

DRKS-No. according to Study Protocol - DRKS00006103 Derivo Final Analysis			
Statistical Analysis Plan (SAP)			
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1. Scope of this document

This statistical analysis plan (SAP) describes the objectives of the final analysis. It defines the analysis populations and the statistical methods to be used. The contents of this document is based on chapter 16.4 of the final study protocol, dated 10/04/2014, protocol amendment 01, dated 27/08/2014 and protocol amendment 02, dated 08/05/2017.

The statistical analysis will be performed according to the Standard Operating Procedures (SOPs) of the Clinical Trials Unit (CTU), University Medical Center Freiburg.

2. Study design

This is an observational, multicentre trial.

3. Study objectives and endpoints

The aim of this trial is to assess the morbidity and mortality in patients with intracranial aneurysms 18 months after aneurysm treatment with the Derivo flow-diverter.

3.1 Study objectives

3.1.1 Primary objective

Clinical outcome 18 months after aneurysm treatment with the Derivo flow-diverter.

3.1.2 Secondary objectives

- Technical success rate
- Complication rate of aneurysm treatment with the Derivo® flow-diverter
- Initial clinical and angiographic outcome as well as mid-term and long-term angiographic follow-up results
- Assessment of quality of life
- Collection of AEs and AEs during treatment, during hospitalization, during follow-up

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3.2 Study endpoints

The endpoints described in the study protocol in section 4 are as follows.

3.2.1 Primary endpoint

Modified Rankin score at 18 months

3.2.2 Secondary endpoints

Procedural result

- Number of flow-diverters successfully deployed over aneurysm neck in relation to the number of attempted flow-diverter treatments as determined by the core-lab.
- Wall apposition of the flow-diverter(s) per patient as determined by the core-lab:
 1. correct wall apposition
 2. gap between FD and vessel wall <25% of vessel diameter
 3. gap between FD and vessel wall >25% of vessel diameter
- Time needed for Derivo deployment.
- Initial angiographic outcome: Core-lab evaluation of final controls with respect to the scale of Szikora Flow modification after FD implantation is classified as:
 1. complete stasis (if no contrast media entered the aneurysm following deployment of the Pipeline FD)
 2. significant flow reduction (if contrast stagnation was seen within the aneurysm at the late venous phase of the angiographic series)
 3. slow flow (if the contrast circulation within the aneurysm became slower but without contrast stagnation into late venous phase images)
 4. unchanged
- In those patients where additional coils are being used for aneurysm treatment the Montreal classification will apply for determining the treatment result in addition to the Szikora classification.
 1. Complete aneurysm occlusion
 2. Neck remnant
 3. Aneurysm remnant.

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- Procedural complication rate of aneurysm treatment

Post-procedural result

- Number of new neurological deficits immediately after flow-diverter implantation
- Initial clinical outcome: Comparison between initial mRs and mRs upon discharge. In those patient that had a procedural complication with subsequent stroke NIHSS upon discharge.
- Midterm (3-6 months) clinical outcome: mRs
- Midterm (3-6 months) and long-term (12-18 months) angiographic outcome: Core-lab evaluation of angiographies with respect to the classification of Kamran Grading the degrees of aneurysm occlusion and after FD treatment:

Grade 0: No change in sac filling despite device deployment

Grade 1: Any change in endosaccular blood flow but with at least 50% of the sac filling.

Grade 2: Less than 50% of the sac filling

Grade 3: The same but filling is restricted to a region which is smaller than the width of the original neck.

Grade 4: Represents complete sac occlusion with a parent artery.

- In those patients were additional coils are being used for aneurysm treatment the Montreal classification will apply for determining the treatment result in addition to the Kamran grading system.
- SF-12 before treatment, after 3-6 and 12-18 months
 The SF-12 is a shorter version of the SF-36 that uses just 12 questions to measure functional health and well-being from the patient's point of view. The SF-12 contains 12 items from the original SF-36, across all dimensions. The 12 items include the self-assessment of health, physical functioning; physical role limitation; mental role limitation; social functioning; mental health and pain. The instrument was designed to reduce respondent burden while achieving minimum standards of precision.

