UNIKLINIK KÖLN
Institut für Medizinische Statistik, Informatik und Epidemiologie

IMSIE

Direktor: Prof. Dr. W. Lehmacher

Statistical Analysis Plan

Study title	**Vi**trectomy **p**lus **e**ncircling band vs. vitrectomy alone for the treatment of pseudophakic **r**etinal detachment (VIPER)
Treatments under investigation	Experimental group 1 (E1): Surgical therapy of pseudophakic retinal detachment with encircling band and 20 gauge vitrectomy with gas; Experimental group 2 (E2): small gauge (23 or 25G) vitrectomy.
Comparator	Control group (C): Surgical therapy of pseudophakic retinal detachments by 20 gauge vitrectomy with gas without encircling band
Indication	pseudophakic retinal detachment
Number of subjects	(C): 100 patients; (E1): 100 patients; (E1): ≈33 patients
Study registration no.	DRKS-ID: DRKS00003158 (4.7.2011)
Development phase	Phase IIb/III (non-AMG / non-MPG)
First patient in	Planned: 03/2011, in fact: 30/06/2011
Last patient in	Planned: 03/2012, in fact: 22/08/2013
Last patient out	Planned: 09/2012, in fact: 04/2014
Principal investigator	Prof. Dr. P. Walter; Department of Ophthalmology; University Hospital Aachen
Statistics	Prof. Dr. M. Hellmich, Dr. P. Schiller
Version	V1 based on the VIPER Study Protocol, Version V5-11 dated 24/03/2011 *(including commentary and correspondence with Ethics Committee of 19.11.2012)*

Approved by:

Prof. Dr. P. Walter,
Principal Investigator

Place and date	Signature

Prof. Dr. Martin Hellmich,
Statistician

Place and date	Signature

Dr. Petra Schiller,
Statistician

Place and date	Signature

Content

1 List of abbreviations

Abbreviation	Meaning
AE	Adverse Event
C	Control Group
CRF	Case Report Form
E1	Experimental Group 1
E2	Experimental Group 2
ETDRS	Early treatment of diabetic retinopathy study
IOL	Intraocular lens
IOP	Intraocular pressure
ITT	Intention-to-treat
PP	per protocol
RWTH	Rheinisch Westfälische Technische Hochschule
SAE	Serious Adverse Event

2 Background

2.1 Trial objective

The primary objective is to investigate the efficacy of an encircling band in addition to a 20-gauge vitrectomy with gas in the treatment of pseudophakic retinal detachments. The main endpoint criterion is the absence of any situation leading to additional retina re-attaching surgical procedure during the follow-up.

The secondary objective is to investigate if 23/25 gauge transconjunctival vitrectomy with gas is not-inferior to 20-gauge vitrectomy with gas in the treatment of pseudophakic retinal detachment without encircling band.

2.2 Trial design

This study is conducted as a multicentre, multinational, open, randomised controlled clinical trial with three parallel treatment arms.

3 Aim

As stated in the protocol (p. 41) further details of the statistical and analytical plan will be layed out in the statistical analysis plan. The purpose of this SAP is to specify the details with regard to the preparation of the data and to the statistical analysis. This will include a description of deviations emerging during the realisation of the trial affecting the data analysis.

4 Sample size calculation

In the SPR study 11.4% (=10/88) of pseudophakic patients who had received combined primary vitrectomy and scleral bluckling suffered from a re-detachment, in contrast to 40.9% (=18/44) of pseudophakic patients who received primary vitrectomy only. Thus, carefully assuming event fractions of 15% vs. 35%, 82 Patients per group will be required to give the corrected chi-square test 80% power at two-sided significance level 5%. Accounting for stratification and 10% attrition fraction, 100 patients will be allocated to arms (C) and (E1). After reaching this target, recruitment to the whole trial will be stopped, i.e. when, according to expectation, about 33 patients have been allocated to group (E2). Thus, the comparison of (E2) and (C) will/can be explorative only. Note that the number of patients required to yield convincing results with adequate power and precision is about 1400 per group.

5 Randomization

Randomisation was stratified by surgeon (permuted blocks of varying length) implemented using a 24/7-Internet-service. As fallback procedure sequentially numbered opaque envelopes may be provided containing the allocation details.

6 Monitoring and Data management

Monitoring (ZKS): In this trial, three standard treatments are compared, which are part of daily routine in the participating study sites. Therefore there are very low study specific risks. For this reason, central quality assurance measures are regarded sufficient and will be applied and performed by data management personnel. There will be no on site monitoring in the respective study centers.

