperfusion syndrome
- Hypotension / hypertension
- Infection and pain at insertion site
- Ischemia / infarction of tissue / organ
- Ischemic stroke
- Myocardial infarction (MI)
- Pain and tenderness
- Pseudoaneurysm, femoral
- Reduced blood flow
- Renal failure / insufficiency
- Restenosis of stented segment
- Seizure
- Sepsis
- Severe unilateral headache
- Stroke / cerebrovascular accident (CVA) or other neurological complications (e.g., paralysis, paraplegia or aphasia)
- Surgery required due to device failure
- Temporary or total occlusion of carotid artery
- Thromboembolic episodes
- Thrombophlebitis
- Transient ischemic attacks (TIA)
- Vascular access complications (e.g., bleeding, vessel damage, pseudoaneurysm and infection)
- Ventricular fibrillation
- Vessel dissection, perforation, or rupture
- Vessel spasm or recoil
- Vessel thrombosis (partial blockage)
- Unstable angina pectoris



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

## 8.2. Minimization of Risks

Potential risks associated with the use of the GORE® Carotid Stent may be minimized by the following activities:

- The Sponsor has performed qualification testing on the device and device components and appropriate quality control measures have been implemented into production.
- Investigators will be selected who are knowledgeable and experienced in carotid artery stenting procedures.
- Comprehensive Site Investigator and staff training will be conducted to share information regarding design and proper use of the GORE® Carotid Stent.
- The Site Investigator, Sub-Investigators, Clinical Study Coordinator(s) or designee at each Site will be trained to the protocol and Subject follow-up requirements.
- Protocol inclusion/exclusion criteria and follow-up schedules are designed to select appropriate subjects and identify potential complications early.
- Subjects will be assessed post-procedure and subsequently on a regular basis to collect information on the subject's status and any reportable adverse events.
- Data completed by the Sites will be monitored to evaluate protocol compliance and the data for accuracy and subject safety.
- Safety and efficacy data obtained during the clinical study will be shared with the Site Investigators to aid understanding of the device and potential complications associated with its use.

## 8.3. Summary of Expected Benefits

The GORE® Carotid Stent is expected to be safe and effective when used to treat stenosis of the carotid artery. The intent is to increase blood flow to the brain while decreasing the narrowing in the artery, and to help prevent future strokes.



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## 9. Adverse Events and Safety Monitoring

Adverse Events (AEs) are defined as any untoward medical occurrences in a subject whether device-related or not.

### 9.1. Anticipated Adverse Events

Anticipated Adverse Events are complications that are known to be associated with carotid artery stenting. Potential complications of carotid artery stenting are listed in Section 8 above. If a complication occurs that is not on the list of known, potential complications and the investigator believes that the complication is a potential UADE (Unanticipated Adverse Device Effects, see section below), the site should immediately contact the Sponsor to determine reporting requirements.

Anticipated Adverse Events are complications that are known to be associated with carotid artery stenosis patients undergoing an angioplasty and stenting procedure. See Section 8, Risk Assessment.

#### 9.1.1. Adverse Event Relationship

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the carotid stent, embolic protection device, procedure, medication, or disease. Only one primary relationship will be assigned to each reported AE.

##### **Study Device-related**

The functioning or characteristics of the device caused or contributed to the Adverse Event.

##### **Embolic Protection System (EPD)-related**

The functioning or characteristics of the EPD caused or contributed to the Adverse Event.

##### **Study Procedure-related**

The study index procedure (and not the device or EPD) caused or significantly contributed to the Adverse Event.

##### **Medication-related**

The Adverse Event was a result of medical therapy prescribed by the study protocol and not the device, EPD, or procedure.

##### **Disease-related**

The Adverse Event was a result of the underlying disease progression for which the study procedure is being performed, and not the device, EPD or procedure.



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

**Not related**

An Adverse Event which cannot be attributed to the device, EPD, procedure, medication or disease.

**Unknown relationship**

The relationship of the Adverse Event to the device, EPD, procedure, medication or disease cannot be determined.

**9.1.2. Adverse Event Classification**

Each AE will be assessed by the Investigator to determine if it is a Serious Adverse Event as defined below:

**Serious Adverse Event**

A Serious Adverse Event is an adverse event that

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

**9.1.3. Adverse Event Reporting and Coding**

AEs will be reported on the appropriate case report form (CRF) for that visit and documented in the subject's permanent medical record. The Investigator at each Site is ultimately responsible for reporting AEs to the Sponsor.

The following information on each reported Adverse Event will be collected:

- Adverse Event Name
- Adverse Event Onset Date
- Relationship
- Classification Serious
- Treatment
- Outcome
- Resolution Date

Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Adverse event submission guidelines:



**CONFIDENTIAL INFORMATION**



- Adverse event reporting begins once the patient is enrolled in the study. All adverse events should be reported from enrollment through study completion/discontinuation.
- Provide a diagnosis if possible. If unable to provide diagnosis, report the symptoms as separate events. Adverse Events should be reported using the full name without abbreviations or narratives.
- Adverse events with an outcome status of “Ongoing” should be assessed at each follow-up evaluation to determine if the event has resolved. Adverse events ongoing at study completion/discontinuation should be left as “Ongoing” on the AE case report form.