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4. Interim analyses

As outlined in the study protocol, two different types of interim analyses will be performed during the study and have to be distinguished. The first ~~in~~-Interim Analysis was already performed and is described in the SAP for the Interim Analysis dated 13/05/2016 Version 01. The second interim analysis is described in a second SAP dated 26/06/2017, Version 01. For details see both documents.

5. Analysis sets

5.1 Definition of full analysis set

The full analysis set (FAS) includes all patients who gave informed consent, and who actually received a Derivo flow diverter.

The analysis of the primary endpoint Modified Rankin score at 18 months will be done according to the intention-to-treat (ITT) principle, i.e. based on the 'full analysis set'.

Patients with major protocol deviations are excluded. Major protocol deviations are:

- missing informed consent
- patients not treated with DERIVO flow diverter
- Patients who were registered after treatment

5.2 Definition of per-protocol set

The per-protocol set (PP) is a subset of the patients in the FAS and includes only patients for whom no major protocol violations are known.

5.3 Definition of safety analysis set

The safety analysis set (SAF) includes all patients who received a DERVIO flow diverter. Thus the SAF includes the same patients as the FAS and will therefore not be listed separately.

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6. Statistical methods

The statistical methods described in this SAP are in accordance with the analysis planned in the study protocol.

6.1 Software

Statistical programming will be performed with the Statistical Analysis System (SAS) Version 9.4.

6.2 Data listings

In all patient data listings the membership of the patients to the different analysis sets FAS and PP is indicated. The listings containing baseline variables and efficacy variables will in general be given for the FAS. The listings containing safety variables will in general be given in the SAF.

6.3 Descriptive statistics

Continuous data will be summarized by arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories.

Categorical data will be summarized by the total number of patients in each category and the number of missing values. Relative frequencies are displayed by the total % (100 times the number of patients divided by the total number of patients).

Medical data documented at different time points, e.g. laboratory data, will be summarized by shift tables.

6.4 Data handling

6.4.1 Missing values

Unless otherwise stated in particular cases, missing values are not replaced and only observed cases are analysed.

Partially missing dates are treated as follows. If the day of a date variable is unknown, a value '15' will be inserted as day, and in the listings a footnote will indicate that the day was unknown. If the day and the month of a date variable are unknown, a value '1st July' will be inserted as day and month, and in the listings a footnote will indicate that the day and month were unknown. If a date is missing completely, no insertion will be done.

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For patients with missing data for the primary endpoints, the last available outcome measurement will be used for the calculation of the primary endpoint and further secondary endpoints.

6.4.2 Outliers

Not applicable.

6.4.3 Coding

The following systems for coding the data will be used:

Adverse Events

For the final analysis, all AEs will be coded using the latest version of MedDRA available at that time. If more than one symptom or diagnosis was reported in the description of the same AE, the AE was split by the medical reviewer.

6.4.4 Further details and conventions

Incorporation of time variables

Duration of time in days will in general be calculated as end date – start date +1.

If a time-interval is given instead of an exact time, the mean is used. For example, if time to fall asleep is reported as 23:00 to 23:30, the value 23:15 is chosen for the analysis.

7. Study patients

7.1 Patient recruitment, disposition of patients

Patient recruitment over time and patient recruitment by clinical centre will be graphically displayed for the FAS.

Disposition of patients will be listed in total in the FAS. This will include date of informed consent, start date of treatment, date of hospital discharge, date of last follow-up visit, date of study end in case of study discontinuation, reason for study end.

The number of patients in the FAS and in the PP set will be given in total.

A flow chart of the patient flow will be given.

7.2 Screening failures

All patients who gave informed consent but were not treated with a DERIVO flow diverter are considered as screening failures.