Data management (ZKS): The IT infrastructure and data management staff will be supplied by the ZKS Cologne. The trial database will be developed and validated before data entry based on standard operating procedures at the ZKS Cologne. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The ZKS Cologne Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details are specified in the data management manual.

7 Analysis sets

The flow of patients through the course of the trial will be presented according to the CONSORT style flow chart. Numbers of patients screened, randomized, treated and analysed will be given for all groups as well as reasons for discontinuation of treatment or exclusion of analysis sets.

7.1 Definitions

Intention-to-treat (ITT) population: All enrolled trial subjects which were enrolled and randomized and which received the initial surgery (excluding those, for which no informed consent is available). The analysis will be done according to the intention-to-treat principle, that is, all patients will be evaluated for the group to which they have been assigned.

Note 1: Patients who switched arms will be included in the FAS and will be analysed according to ITT. A time slot of 23 to 30 weeks will be accepted for the examination of the primary endpoint. If no information on endpoints is available in this time slot, however the patient is event-free at a later visit, this information will be used as substitute. A missing primary endpoint is considered a treatment failure.

Per-protocol (PP) population: All randomized trial subjects who were treated and observed according to protocol that is all trial subjects of the ITT-population with the exception of patients who fulfill one of the following criteria (major protocol deviations):

- Patient has not received the randomized treatment (switched arms, received no study treatment)
- Patients with major protocol violations according to assessment (see Appendix 16.2)
- Patients not evaluable due to early discontinuation
- Patients with relevant deviations from trial schedule (for example start of treatment before randomization, examination of primary endpoint outside the time frame of 23 – 30 weeks)

Valid-for-Safety population (or as treated population): all randomized trial subjects which received the initial surgery. Analysis will be as treated.

7.2 Application

The primary analysis will be according to intention-to-treat, i.e. all patients of the ITT-population will be analyzed as assigned. A missing primary endpoint is considered a treatment failure. The primary analysis will include the confirmatory analysis of the efficacy endpoint (test of superiority of E1 vs. C), the exploratory analysis of the non-inferiority hypothesis (E2 vs C) and the exploratory analysis of all other listed endpoints.

The secondary analysis is done based on the per-protocol-population. With regard to the superiority hypothesis (E1 vs. C) the analysis of the PP-set is considered as a sensitivity analysis. In case of the non-inferiority hypothesis (E2 vs. C) the ITT and PP analyses are considered as equally important.

The valid-for-safety analysis includes the exploratory analysis of all safety endpoints and adverse events. Patients will be analysed for the treatment which they had received.

All defined endpoints will be analysed in the stated three trial populations (ITT, PP, VFS).

Further sensitivity analyses will be done based on the patients belonging to the ITT-population using (a) the last-observation-carried-forward method and (b) multiple imputation of missing endpoints (primary and secondary).

7.3 Major protocol violations / Withdrawals

Decisions concerning evaluation of potential protocol violations in the context of definition of the study populations (ITT, PP, VFS) will be agreed between the Principal Coordinating Investigator and the responsible Statisticians. The Principal Coordinating Investigator will assess the clinical characteristics including the control of the actually received treatment in relation to the randomized treatment. Further clinical experts will be involved if necessary. In addition, patients with deviation the trial schedule will be filtered out by appropriate algorithms. A listing of patients with (major) protocol deviation and the reason for the deviation will be added to the final report.

8 Trial centres

The course of recruitment and numbers of patients per centre will be presented (total, by group; listings and graphics).

9 Analysis variables

9.1 Demography and baseline characteristics

- Demography: Age, gender
- Baseline characteristics: study eye, preoperative refraction status (sph, cyl, °A), intraocular pressure, visual acuity (1m and 4m) and anatomical findings, vitreous situation at start of surgery, time between symptoms and surgery

9.2 Primary variable

The primary variable is the “absence of an indication for any retina reattaching procedure during the follow-up of 26 weeks” (such procedures are additional gas injections, additional vitrectomy or additional buckling procedure).

The assessment of the primary endpoint will be done based on the data on anatomical finding, adverse events and the fundus drawing by the clinical endpoint committee consisting of Prof. Dr. P. Walter, Dr. B. E. Mazinani and Dr. S. Baumgarten (see Appendix 16.2).

