Study of the GORE® EXCLUDER® Endoprosthesis in the treatment Of infra-renal Abdominal Aortic Aneurysms

Protocol number: FPR 12-02

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

[redacted]

STATISTICAL ANALYSIS PLAN

Gore-excluder_SAP_V4.0

Sponsor : W.L. GORE

Device : GORE® EXCLUDER®

Protocol Nr: FPR AAA 12-02

[redacted]

Study of the GORE® EXCLUDER® Endoprosthesis in the treatment of infra-renal Abdominal Aortic Aneurysms (AAA)

Statistical Analysis Plan

Versions	Date	Documents used / comments
Version 4.0	15/11/2017	SAP 3.4 + SAR comments from WL Gore (by E-mail 19DEC2017) + Protocol version 5.1 29FEB2012
Version 3.4	13/11/2017	SAP 3.3 + SAR comments from WL Gore (by E-mail 19DEC2017) + Protocol version 5.1 29FEB2012
Version 3.3	20/12/2017	SAP 3.2 + SAR comments from WL Gore (by E-mail 19DEC2017) + Protocol version 5.1 29FEB2012
Version 3.2	30/11/2015	SAP V3.1 + SAR comments from WL Gore (26NOV2015) + protocol version update + Listing 4 title modification + Call (30NOV2015)

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STATISTICAL ANALYSIS PLAN

Versions	Date	Documents used / comments
Version 3.1	26/11/2015	SAP V3.0 + SAR comments from WL Gore (25NOV2015) + update of WL Gore address + update of signature page + update of protocol version + update of number of sites involved
Version 3.0	25/11/2015	SAP V2.1 + SAR comments from WL Gore (19NOV2015) + Modification of Table 3, Table 4, Table 5 and Table 28 titles + Addition of listing "Implantation main indication" + change Listing 5: "Other abnormalities observed" into "Occlusion, stenosis and other abnormalities observed"
Version 2.1	27/10/2014	SAP V2.0 + Clarification of the SAF population definition + Listing 3 title modification
Version 2.0	13/10/2014	SAP V1.1 + update of AAA following CRF modification
Version 1.1	26/07/2013	SAP V1 + update of derived criteria calculation section + addition of statistical tables and listings
Version 1	12/04/2013	Protocol Number FPR AAA 12-02 (Version 5.1)

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STATISTICAL ANALYSIS PLAN

Gore-excluder_SAP_V4.0.doc
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[redacted]

SIGNATURE PAGE

STUDY OF THE GORE® EXCLUDER® ENDOPROSTHESIS IN THE TREATMENT OF INFRA-RENAL ABDOMINAL AORTIC ANEURYSMS (AAA)

Version 4.0

W.L. GORE & ASSOCIÉS S.A.R.L.

Name	Position	Date	Signature
Abe Letter	Clinical Biostatistician	15-NOV-2018	
Alexandre Figard	Clinical Study Manager	19-NOV-2018	

[redacted]

[redacted]

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List of abbreviations and definition of terms

AAA	Abdominal Aortic Aneurysms
AE	Adverse Event
FUP	Follow-up
ICU	Intensive Care Unit
ITT	Intent-To-Treat population
LPP	List of products
LPPR	List of products and refundable services
SAF	Safety population
SAP	Statistical Analysis Plan

1. OVERVIEW

This statistical analysis plan (SAP) describes the planned statistical analyses of the data collected in the course of the Register Gore® Excluder® AAA France.

This SAP provides additional details concerning the statistical analyses outlined in the protocol (version dated 29FEB2012). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data.

1.1. Study Objective

The objective of this study is to assess the usefulness of the technique by documenting overall mortality, complications (endoleak, migration), the rate of surgical conversion, the evolution and rupture of the aneurysm, in the long term, that is, 5 years, on a cohort of patients representative of the population treated in real life conditions.