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Those patients are excluded from all of the analyses sets (FAS, PP) and therefore neither contributes to the efficacy nor to the safety analyses.

7.3 Protocol deviations

All violations of eligibility criteria, i.e. the inclusion and exclusion criteria will be listed by patient. To summarize the frequency of different eligibility violations, the number and percentage of patients for whom the eligibility violation occurred will be given in total in the FAS.

All protocol violations leading to an exclusion of the patients from the FAS and/or PP set will be listed by patient and number and percentage of patients for whom the violation occurred will be summarized in total in the FAS.

7.4 Compliance with planned visits

The following information will be given by visit (cumulative over patients and centres), and by centre (cumulative over patients and visits):

- Number of patients and percentage, for whom the visit has been performed within the required time interval
- Number of patients and percentage, for whom the visit has been performed outside the required time interval
- Number of patients and percentage, for whom the visit has not been performed

7.5 Description of patients' baseline characteristics

Demographic and other baseline characteristics will be listed by patient and summarized in total in the FAS. These factors include demographic variables: age, sex, and disease factor such as if the aneurysm is symptomatic, headache, neurologic deficit due to mass effect, seizures, Ischemia or other symptoms.

Furthermore side, type, type partially thrombosed, size (DSA) in mm – length, size (DSA) in mm – width, size (DSA) in mm – depth, neck (DSA) in mm, side branch deriving from aneurysm, diameter parent vessel, distal end FD, diameter parent vessel, aneurysmal neck, diameter parent vessel, proximal end FD will be summarized.

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7.6 Study treatment/Extent of exposure, concomitant medication

7.6.1 Pre Treatment

The following information on pre-treatment will be listed by patient and summarized in total in the FAS: Pre-Treatment yes/no, Coils, Stent, Flow Diverter, intraaneurysmal device, or other pre-treatment.

7.6.2 Treatment with DERIVO flow diverter

The total number of flow diverters used and the duration of the procedure will be summarized in total in the FAS.

7.6.3 Specification of DERIVO flow diverter

The following variables will be summarized in total in the FAS:

Flow diverter number (FD)

Flow diverter deployed (diameter x length)

With tip

Flow diverter deployed other

Placement of FD in target vessel

Placement of FD in target vessel (text)

FD couldn't be delivered into micro catheter

FD couldn't be delivered through micro catheter

FD wouldn't open within target vessel

FD displaced distally

FD displaced proximally

Thrombemboly distally to FD

Thrombus within FD

Thrombotic occlusion of the FD

Thrombus proximally of FD

FD displaced into the aneurysm

Other procedural complication (FD)

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7.6.4 Concomitant medication

All medications administered before intervention (ASS, Plavix, Heparin, ReoPro, Integrilin and other medication before intervention) will be listed by patient. Concomitant treatment with Heparin and antiplatelet therapies during follow up will be summarized.

The number of patients and the percentage of the total number of patients in the FAS are given.

8. Efficacy evaluation

The patient data listings specified in this paragraph will be given for FAS. Summarizing tables will be given for both populations FAS and PP.

8.1 Analyses of primary endpoint

The mRs at 18 months after treatment will be given using frequency tables.

8.2 Analyses of secondary endpoints and CORELab Data

The number of flow diverters successfully deployed, the correct wall apposition, the time needed for the Derivo® deployment, the evaluation on the Szikora score, Montreal Scale and the procedural complication rate will be summarized descriptively using frequency tables (binary, ordinal data), means and standard deviations (continuous data) for all patients of the analysis set.

This will also be done for the post-procedural secondary outcomes, number of neurological deficits, the midterm mRs (ordinal) and the CoreLab evaluation of the mid-term and long-term evaluations with respect to the classification of Kamran, Raymond Scale and Montreal Scale.

Quality of life will be measured with the SF12. The two summary scales per measurement will be evaluated based on the method implemented in the software program (SAS version 9.2 or higher) provided along with the questionnaire. Change from baseline at discharge will be evaluated for both summary scales.