9.3 Secondary variables

9.3.1 Efficacy

- Visual acuity at the end of follow-up (after 26 weeks) as measured by ETDRS charts
- Refracti*on* status (sph, cyl, °A)
- Retina reattachment rate
- Anatomical situation of the anterior and posterior segment
- Occurrence of PVR, Grade C according to Machemer

9.3.2 Safety/Tolerability

- Intraoperative complications in general
- specific intraoperative complications
- Adverse events

9.3.3 Quality of life

not applicable

9.3.4 Health economics

not applicable

10 Handling of missing values and outliers

10.1 Missing values

For the primary analysis a missing primary endpoint is considered a treatment failure. Further sensitivity analyses will be done based on the patients belonging to the ITT-population using (a) the last-observation-carried-forward method and (b) multiple imputation of missing endpoints (SPSS Statistics 22 command MULTIPLE IMPUTATION, full conditional specification). For imputation of endpoints a core set of indicators will be employed: age, gender, randomized treatment and visual acuity (at baseline and at visits).

10.2 Outliers

The presence and influence of outliers (i.e. values very distant from the centre of the empirical distribution) will be investigated. If relevant, robust statistical methods based on quantiles or ranks will be used.

11 Statistical analyses / methods

11.1 Patients

Course of recruitment (cumulative number of patients by months) and number of patients per centre will be displayed graphically.
A standard CONSORT-style flow chart will be generated with information on the number of patients assessed for eligibility, randomized patients, treated patients and withdrawals (Schulz et al., 2010).
Number of documented follow-up-visits (examination) and median follow-up- time (total, per group) will be given.

11.2 Demography and baseline characteristics

Analysis of the patient characteristics is primarily descriptive, with mean, standard deviation, median, minimum and maximum, first and third quartile. For binary and categorical data the number of events and proportions will be given.
The listed patient characteristics will be reported as total and separately for the three groups with descriptive summary measures.

- **Gender, age, study eye (left/right)**
  n, % of patients; valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum
- **Preoperative refraction status (sph, cyl, °A)**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum
- **Preoperative Visual acuity 1m: pre-op log MAR Visus (derived from raw data)**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum
- **Preoperative Visual acuity 4m: pre-op log MAR Visus (derived from raw data)**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum

- **Vitreous situation at start of surgery**
  n and % of patients with 1 = fully attached, 2 = partly detached, 3 = fully detached, 4 = hemorrhage, 9 = other (specify - text)
- **Intraocular pressure**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum

11.3 Prior or concomitant medication and diseases

Prior or concomitant medication (including pain medication due to postoperative pain) was not enquired in the eCRF. Medical history in terms of previous surgeries is recorded and will be analysed. Results will be reported as total and separated by group.

- **cataract surgery**
  n and % of patients with no event, accidental capsulotomy, IOL fixation problems, post-op inflammation or other
- **previous retinal procedures:**
  n, % of patients with Laser, Cryo, Gas injection, Anti VEGF Injection

11.4 Exposition to treatment/Compliance

In this trial the treatments under investigation are surgery methods. Results will be displayed as total and separated by group.

- **Anaesthesia**
  n, % of pts with 1 = ITN, general, 2 = Analgosedation, 3 = Retrobulbar, 4 = Parabulbar, 5 = Subtenon, 6 = Eye drops, 9 = Other
- **Surgery procedure performed**
  n, % of patients with type of procedure separately per procedure 1-3 [1 = 20 G + Cerclage (2mm), 2 = 20 G + Cerclage (3mm), 3 = 20 G + Cerclage (4mm)], procedure 4 [20 G (- Cerclage)], procedure 5 [23 G], procedure 6 [25 G]
- **Type of endotamponade**
  n, % of patients with type of endotamponade separately per type 1-3 [1 = SF6, 2 = C2F6, 3 = C3F8], 4-6 [4 = Silicon Oil 1000, 5 = Silicon Oil 2000, 6 = Silicon Oil 5000], 7 = heavy Silicon Oil, 8 = Air
- **Applied concentration of Endotamponade** (with regard to the type)
  n, % of patients with specific concentration of endotamponade
- **Type of Endodrainage**
  n, % of patients with type of 1 = Air, 2 = Decalin, 3 = Octalin, 4 = F6H8
- **Endolaser**
  n, % of patients with / without usage of endolaser