1.2. Study Design

The study is a observational, prospective and multicentric register of the GORE® EXCLUDER® AAA Endoprosthesis used to treat infrarenal abdominal aortic aneurysms in which 180 patients are enrolled from 29 sites and followed during 5 years minimum.

1.3. Study Plan

1.3.1. Sample Size

A total of 180 patients are enrolled in this study, [redacted]

1.3.2. Patient's Follow-up

8 visits are scheduled:

- Visit 1 : Baseline
- Visit 2 : Procedure
- Visit 3 : Discharge
- Visit 4 : Post operatory (or in the month following the surgery)
- Visit 5 : 6 months Follow-up
- Visit 6 : 1 year Follow-up
- Visit 7 : 2 years Follow-up
- Visit 8 : 3 years Follow-up
- Visit 9 : 4 years Follow-up
- Visit 10 : 5 years Follow-up

1.3.3. Study Device

The studied device is the GORE® EXCLUDER® Endoprosthesis and any evolution registered on LPP.

[redacted]

1.3.4. Study Assessments

The following flowchart applies to the study:

	Post operatory follow-up (D1 à D30)	Follow-up at 6 months	Follow-up at 1, 2, 3, 4 and 5 years	Intermediate follow-up***
Clinic exam	X	X	X	X
Abdominal X-ray without preparation under 3 angles (face, profile and 3/4)	X[1]	X*	X*	X*
Tomography with contrast product	X	X	X	X
MRI	X*	X*	X*	X*
Vascular echo-doppler	X**	X**	X**	X**

* if tomography with contrast product cannot be performed
** If MRI cannot be performed
*** Intermediate follow up are realized only if leak, deterioration of endoprosthesis or evolution of aneurysms are noticed in the last follow up. The follow-up needs to be done within 3 months after the exam which noticed the anomaly.

(1) Radiography in postoperative follow-up will not be necessary in case of 3D reconstruction performed during tomography.

2. STATISTICAL METHODS

2.1. General Statistical Considerations

2.1.1. Time Points Definition

Baseline data is defined as the last available observation recorded before the first study device exposition for the patient.

Visit(n) data is defined as the last available observation on or before the Visit(n) time point following the first study device exposition for the patient.

Endpoint data is defined as the last follow-up at 5 years or, if the data is missing, as the last available observation recorded for the patient.

If the hospital discharge visit did not occur before the post-operatory follow-up, it will be considered as an unscheduled visit.

2.1.2. Derived Criteria Calculation

- Age classes will be the following:
  - Age < 80 years
  - Age ≥ 80 years
- Body Mass Index will be calculated as :
  BMI = weight (kg) / (height (m))²
- Duration between two dates i and j will be calculated as:
  Duration i, j = Date j - Date i +1
- If no clinical exam is done at a particular visit, the visit date will be the last imaging exam date reported for this visit.
- Total study duration will be calculated as:
  Total study duration = study exit date - procedure date +1
  If the procedure date is not available, the baseline will be used instead.

- Study follow-up duration will be calculated as:
  Study follow-up duration = last FUP date available - procedure date +1
  If the procedure date is not available, the baseline will be used instead.
- Surgical risk for patient (AFSSAPS' criteria) :
  A patient is considered as "at high risk" (surgical risk = High instead of Normal) if at least one of the following criteria is met:
  - Age ≥ 80 years
  - Coronary artery disease (history of myocardial infarction or angina) with positive functional testing and coronary lesions for which revascularization is impossible or not indicated
  - Cardiac failure with patent clinical manifestations
  - Inoperable aortic stenosis
  - LVEF < 40 %
  - Chronic respiratory failure objectified by one of the following criteria
    - FEV < 1.2 l/sec
    - VC < 50% of the predicted value according to age, sex and weight
    - Arterial blood gases in the absence of oxygen : $PaCO^2$ > 45 mm Hg or PaO^2 < 60 mm Hg
    - Home Oxygen Therapy
  - Renal failure, if serum creatinine > 200 µmol / L before injection of contrast medium
  - Hostile abdomen, including the presence of ascites or other signs of portal hypertension
- If more than one imaging technique are used to measure the maximum AAA diameter, and all the measures are not the same, the maximum AAA diameter will be the one measured by the more precise technique based on the following:
  CT with contrast > MR with contrast > CT without contrast > MR without contrast > Echo Doppler
  More precise ----------> Less precise
- The maximum aneurysm diameter classes will be the following:
  - "Small": maximal AAA diameter less than 5 cm
  - "Average": maximal AAA diameter between 5 and 7 cm
  - "Large": maximal AAA diameter more than 7 cm
- The diameter increase will be analyzed as follows:
  If the diameter observed is at least 5 mm greater than the largest aneurysm diameter (observed at the first post-op control) then there is a diameter increase.
- The migration will be analyzed as follows:
  - Distal migration is defined as a distal movement strictly greater than 10 mm since the first post-op control.
  - A proximal migration is defined by a proximal movement either strictly greater than 10 mm or which covers one of the renal arteries since the first post-op control.