#### **9.1.4. Subject Death**

If a subject dies while participating in the study, the cause of death will be reported as the adverse event and “death” reported as the event outcome on the AE case report form. If the subject has other ongoing adverse events at the time of death, the outcome status of those events should be reported as “resolved” on the AE case report form.

The Investigator should obtain all medical records including death certificate and autopsy report for inclusion in reporting to the Clinical Events Committee.

## **9.2. Unanticipated Adverse Device Effects (UADE)**

An unanticipated adverse device effect (UADE) is defined in 21 CFR 812.3(s) as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or protocol.

The Sponsor is required to notify FDA within (10) days of any unanticipated adverse device effect. The Sponsor is required to notify PMDA within (15) days of any unanticipated adverse device effect not resulting in death; the Sponsor is required to notify PMDA within (7) days of any unanticipated adverse device effect resulting in death or which may result in death. If a complication occurs that the Investigator believes may be a potential UADE, the Site should immediately contact the Sponsor to determine reporting requirements. In addition, when there is a reason to believe a device may have malfunctioned, causing potential harm to a patient, the Site should immediately notify the Sponsor.

The Investigator will submit to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than ten (10) days after the Investigator learns of the effect. All UADEs must be documented by the Investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken and outcome. Copies of all supporting documents should be submitted concurrently with the appropriate CRF.

A report from the Sponsor will be submitted to the FDA and to all reviewing IRBs and participating Investigators within 10 working days after the Sponsor first receives notice of the effect.



#### **CONFIDENTIAL INFORMATION**

### **9.3. Data and Safety Monitoring Board**

An independent Data and Safety Monitoring Board (DSMB) will oversee conduct of the study. The DSMB will review accumulating study safety data on a regular basis and will advise the Sponsor regarding the continuing safety of study subjects as well as the continuing validity and scientific merit of the study. The DSMB will be comprised of an interdisciplinary team of at least 3 members (2 voting physicians, and one voting statistician) with pertinent expertise in carotid stenting who are not directly involved in the conduct of the study. The members will be compensated for their involvement in the DSMB, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under pre-specified procedures as outlined in the DSMB Charter in accordance with the FDA's Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees. The DSMB will be responsible for conducting periodic reviews of aggregate data on a prescribed basis. The frequency of data review and other roles and responsibilities of the DSMB will be specified in the DSMB Charter.

Based on the safety data review, the DSMB will make recommendations to the Sponsor. Recommendations may include study continuation with or without major or minor modifications, temporary suspension of enrollment and / or study intervention until some uncertainty is resolved. All final decisions regarding study modifications rest with the Sponsor.

### **9.4. Clinical Events Committee**

An independent Clinical Events Committee (CEC) will review potential primary endpoint events and adjudicate events based on endpoint definitions in the study protocol. The CEC will be comprised of an interdisciplinary team with pertinent knowledge in carotid stenting or the cardiovascular and/or nervous system who are not directly involved in the conduct of the study. The members will be compensated for their involvement in the CEC, including reimbursement for reasonable travel expenses to attend meetings.

This committee will operate under pre-specified procedures as outlined in the CEC Charter. The adjudication process will be initiated after a potential primary endpoint event is reported by the site.



**CONFIDENTIAL INFORMATION**

## 10. Statistical Analysis

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

[REDACTED]

**Abstract**

<p> <b>1.1</b> The following information is provided for the year ended 31 March 2014:</p> <p> <b>1.1.1</b> The company's revenue is £100,000.</p> <p> <b>1.1.2</b> The company's expenses are £80,000.</p> <p> <b>1.1.3</b> The company's profit is £20,000.</p> <p> <b>1.1.4</b> The company's assets are £120,000.</p> <p> <b>1.1.5</b> The company's liabilities are £100,000.</p> <p> <b>1.1.6</b> The company's equity is £20,000.</p> <p> <b>1.1.7</b> The company's cash is £10,000.</p> <p> <b>1.1.8</b> The company's debt is £90,000.</p> <p> <b>1.1.9</b> The company's net worth is £20,000.</p> <p> <b>1.1.10</b> The company's total value is £120,000.</p>	<p> <b>1.2</b> The following information is provided for the year ended 31 March 2015:</p> <p> <b>1.2.1</b> The company's revenue is £110,000.</p> <p> <b>1.2.2</b> The company's expenses are £85,000.</p> <p> <b>1.2.3</b> The company's profit is £25,000.</p> <p> <b>1.2.4</b> The company's assets are £130,000.</p> <p> <b>1.2.5</b> The company's liabilities are £105,000.</p> <p> <b>1.2.6</b> The company's equity is £25,000.</p> <p> <b>1.2.7</b> The company's cash is £11,000.</p> <p> <b>1.2.8</b> The company's debt is £94,000.</p> <p> <b>1.2.9</b> The company's net worth is £25,000.</p> <p> <b>1.2.10</b> The company's total value is £130,000.</p>
--	--

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

## 10.4. Data Analysis

### 10.4.1. Timing of Analyses

The primary endpoint analysis will occur when enrollment and one year follow-up are complete. No interim analyses of the study hypotheses are planned.

### 10.4.2. Baseline Characteristics

Subject demographics, clinical history, risk factors, and preprocedure lesion characteristics will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample).