- **Exocryo**
  n, % of patients with / without usage of exokryo

- **Transscleral Laser**
  n, % of patients with / without usage of trans. laser

- **Indirect Laser**
  n, % of patients with / without usage of indirect laser

- **Endocryo**
  n, % of patients with / without usage of endokryo

- **Observation system**
  n, % of patients with type of observation system 1 = wide angle view > 120°, contact, 2 = wide angle view > 120 °, non-contact (e.g.Biom), 3 = indirect via Ophthalmoscope, 4 = direct, < 120 °, contact lens system (e.g. Hoffmann lens, o.s.), 9 = other

- **Duration of operation (time between cut and suture) in min**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum

- **Number of retinal breaks**
  n, % of patients with specific numbers of breaks

- **Findings at the end of surgery**
  n, % of patients with retina fully attached (=1)

11.5 Primary analysis

The primary objective will be evaluated for superiority by Cochran-Mantel-Haenszel method stratified by surgeon. For the exploratory comparison of (C) and (E2) a non-inferiority margin of 1.25 (odds ratio) will be employed. Heterogeneity (i.e. due to surgeon or centre) will be investigated (Breslow-Day test). Forest plots will be done.
More complex statistical methods, i.e. logistic regression, GEE and multiple imputation methods, will be used for sensitivity analysis.

11.6 Secondary analyses

The secondary variables will be evaluated by Cochran-Mantel-Haenszel methods (nominal variables) or linear models (metric variables), respectively, stratified by surgeon.
Mixed models for repeated measures (MMRM), GEE and multiple imputations methods will be used for sensitivity analysis.

11.6.1 Efficacy

- **Visual acuity at the end of follow-up (after 26 weeks) as measured by ETDRS charts** *(calculated including hand movement, finger counting)*
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum

- **Refraction status after 26 weeks(Sph, cyl, °A)**
  valid count, mean, sd, minimum, 25th percentile, median, 75th percentile, maximum
- **Retina reattachment rate after 26 weeks**
  n, % of pts. with fully attached retina after 26 weeks (as documented in anatomical finding); in addition: sequence of reattachment rate, time to retina re-attachment procedure (Kaplan-Meier-curve)
- **Anatomical situation of the anterior and posterior segment after 26 weeks**
  n, % of pts with specific anatomical finding (lids, conjunctiva, cornea, anterior chamber, iris, IOL, vitreous cavity)
- **Occurrence of PVR, Grade C according to Machemer after 26 weeks**
  n, % of pts. with PVR Grade C [anatomical finding, retina]

11.6.2 Safety/Tolerability

11.6.2.1 Intraoperative complications

- **in general**
  n, %. of pts with any complication by group
  n, %. of pts with any complication by number of complications
- **specific intraoperative complication**
  n, %. of pts with specific intraoperative complication
  - Iatrogenic breaks [compl_op1]
  - Intraocular hemorrhage anterior chamber [compl_op2]
  - Intraocular hemorrhage vitreous [compl_op3]
  - Intraocular hemorrhage subretinal [compl_op4]
  - Expulsive hemorrhage [compl_op5]
  - Subretinal drainage fluids [compl_op6]
  - Scleral perforation during buckling [compl_op7]
  - Subretinal infusion [compl_op8]
  - Corneal edema (abrasion) [compl_op9]
  - IOL myst [compl_op10]
  - Sclerotomy insufficiency, leaking [compl_op11]
  - Other intraoperative complications [compl_op99]
  - Ocular hypertony [IOP > 30 mmHg]

11.6.2.2 Adverse events

The proportion of patients with at least one adverse event, or serious adverse event, respectively, will be reported for all groups. All adverse events will be presented by severity, causal relation to the intervention, and category. The original description will be listed.

11.6.2.3 Laboratory parameters

not applicable

11.6.2.4 Vital signs

not applicable

11.6.2.5 Pharmacokinetics

not applicable

11.6.3 Life quality

not applicable

11.7 Planned subgroup analyses

Men (expected 73%) and women will be analysed together as well as separately. Further subgroup analyses (which were not defined in the protocol, thus exploratory) may be done with respect for the time from symptoms to surgery and regarding the location of breaks (above, beneath).

11.8 Interim analyses

not applicable

12 Deviations from the protocol

12.1 Assessment of primary endpoint

The primary endpoint, “absence of an indication for any retina reattaching procedure during the follow-up [26 wks]”, is not explicitly recorded in the CRF. Therefore an endpoint-committee will be established, to assess the relevant data and to determine, whether a patient reached the primary endpoint or not.
For the assessment of the endpoint a listing of relevant data will be prepared, that is, of data related to retinal attachment recorded as anatomical findings (see appendix). Furthermore, the documented AE of the patient as well as the fundus drawing will be taken into account. All visits including unscheduled visits between initial surgery and end of follow up after 26 weeks will be considered. The same applies for any AE/SAE documented during the follow up period of 26 weeks.
The results of the assessment will be documented on an additional report form which will be signed by the committee members (see Appendix). The additional data will be entered in the trial data base.