  If at least one of the two migrations is observed then migration = "Yes"
- Endoleak will be analyzed as follows:
  If an endoleak (I, II or III) appears during follow-up then Endoleak = "Yes"

2.1.3. Handling Missing Data

No replacement of missing data is planned.

In case of missing data, the patient will be considered as censured at his/her last available observation in survival analyses.

In case of partially missing death dates (day of death missing) confirmed as unknown by the site, the first day of the month will be imputed. If the death occurs in the same month as last follow-up then the later day of the two will be imputed.

2.1.4. Descriptive Statistics in Summary Tables

- *Continuous variables* will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.
- *Categorical variables* will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Percentages will be calculated on the number of non-missing observations, and will be displayed using one decimal. The number of missing observations will also be specified.

2.1.5. Inferential Analysis

No inferential analysis is planned for the first analysis part of this study.

2.1.6. Data Listings

Patient data listings will be selected to be supportive of summary statistical tables, including derived/calculated data from statistical process. These key data listings will be performed on selected analysis sets according to the focus of the listings and will be sorted by patient number or visit.

[redacted]

2.3. Analysis Sets

2.3.1. Definition of patient populations

2 populations will be defined:

- The Safety (SAF) population will include all patients enrolled in the study and who have signed their informed consent or accept the use of their data.
- The Intent-to-Treat (ITT) population will include all safety patients who underwent surgery (i.e. who used at least one GORE® EXCLUDER® AAA Endoprosthesis).

2.4. Statistical Analyses

2.4.1. Patient Disposition

All the following tables will be presented on SAF population instead otherwise described.

- The number of patients included/non included will be presented by sites.
- A study flowchart table will be presented on SAF and ITT populations.
- The number of patients withdrawn will be presented by reason of interruption and a list of these reasons will be provided.
- Study duration:
  - The total study duration (between procedure and study exit) will be presented globally.
  - The study follow-up duration (between procedure and the last available follow-up) will also be presented in intermediary report(s).

- All deviations reported by the investigators will be listed.

2.4.2. Patient Characteristics

Descriptive statistics will be used to draw up a recapitulation of ITT patients characteristics at baseline and procedure.

2.4.2.1. Baseline

- Demographics
- Medical condition
- Surgical Risk
- Aneurysm characteristics

2.4.2.2. Procedure

- Implantation main indication (a listing will also be presented).
- Implantation parameters (all patients not implanted with GORE® EXCLUDER® AAA Endoprosthesis bifurcated will be listed)
- Procedure evaluation and results (a listing of all associated surgical/endovascular procedures details and a listing of all other abnormalities observed will be presented)
- GORE® EXCLUDER® AAA Endoprosthesis details (listing)
- Discharge: Stay in ICU

2.4.3. Endpoints Analyses

The endpoint analyses will be performed on the ITT population.

Primary analysis consists to study the 5-year mortality of patients who received the endoprosthesis. Secondary analyses consist to study the other safety parameters on patients who received the endoprosthesis.