### 10.4.3. Analysis Sets

The primary endpoint will be analyzed both on an intent-to-treat basis and on a per-protocol basis. The primary analysis set for testing of the primary endpoint is the per-protocol analysis set.

#### Intent-To-Treat (ITT) Analysis Set

The ITT analysis set is defined as all enrolled subjects with adequate informed consent, regardless of whether the study stent was implanted. Because technical failures (test device attempted but not implanted) are followed only to 30 days, this set will be used in the analysis of safety endpoints (major, serious, and nonserious adverse events) to 30 days and secondary endpoints evaluated at procedure, discharge, and 30 days.

#### Per-Protocol Analysis Set (Primary Analysis Set)

For per-protocol analysis, only subjects who had the study stent implanted in the target vessel and had no major protocol deviations will be included in the analysis. Major protocol deviations are defined as protocol deviations with a level of seriousness such that inclusion of the subject(s) would unacceptably bias the primary endpoint analysis. An example of a major protocol deviation might be failure to satisfy eligibility criteria to a degree where the subject does not fit the underlying scientific model for the treatment.

The per-protocol set will be used for the primary analyses of the primary endpoint. Ideally, this analysis set will consist of all subjects from the ITT set with technical success (test device implanted).

The Per-Protocol set will be used in additional analyses of the primary and secondary endpoints.

The primary safety and efficacy endpoints will also be analyzed controlling for the following baseline covariates: age, sex, and race/ethnicity.

Additional subgroup analyses may be performed based on variables identified to be significant predictors ( $p$ -value $<0.05$ ) in multivariate analyses.



CONFIDENTIAL INFORMATION

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

#### **10.4.4. Pooling of Data**

Site data will be pooled based on clinical comparability, i.e., the sites used a common protocol, the sponsor adequately monitored the study to assure protocol compliance, and the data gathering and validation mechanisms were the same across all study sites.

Analyses to justify pooling will include the following:

- The primary endpoint will be presented by institution.
- An assessment of the poolability of the sites using a 2-by-(number of sites) contingency table of MAE outcome versus site. Fisher's Exact Test will be used to assess homogeneity. Sites with fewer than five subjects will be combined based on geographic region.
- If the sites are found to be significantly heterogeneous with respect to the primary endpoint, additional analyses will be conducted to assess differences between sites in baseline and procedural variables that might explain differences in primary outcome.

#### **10.4.5. Statistical Analysis of Primary Endpoint**

The primary endpoint of 1-year MAE is subject-based. A one-sided 95.1% upper confidence bound will be calculated (using the standard error based on  $H_0$ ) and compared to the prespecified performance goal. If this bound is less than the performance goal, then the primary endpoint is met and the GORE® Carotid Stent will have demonstrated acceptable performance. The  $P$  value for the corresponding one-sided normal approximation to the binomial test will be reported. The primary hypothesis test will use  $\alpha=0.049$  to ensure an overall Type-1 error rate  $\leq 0.05$ .

#### **10.4.6. Sensitivity Analyses**

Sensitivity analyses of the primary endpoint will be conducted and will include, at a minimum, a worst-case analysis and tipping point analysis.

#### **10.4.7. Statistical Analysis of Secondary Endpoint(s)**

Secondary endpoints (subject-based unless otherwise specified) will be descriptive only; no formal statistical hypotheses will be tested. Secondary endpoints will be summarized at the specified time points using the descriptive statistics described above. No claims of statistical significance will be made based on secondary endpoint results.  $P$  values from these tests will not be reported in labeling, but may be used for scientific presentations and/or manuscripts.

### **10.5. Publication Plan**

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a trials-registration policy as a condition for publication. This policy requires that all clinical trials be registered in a public trials registry. The Sponsor will register the study and post results as required by this policy and applicable U.S. laws and regulations.



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It is the intent of the sponsor that the multicenter results of this study will be submitted for publication. A publications committee will be established to review the multicenter results and develop publications at the completion of the study. The timing of the multicenter publication may be dependent on regulatory submissions and approvals. Individual investigative sites should coordinate requests for publication through the publications committee or the sponsor.

## 11. Ethical and Regulatory Considerations

### 11.1. Statement of Compliance

The study will be conducted in compliance with this protocol, International Conference on Harmonization Good Clinical Practice E6 (ICH-GCP), and applicable local regulatory requirements.

The following are applicable to this study:

21 CFR Part 11	Electronic Records; Electronic Signatures
21 CFR Part 50	Protection of Human Subjects
21 CFR Part 54	Financial Disclosure By Clinical Investigators
21 CFR Part 56	Institutional Review Boards
21 CFR Part 812	Investigational Device Exemptions
ICH-GCP E6	International Conference on Harmonisation Regulations Guideline For Good Clinical Practice

### 11.2. Compliance Responsibilities

The Sponsor will conduct the clinical study in accordance with all applicable regulations and laws. The Sponsor will be responsible for documenting that Investigators have the necessary skills, training and information to properly conduct the clinical study. The Sponsor will ensure proper monitoring of the clinical study and ensure the Site has obtained IRB approval prior to enrollment. The Sponsor will provide information to the Investigators, the reviewing IRB and governing regulatory agencies concerning the progress and any new material information about the clinical study.