For patients who received additional coiling the procedural, mid-term and long-term angiographies will also be summarized using the Montreal classification.

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9. Safety evaluation

All safety parameters will be listed by patient and summarized in total in the SAF set.

9.1 Documented Complications

All documented procedural complications and complications during follow-up are reported. They are listed by patient providing the following information:

- *Patient identifier, age, sex*
- *The selected procedural complications documented in the CRF*
- *Complications during follow up: stroke, death*

The complications are displayed in summary tables by treatment as follows:

The total number of complications, the minimum, maximum and mean number of complications per patient, the total number of follow-up days (number of days in the observation period for complications), the number of complications per follow-up -day (total number of complications divided by the total by the number of follow-up days), the number of patients who had at least one complications.

Incidences of complications will be calculated with 95%-confidence intervals.

9.2 Deaths

All deaths that occurred during the study, including the post treatment follow-up period, will be listed and summarized in total and by received treatment in the FAS.

9.3 Laboratory data

No laboratory data is assessed.

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10. History of changes

List of changes to the previous version of this SAP:

Versions No.	Section No.	Description of Changes	Reason for Change
01	N/A	First Version	N/A

11. List of abbreviations

AE	Adverse event
CRF	Case report form (= Prüfbogen bzw. Dokumentationsbogen, documentation sheet/form)
CTU	Clinical trials unit
DMC	Data monitoring committee
eCRF	electronic case report form
FAS	Full analysis set
GCP	Good clinical practice
ICH	International conference on harmonization
MedDRA	Medical dictionary for regulatory activities
QOL	Quality of life
PI	Principal Investigator
p.o.	per os
PP	Per protocol set
PR	Partial response
PT	MedDRA preferred term
QOL	Quality of life
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis system
SDV	Source data verification
SOC	MedDRA System organ class

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SOP Standard operating procedure
SUSAR Suspected unexpected serious adverse reaction
Vdue Number of patients for whom the visit is due
WHO-DD WHO drug dictionary

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12. Appendix

12.1 List of tables

A1 Disposition of patients and protocol deviations

Number	Title
A1-1	Disposition of patients
A1-2	Compliance with planned visits
A1-3	Violations of inclusion-/exclusion criteria
A1-4	Protocol deviations leading to an exclusion from the FAS set
A1-5	Protocol deviations leading to an exclusion from the PP set

A2 Demography and baseline characteristics

Number	Title
A2-1	Demographics (sex, age)
A2-2	Details of Aneurysm
A2-3	Pre-treatment

A3 Treatment with Flow-Diverter

Number	Title
A3-1	Treatment with Flow-Diverter - Preparation
A3-2 -- 15	Treatment with Flow-Diverter – Procedure, Specifications DERIVO
A3-3	Treatment with Flow-Diverter –
A3-4	Concomitant medication

A4 Clinical results

Number	Title
A4-1	Neurological deficit (after placement, at discharge,

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	FU 1, FU 2)
A4-2	Modified Rankin Score (at discharge, FU 1, FU 2)
A4-3	CoreLab: Wall apposition of flow diverter
A4-4	CoreLab: Szikora classification
A4-5	CoreLab: Montreal classification
A4-6	CoreLab: Kamran classification

A5 Safety data

Number	Title
A5-1	Complications: During treatment
A5-2	Complications: procedural complications
A5-3	Complications: During hospitalisation
A5-4	Complications after procedure during follow-up

A6 SF-12

Number	Title
A6-1	SF-12 at discharge
A6-2	SF-12 at follow-up (3-6 months)
A6-3	SF-12 at follow-up (12-18 months)
A-4	SF-12 at follow-up (12-18 months), difference to baseline

12.2 List of figures

Number	Title
B-1	CONSORT Diagram

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12.3 List of listings

C1 Safety data

Number	Title
C5-1	Complications

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