The dates to be used for the “aneurysm diameter evolution” survival analysis will be the date of the imaging exam on which it has been reported. If it is missing, the corresponding “clinical exam” date will be used instead.

The same will be done for the “endoleak complication” and “device migration” survival analyses.

2.4.3.1. Primary Analysis

The 5-year mortality survival curve will be described according to the Kaplan-Meier method. The associated Kaplan-Meier estimators will be calculated. Only events occurring up to 5 years (1826 days) of follow-up will be analyzed for mortality survival curve.

2.4.3.2. Secondary Analyses

The surgical conversion rate during procedure and the corresponding 95% confidence interval will be provided.

The following parameters will be presented using the Kaplan-Meier survival curves:

- Mortality related to the aneurysm
- Aneurysm diameter evolution
- Endoleak complication, for each type (I, II and III)
- Device migration overall and by type (distal, proximal)
- Re-intervention

For the parameters “Aneurysm diameter evolution”, “Endoleak complication” and “Device migration”, the date to be used for the survival analysis is the date of the first visit where the parameter is reported. Only events occurring up to 5 years (1826 days) of follow-up will be analyzed for these survival curves.

[redacted]

3. STATISTICAL SOFTWARE

All statistical outputs (summary tables and data listings) will be generated using SAS® version 9.4 or later.

4. LAYOUT OF THE STATISTICAL TABLES

4.1. Quantitative variables

4.1.1. Without group (Type 1)

	N	Missing	Mean	S.D.	Median	Min,Max	Q1-Q3
Variable	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X

4.1.2. By group (Type 2)

	Group	N	Missing	Mean	S.D.	Median	Min,Max	Q1-Q3
Variable	Group 1	XX	XX	XX,Z	XX,Z	XX,Z	XX,Z , XX,Z	XX,Z - XX,Z
	Group 2	XX	XX	XX,Z	XX,Z	XX,Z	XX,Z , XX,Z	XX,Z - XX,Z
	…	…	…	…	…	…	…	…
	Total*	XX	XX	XX,Z	XX,Z	XX,Z	XX,Z , XX,Z	XX,Z - XX,Z

4.2. Qualitative variables

4.2.1. Without group (Type 3)

		POP (N=XX)
Variable	N	XX
	Mod 1	XX (XX.X%)
	IC 95% (Mod 1)*	[XX.X ; XX.X]
	…	…
	Mod n	XX (XX.X%)
	IC 95% (Mod n)*	[XX.X ; XX.X]
	Missing	XX

* if needed

4.2.1. By group (Type 4)

		Group			
		Group 1 (N=XX)	Group 2 (N=XX)	…	Total* (N=XX)
Variable	N	XX	XX	…	XX
	Mod 1	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
	IC 95% (Mod 1)*	[XX.X ; XX.X]	[XX.X ; XX.X]	…	[XX.X ; XX.X]
	…	…	…	…	…
	Mod n	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
	IC 95% (Mod n)*	[XX.X ; XX.X]	[XX.X ; XX.X]	…	[XX.X ; XX.X]
	Missing*	XX	XX	…	XX

* if needed

4.2.2. Conditional variables (Type 5)

Variable / Conditional variable	Population* (N=XX)	Group 1* (N=XX)	…	Group n* (N=XX)
Mod 1	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
Conditional Mod 1	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
…	…	…	…	…
Conditional Mod n	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
…	…	…	…	…
Mod n	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
Conditional Mod 1	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)
…	…	…	…	…
Conditional Mod n	XX (XX.X %)	XX (XX.X %)	…	XX (XX.X %)

* if needed

4.3. Other type of tables

4.3.1. Flowchart (Type 6)

Populations / Reasons	SAF population	ITT Population
Baseline	XX (XX.X %)	XX (XX.X %)
Study exit reason 1*	XX (XX.X %)	XX (XX.X %)
Study exit reason 2*	XX (XX.X %)	XX (XX.X %)
…	…	…
5 Year FUP*	XX (XX.X %)	XX (XX.X %)