The Investigator will conduct the clinical study in accordance with all applicable regulations and laws, any relevant agreements, the study protocol, and all approval conditions of the reviewing IRB and governing regulatory agencies. The Investigator will ensure IRB approval is obtained prior to enrollment, maintained throughout the course of the study, and that all IRB reporting requirements are met. The Investigator is responsible for protecting the rights, safety, and welfare of subjects under the Investigator's care and for the control of devices under investigation. The Investigator is also responsible for ensuring that informed consent is properly obtained.



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### **11.3. Informed Consent**

The Investigator shall ensure that all potential subjects for this study are provided with a consent form describing this study and sufficient information to make an informed decision about their participation.

The formal consent of a subject, using the IRB-approved consent form, must be obtained by the Investigator before that subject undergoes any study procedure. The consent form will be signed and personally dated by the subject, and the person who conducted the informed consent discussion. The original signed informed consent form will be retained in the subject records. A copy of the informed consent document will be given to the subject for their records. Any significant, new information which emerges while the study is in progress that may influence a subject's willingness to continue to take part in the study will be provided.

The Investigator shall ensure that documentation of the acquisition of informed consent is recorded in each subject's records in accordance with applicable regulations.

### **11.4. Independent Ethical Review**

The Investigator shall not enroll any subjects prior to obtaining approval for the study from a properly constituted independent IRB.

The Investigator will submit the protocol, informed consent forms, and other information to be provided to subjects, such as survey instruments or questionnaires, and any proposed advertising/recruitment materials for written approval.

### **11.5. Conflict of Interest**

All Investigators will follow their Site's conflict of interest policies.

Investigators will provide Sponsor with sufficient accurate financial disclosure information to allow Sponsor to submit a complete and accurate certification or disclosure statement as required under 21 CFR 54, Financial Disclosure by Clinical Investigators. Investigators will promptly update this information if any relevant changes occur during the course of the investigation and for one (1) year following completion of the study.

### **11.6. Confidentiality**

All subject records will be kept confidential to the extent provided by applicable laws and regulations. The study monitors and other authorized representatives of the Sponsor may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records.

Such records may also be reviewed by the Site's IRB and other regulatory bodies.

The Investigator will inform the subjects that their records may be reviewed.



**CONFIDENTIAL INFORMATION**

## 12. References

- <sup>1</sup> Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. Endarterectomy for asymptomatic carotid artery stenosis.. JAMA 1995; 273:1421-8.
- <sup>2</sup> American Heart Association. Heart Disease and Stroke Statistics – 2006 Update. Dallas, TX.
- <sup>3</sup> Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1991;32: 445-53.
- <sup>4</sup> Moore WS, Barnett HJ, Beebe HG, Bernstein EF, Brener BJ, Brott R et al. Guidelines for carotid endarterectomy. A multidisciplinary consensus statement from the Ad Hoc Committee, American Heart Association. Circulation 1995;91:566-79.
- <sup>5</sup> Greenstein AJ, Chassin MR, et al. Association between minor and major surgical complications after carotid endarterectomy: Results of the New York Carotid Artery Surgery study. J Vasc Surg 2007;46:1138-46.
- <sup>6</sup> Yadav JS, Wholey MH, Kuntz RE, et al : Protected carotid-artery stenting versus endarterectomy in high risk patients. N Engl J Med 2004;351:1493-1501
- <sup>7</sup> Hassoun HT, Malas MB, Freischlag JA. Secondary Stroke Prevention in the Era of Carotid Stenting. Arch Surg 2010;145(10):928-935.
- <sup>8</sup> Chung C, Shah TR, Han D, Marin ML, Faries PL. Carotid Stenting Trials: What Have they Taught Us? Persp in Vasc Surg and Endovasc Ther 2010;22(2):93-103.
- <sup>9</sup> Brott TG, Hobson RW, Howard G, et al. Stenting versus endarterectomy for treatment of carotid artery stenosis. N Engl J Med 2010;363:11-23.
- <sup>10</sup> Pierce DS, Rosero EB, Modrall G, et al. Open-cell versus closed-cell stent design differences in blood flow velocities after carotid stenting. J Vasc Surg 2009;49:602-6.
- <sup>11</sup> Siewiorek GM, Endor FA, Wholey MH. Clinical Significance and Technical Assessment of Stent Cell Geometry in Carotid Artery Stenting. J Endovasc Ther 2009;16:178-188.
- <sup>12</sup> Müller-Hülsbeck S, Preuß H, Elhöft H. CAS: Which stent for which lesion. J Cardiovasc Surg 2009;50:767-72.
- <sup>13</sup> Hathout GM, Fink JR, El-Saden SM, Grant EG. Sonographic NASCET Index: A New Doppler Parameter for Assessment of Internal Carotid Artery Stenosis. Am J Neurorad 2005;26:68-75.
- <sup>14</sup> AbuRahma AF, Snodgrass KR, Robinson PA, Wood DJ, Meek RB, Patton DJ. Safety and durability of redo carotid endarterectomy for recurrent carotid artery stenosis. Am J Surg 1994;168:175–8.
- <sup>15</sup> Das MB, Hertzner NR, Ratliff NB, O'Hara PJ, Beven EG. Recurrent carotid stenosis. A five year series of 65 operations. Ann Surg 1985;202:28–35.
- <sup>16</sup> Francfort JW, Gallagher JF, Penman E, Fairman RM. Surgery for radiation- induced symptomatic carotid atherosclerosis. Ann Vasc Surg 1989;3:14–9.
- <sup>17</sup> Gasecki AP, Eliasziw M, Ferguson GG, Hachinski V, Barnett HJ. Long-term prognosis and effect of endarterectomy in patients with severe carotid stenosis and contralateral carotid stenosis or occlusion: results from NASCET. North American Symptomatic Carotid Endarterectomy Trial (NASCET) group. J Neurosurg 1995;83:778–82.
- <sup>18</sup> Goldstein LB, McCrory DB, Landsman PB, et al. Multi-center review of preoperative risk factors for carotid endarterectomy in patients with ipsilateral symptoms. Stroke 1994;25:1116–21.
- <sup>19</sup> Goldstein LB, Samsa GP, Machtar DB, Oddone EZ. Multi-center review of preoperative risk factors for endarterectomy for asymptomatic carotid artery stenosis. Stroke 1998;29:750–3.
- <sup>20</sup> Hamdan AD, Pomposelli FB, Jr., Gibbons GW, Campbell DR, LoGerfo FW. Renal insufficiency and altered postoperative risk in carotid endarterectomy. J Vasc Surg 1999;29:1006–11.
- <sup>21</sup> Hertzner NR, O'Hara PJ, Mascha EJ, Krajewski LP, Sullivan TM, Beven EG. Early outcome assessment for 2228 carotid endarterectomy procedures: the Cleveland Clinic experience from 1989 to 1995. J Vasc Surg 1997;26:1–10.
- <sup>22</sup> Little NS, Meyer FB. Carotid endarterectomy: indications, techniques, and Mayo Clinic experience. Neuro Med Chir (Tokyo) 1997;37:227–35.
- <sup>23</sup> Magnadottir HB, Lightdale N, Harbaugh RE. Clinical outcomes for patients at high risk who underwent carotid endarterectomy with regional anesthesia. Neurosurgery 1999;45:786–9.
- <sup>24</sup> McCrory DB, Goldstein LB, Samsa GP, Landsman PB, Moore WS, Machtar DB. Predicting complications of carotid endarterectomy. Stroke 1993;24:1285–91.