12.2 Assessment of protocol deviations

Decisions concerning the evaluation of potential protocol violations done by the Principal Coordinating Investigator will be documented on an additional report form (see Appendix 16.2). The additional data will be entered in the trial data base.

12.3 Items not documented

Postoperative pain or pain medication was not enquired in the eCRF and therefore will not be analysed. The same applies to prior or concomitant medication. Furthermore, the Number of retina specific procedures (beyond the primary event) could not be recorded.

13 Interpretation of results

In the trial 2 hypothesis will be investigated. With regard to the superiority hypothesis (E1 vs. C) the analysis of the ITT-set is considered to be the primary analysis. The analysis of the PP-set is considered as a sensitivity analysis.
In case of the non-inferiority hypothesis (E2 vs. C) the ITT and PP analyses are considered as equally important.
It is expected that all analyses show results of the same direction (E1 is superior to C or vice versa). If the findings of the per-protocol analysis, or the as-treated analysis do not confirm those of the ITT-analysis, the different results will be explicitly referred to and interpreted with caution in the final report.

14 Software

SPSS Statistics 22 (IBM Corp., Armonk, NY, USA)

15 References

- Mantel, N., Haenszel, W., 1959. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl cancer Inst., 22:719-748
- Schafer, J. L. 1997. Analysis of Incomplete Multivariate Data. London: Chapman and Hall

16 Appendices

16.1 Reference ranges of laboratory parameters

not applicable

16.2 Additional report forms

Assessment of the primary endpoint

VIPER study document (confidential)

VIPER Clinical Endpoint Assessment

Centre _____ Site

Pat-ID |__|__| - |__|__|__|__| patid

Result of CEC Indic_yn

☐ Absence of indication for any retina reattaching procedure during the follow-up [1]

☐ Indication for any retina reattaching procedure during the follow-up. Please give details below. [2]

Indication for retina reattaching procedure

Visit Indic_vis

☐ Visit w6 [1]
☐ Visit w12 [2]
☐ Visit w26 [3]
☐ Unscheduled visit 1 [4]
☐ Unscheduled visit 2 [5]

Visit Date |__|__| . |__|__| . |__|__|__|__| indic_dat

Type of procedure indic_typ

☐ Additional gas injection [1]
☐ Additional Vitrectomy [2]
☐ Additional Buckle [3]
☐ Other procedure, please specify: [4]

_____ Indic_typ_txt

Documentation of procedure / Indication for procedure indic_doc

☐ Anatomical finding [1]
☐ Fundus drawing [2]
☐ AE/SAE [3]
☐ Other, please specify: [4]

_____ Indic_doc_txt

Fundus drawing plausible fu_plaus_yn

☐ Yes [1]
☐ No, please specify: [0]

_____ fu_plaus_txt

Comment _____ indic_txt

Date |__|__| . |__|__| . |__|__|__|__| assess_dat

(Date of assessment)

CEC-member _____ assess_nam

(Name, block letters)

Signature _____ assess_sign

(Please sign printout.)

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Assessment of protocol deviations

VIPER study document (confidential)

VIPER **Assessment of Protocol Violations**

Centre _____ Site

Pat-ID |__|__| - |__|__|__|__| Patid

Protocol violation pv_yn

- ☐ No [0]
- ☐ Yes (please specify treatment or other indication) [1]

Application of treatment which is not allowed (trial protocol 4.6.2) pv_treat

- ☐ Use of Triamcinolone or other means to visualize the vitreous [1]
- ☐ Use of silicone oil [2]
- ☐ Prophylactic circumferential laser treatment [3]
- ☐ Prophylactic circumferential cryo treatment [4]
- ☐ Peeling of the internal limiting membrane [5]
- ☐ Other procedure, please specify: [6]

_____ pv_treat_txt

_____

Other indication for protocol violation pv_oth

- ☐ No [0]
- ☐ Yes, please specify: [1]

_____ pv_oth_txt

_____

Date |__|__|.|__|__|.|__|__|__|__| pv_ass_dat

(Date of assessment)

Name _____ pv_ass_nam

(Name, block letters)

Signature _____ pv_ass_sign

(Please sign printout.)

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