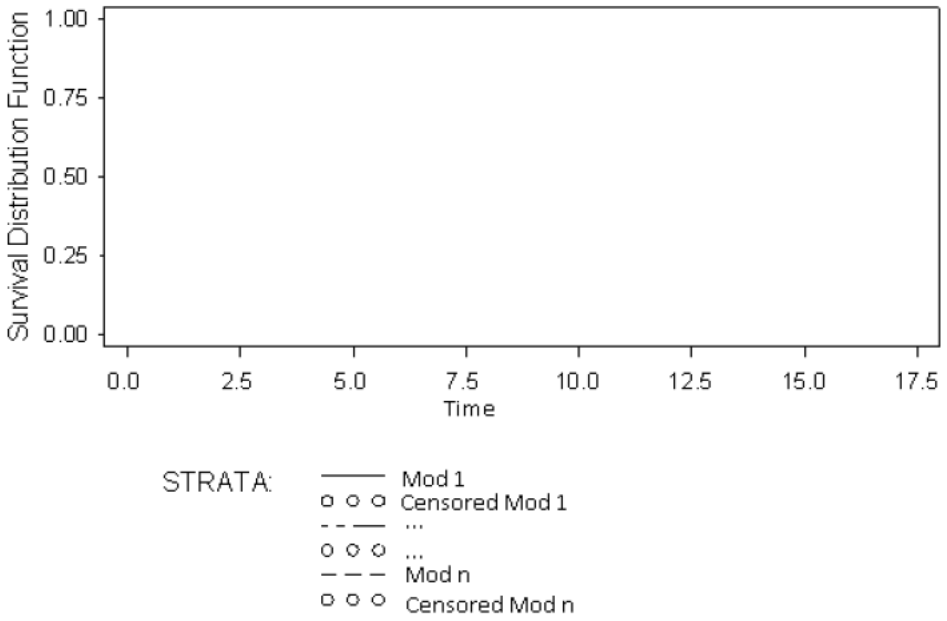
* if any

4.3.2. Adverse Events (Type 9)

	POP (N=XX)		
Adverse events	NAE (1)	n (2)	% (3)
AE type 1	XX	XX	XX.X
AE type 2	XX	XX	XX.X
…	XX	XX	XX.X
AE type n	XX	XX	XX.X

(1) : Number of adverse events
(2) : Number of patients
(3) : (n / N)*100 (N : number of patients)

4.3.3. Survival curve (Type 10)



Summary table

	Mod 1 (n=X)	…	Mod n* (n=X)
Nb of patients	X	…	X
Nb of patients with an event	X (XX.XX%)	…	X (XX.XX%)
Nb of patients without an event	X (XX.XX%)	…	X (XX.XX%)
Survival rate	XX %	…	XX %
Progression-Free survival (days)		…	
Median	XX	…	XX
(95% CI)	(XX, XX)	…	(XX, XX)
25th-75th percentile	XX.X – XX.x	…	XX.X – XX.x
Range	X - X	…	X - X

* If any

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5.1.1. Patient Disposition

5.1.1. Patient Characteristics

5.1.1.1. Baseline

5.1.1.2. Procedure

5.1.2. Endpoint analysis

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Table 41 : Migration survival analysis – overall (Type 10)
Table 42 : Migration survival analysis – distal (Type 10)
Table 43 : Migration survival analysis - proximal (Type 10)
Table 44 : Re-intervention survival analysis (Type 10)

[redacted]

5.2. Listings

5.2.1. Patient Disposition

Listing 1: Withdrawals
Listing 2: Deviations as reported by investigators

5.2.2. Patient Characteristics

5.2.2.1. Procedure

Listing 3: Implantation main indication
Listing 4: Patient not implanted with GORE® EXCLUDER® AAA Endoprosthesis bifurcated
Listing 5: Associated surgical/endovascular procedures
Listing 6: GORE® EXCLUDER® AAA Endoprosthesis details

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