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MD133246 Protocol Template  
Revision#: 1  
Doc Type: GC

- <sup>25</sup> Meyer FB, Meissner I, Fode NC, Losasso TJ. Carotid endarterectomy in elderly patients. Mayo Clin Proc 1991;66:464–9.
- <sup>26</sup> O'Hara PJ, Hertzner NR, Mascha EJ, Beven EG, Krajewski LP, Sullivan TM. Carotid endarterectomy in octogenarians: early results and late outcomes. J Vasc Surg 1998;27:860–71.
- <sup>27</sup> Rigdon EE, Monajjem N, Rhodes RS. Is carotid endarterectomy justified in patients with severe chronic renal insufficiency? Ann Vasc Surg 1997;11:115–9.
- <sup>28</sup> Rockman CB, Riles TS, Fisher FS, Adelman MA, Lamprello PJ. The surgical management of carotid artery stenosis in patients with previous neck irradiation. Am J Surg 1996;172:191–5.
- <sup>29</sup> Rothwell PM, Slattery J, Warlow CP. Clinical and angiographic predictors of stroke and death from carotid endarterectomy: systematic review. BMJ 1997;315:1571–7.
- <sup>30</sup> Sternbergh WC, III, Garrard CL, Gonze MD, Manord JD, Bowen JC, Money SR. Carotid endarterectomy in patients with significant renal dysfunction. J Vasc Surg 1999;29:672–7.
- <sup>31</sup> Gray WA, Hopkins LN, Yadav S. Protected carotid stenting in high-surgical-risk patients: The ARChER results. J Vasc Surg 2006; 44:258-68.
- <sup>32</sup> Iyer SS, White CJ, Hopkins LN. Carotid Artery Revascularization in High-Surgical-Risk Patients Using the Carotid WALLSTENT and FilterWire EX/EZ. JACC 2008; 51: 427-34.
- <sup>33</sup> Hopkins LN, Myla S, Grube E. Carotid Artery Revascularization in High Surgical Risk Patients With the NexStent and FilterWire EX/EZ: 1-Year Results in the CABERNET Trial. CCI 2008; 71: 950-60.
- <sup>34</sup> Summary of Safety and Effectiveness Data: Protege® Carotid Stent System
- <sup>35</sup> Summary of Safety and Effectiveness Data: Exponent Self-Expanding Carotid Stent with OTW Delivery System
- <sup>36</sup> Summary of Safety and Effectiveness Data: Precise Nitinol Stent System
- <sup>37</sup> Summary of Safety and Effectiveness Data: Xact Carotid Stent System



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

### **13. Study-Specific Appendices**

**Appendix A NIH Stroke Scale**

**Appendix B Modified Rankin Scale**



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MD133246 Protocol Template

Revision#: 1

Doc Type: GC

**Appendix A**  
**NIH Stroke Scale**



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

# N I H STROKE SCALE

Patient Identification. \_\_\_\_-\_\_\_\_-\_\_\_\_

Pt. Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_

Hospital \_\_\_\_ (\_\_\_\_-\_\_\_\_)

Date of Exam \_\_\_\_/\_\_\_\_/\_\_\_\_

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms  $\pm 20$  minutes ☐ 7-10 days  
☐ 3 months ☐ Other \_\_\_\_\_(\_\_\_\_)

Time: \_\_\_\_:\_\_\_\_ ☐ am ☐ pm

Person Administering Scale \_\_\_\_\_

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
<b>1a. Level of Consciousness:</b> The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = <b>Alert</b> ; keenly responsive. 1 = <b>Not alert</b> ; but arousable by minor stimulation to obey, answer, or respond. 2 = <b>Not alert</b> ; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
<b>1b. LOC Questions:</b> The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = <b>Answers</b> both questions correctly. 1 = <b>Answers</b> one question correctly. 2 = <b>Answers</b> neither question correctly.	_____
<b>1c. LOC Commands:</b> The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = <b>Performs</b> both tasks correctly. 1 = <b>Performs</b> one task correctly. 2 = <b>Performs</b> neither task correctly.	_____
<b>2. Best Gaze:</b> Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve palsy (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = <b>Normal</b> . 1 = <b>Partial gaze palsy</b> ; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = <b>Forced deviation</b> , or total gaze paresis not overcome by the oculocephalic maneuver.	_____

# N I H STROKE SCALE

Patient Identification. \_\_\_\_-\_\_\_\_-\_\_\_\_

Pt. Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_

Hospital \_\_\_\_\_(\_\_\_\_-\_\_\_\_)

Date of Exam \_\_\_\_/\_\_\_\_/\_\_\_\_

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms  $\pm$ 20 minutes ☐ 7-10 days  
☐ 3 months ☐ Other \_\_\_\_\_(\_\_\_\_)

<p><b>3. Visual:</b> Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.</p>	<p>0 = <b>No visual loss.</b></p> <p>1 = <b>Partial hemianopia.</b></p> <p>2 = <b>Complete hemianopia.</b></p> <p>3 = <b>Bilateral hemianopia</b> (blind including cortical blindness).</p>	<p>_____</p>
<p><b>4. Facial Palsy:</b> Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.</p>	<p>0 = <b>Normal</b> symmetrical movements.</p> <p>1 = <b>Minor paralysis</b> (flattened nasolabial fold, asymmetry on smiling).</p> <p>2 = <b>Partial paralysis</b> (total or near-total paralysis of lower face).</p> <p>3 = <b>Complete paralysis</b> of one or both sides (absence of facial movement in the upper and lower face).</p>	<p>_____</p>
<p><b>5. Motor Arm:</b> The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = <b>No drift;</b> limb holds 90 (or 45) degrees for full 10 seconds.</p> <p>1 = <b>Drift;</b> limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support.</p> <p>2 = <b>Some effort against gravity;</b> limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.</p> <p>3 = <b>No effort against gravity;</b> limb falls.</p> <p>4 = <b>No movement.</b></p> <p>UN = <b>Amputation</b> or joint fusion, explain: _____</p> <p><b>5a. Left Arm</b></p> <p><b>5b. Right Arm</b></p>	<p>_____</p> <p>_____</p>
<p><b>6. Motor Leg:</b> The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.</p>	<p>0 = <b>No drift;</b> leg holds 30-degree position for full 5 seconds.</p> <p>1 = <b>Drift;</b> leg falls by the end of the 5-second period but does not hit bed.</p> <p>2 = <b>Some effort against gravity;</b> leg falls to bed by 5 seconds, but has some effort against gravity.</p> <p>3 = <b>No effort against gravity;</b> leg falls to bed immediately.</p> <p>4 = <b>No movement.</b></p> <p>UN = <b>Amputation</b> or joint fusion, explain: _____</p> <p><b>6a. Left Leg</b></p> <p><b>6b. Right Leg</b></p>	<p>_____</p>



# N I H STROKE SCALE

Patient Identification. \_\_\_\_-\_\_\_\_-\_\_\_\_

Pt. Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_

Hospital \_\_\_\_\_(\_\_\_\_-\_\_\_\_)

Date of Exam \_\_\_\_/\_\_\_\_/\_\_\_\_

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms  $\pm 20$  minutes ☐ 7-10 days  
☐ 3 months ☐ Other \_\_\_\_\_(\_\_\_\_)

<p><b>7. Limb Ataxia:</b> This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</p>	<p>0 = <b>Absent.</b></p> <p>1 = <b>Present in one limb.</b></p> <p>2 = <b>Present in two limbs.</b></p> <p>UN = <b>Amputation</b> or joint fusion, explain: _____</p>	<p>_____</p>
<p><b>8. Sensory:</b> Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.</p>	<p>0 = <b>Normal;</b> no sensory loss.</p> <p>1 = <b>Mild-to-moderate sensory loss;</b> patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched.</p> <p>2 = <b>Severe to total sensory loss;</b> patient is not aware of being touched in the face, arm, and leg.</p>	<p>_____</p>
<p><b>9. Best Language:</b> A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.</p>	<p>0 = <b>No aphasia;</b> normal.</p> <p>1 = <b>Mild-to-moderate aphasia;</b> some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response.</p> <p>2 = <b>Severe aphasia;</b> all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.</p> <p>3 = <b>Mute, global aphasia;</b> no usable speech or auditory comprehension.</p>	<p>_____</p>
<p><b>10. Dysarthria:</b> If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</p>	<p>0 = <b>Normal.</b></p> <p>1 = <b>Mild-to-moderate dysarthria;</b> patient slurs at least some words and, at worst, can be understood with some difficulty.</p> <p>2 = <b>Severe dysarthria;</b> patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric.</p> <p>UN = <b>Intubated</b> or other physical barrier, explain: _____</p>	<p>_____</p>

# N I H STROKE SCALE

Patient Identification. \_\_\_\_-\_\_\_\_-\_\_\_\_

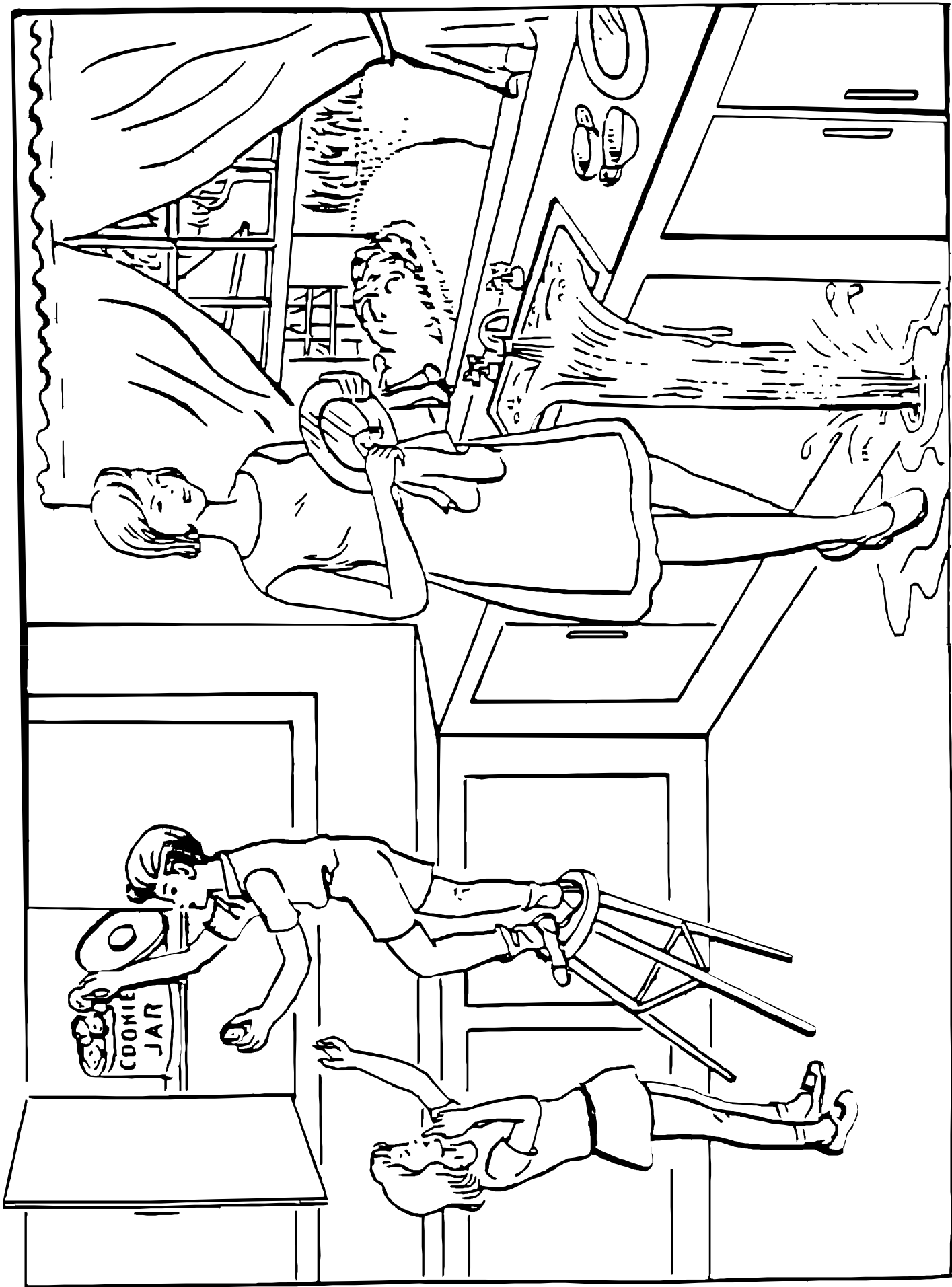
Pt. Date of Birth \_\_\_\_/\_\_\_\_/\_\_\_\_

Hospital \_\_\_\_\_(\_\_\_\_-\_\_\_\_)

Date of Exam \_\_\_\_/\_\_\_\_/\_\_\_\_

Interval: ☐ Baseline ☐ 2 hours post treatment ☐ 24 hours post onset of symptoms  $\pm$ 20 minutes ☐ 7-10 days  
☐ 3 months ☐ Other \_\_\_\_\_(\_\_\_\_)

<p><b>11. Extinction and Inattention (formerly Neglect):</b> Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.</p>	<p>0 = <b>No abnormality.</b></p> <p>1 = <b>Visual, tactile, auditory, spatial, or personal inattention</b> or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</p> <p>2 = <b>Profound hemi-inattention or extinction to more than one modality;</b> does not recognize own hand or orients to only one side of space.</p>	<p>_____</p>
---	--	--------------



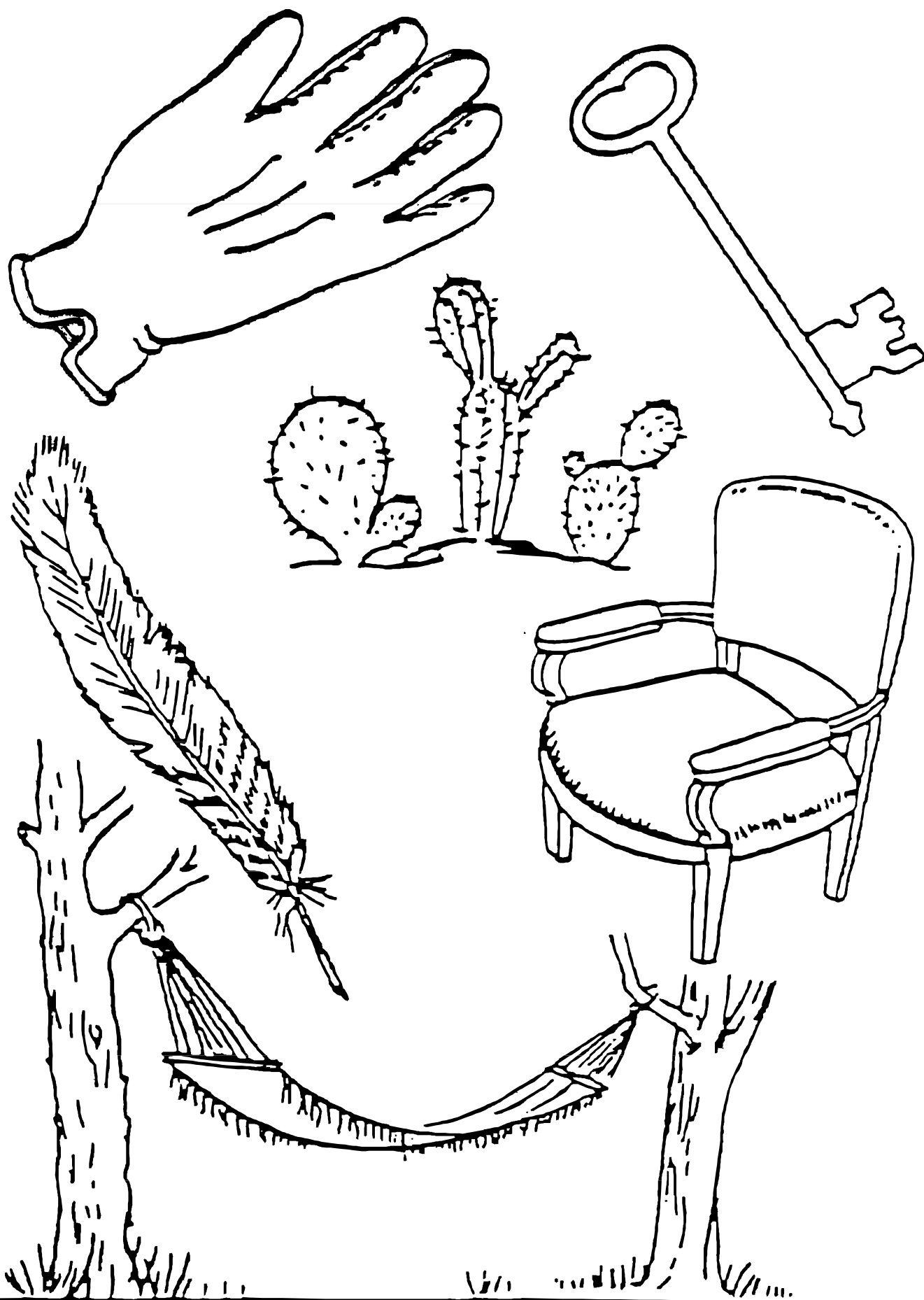
**You know how.**

**Down to earth.**

**I got home from work.**

**Near the table in the dining  
room.**

**They heard him speak on the  
radio last night.**



**MAMA**

**TIP – TOP**

**FIFTY – FIFTY**

**THANKS**

**HUCKLEBERRY**

**BASEBALL PLAYER**

**Appendix B**  
**Modified Rankin Scale**



**CONFIDENTIAL INFORMATION**

MD133246 Protocol Template

Revision#: 1

Doc Type: GC

# MODIFIED RANKIN SCALE

Patient's name:

Hospital number:

CHECK ONE  
GRADE ONLY

## DESCRIPTION

- |   |       |   |
|---|-------|---|
| 0 | ..... | No symptoms at all.   |
| 1 | ..... | No significant disability despite symptoms:<br><i>Able to carry out all usual activities.</i>   |
| 2 | ..... | Slight disability.  |
| 3 | ..... | Moderate disability:<br><i>Requiring some help but able to walk without assistance.</i>   |
| 4 | ..... | Moderate to severe disability:<br><i>Unable to walk without assistance and unable to attend to own bodily needs without assistance.</i> |
| 5 | ..... | Severe disability:<br><i>Bedridden, incontinent and requiring constant nursing care and attention.</i>                                  |
| 6 | ..... | Death.  |