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Vitrectomy with or without encircling band for pseudophakic retinal detachment: a multi-centre, three-arm, randomised clinical trial. VIPER Study Report No. 1—design and enrolment

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ABSTRACT

Purpose Scleral buckling is currently used in addition to vitrectomy for the treatment of pseudophakic retinal detachment (PRD) to better support the vitreous base and better visualisation of the periphery.

Aims The aims of this study are to evaluate (1) whether the combination of 20 G vitrectomy and scleral buckling is superior to 20 G vitrectomy alone (control) (confirmatory), and (2) whether transconjunctival 23/25 G vitrectomy is non-inferior to 20 G vitrectomy (both without scleral buckling) regarding operation success (exploratory).

Methods The VIPER (Vitrectomy Plus Encircling Band Vs. Vitrectomy Alone For The Treatment Of Pseudophakic Retinal Detachment) study is an unmasked, multi-centre, three-arm randomised trial. Patients with PRD were eligible, excluding complicated retinal detachment or otherwise severe ophthalmologic impairment. Patients were randomised to one of three interventions: 20 G vitrectomy alone (control C), combination of 20 G vitrectomy and circumferential scleral buckling (experimental treatment E1) or 23/25 G vitrectomy alone (experimental treatment E2). The primary endpoint is the absence of any indication for a retina re-attaching procedure during 6 months of follow-up. Secondary endpoints include best corrected visual acuity, retina re-attaching procedures, complications and adverse events.

Results From June 2011 to August 2013, 257 patients were enrolled in the study. The internet randomisation service assigned 100 patients each to the treatment arms C and E1, and 57 patients to treatment E2. The imbalance is due to the fact that several retinal surgeons did not qualify for performing E2. The random assignment was stratified and balanced (ie, 1:1 or 1:1:1 ratio) by surgeon.

Conclusions The described study represents a methodologically rigorous protocol evaluating the benefits of three different vitrectomy approaches to PRD. The projected results will help to establish their overall efficacy and will permit conclusions regarding their relative value.

Trial registration number DRKS00003158 (German Clinical Trials Register, DRKS).

INTRODUCTION

Background and rationale

Vitrectomy has been combined with scleral buckling in the treatment of pseudophakic retinal detachment (PRD) ever since vitrectomies have been used to treat this disorder. Retinal surgeons expect additional buckling procedures to provide enhanced support of the vitreous base and better visualisation of the periphery. On the other hand, the additional scleral buckle implies increased invasivity and operation time, it affects the postoperative refraction and the blood circulation of the eye[1] and may entail specific complications such as buckle migration and infection. The literature is inconclusive regarding the question whether these costs of the additional buckle are associated with increased anatomical or functional success. While some studies reported almost complete success of combined surgery,[2 3] other studies comparing vitrectomy versus vitrectomy with additional buckle found no benefit of the latter. Pournaras and Kapetanios achieved excellent re-attachment rates with both techniques (ie, 100% vs 92% at first attempt).[4] Wickham and coauthors compared vitrectomy alone with vitrectomy and scleral buckling in cases with inferior breaks. In both groups, about half of the patients were pseudophacic: 54 and 53%, respectively. The primary re-attachment rate was 89% in the vitrectomy alone group and 73% in the vitrectomy plus buckle group.[5] Stangos and coauthors compared vitrectomy alone with vitrectomy plus scleral buckling for PRD. The re-attachment rate was 97% in the vitrectomy alone group and 92% in the vitrectomy plus buckle group.[6] Recently, data on 4179 patients with retinal detachment have been published based on surveys among retinal surgeons. A subgroup analysis showed a slightly higher failure rate for combined surgery versus vitrectomy alone; however, bias due to differential selection of cases (eg, favouring an additional buckle in difficult situations) cannot be ruled out.[7] All these studies were either retrospective or prospective non-randomised trials. The Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment (SPR) study was a prospective randomised multi-centre trial to compare vitrectomy and scleral buckling in the treatment of phakic or pseudophakic patients with retinal detachment of medium complexity.[8] An ancillary analysis showed that in pseudophakic patients treated with vitrectomy the use of an additional buckle resulted in a significantly lower re-detachment rate of 11.4% versus 40.9% in patients who were treated by vitrectomy alone. However, the use of an additional buckle was not randomly assigned but at the discretion of the treating surgeon. In recent years, transconjunctival 23 G or 25 G surgery has been replacing the 20 G approach with exposition of the sclera. Several

retrospective studies found similar results of the two techniques in the treatment of retinal detachment.[9–13] Again, evidence from randomised trials is still lacking.

Objectives

The primary objective of the VIPER (Vitrectomy Plus Encircling Band Vs. Vitrectomy Alone For The Treatment Of Pseudophakic Retinal Detachment) study is to test the superior efficacy of an additional encircling band in addition to a 20 G vitrectomy with gas (treatment codes E1 and C) in the treatment of PRDs (confirmatory). The primary endpoint is the absence of any situation leading to an additional retina re-attaching surgical procedure during the follow-up. The secondary objective is to investigate whether 23/25 G transconjunctival vitrectomy with gas (E2) is not inferior to 20 G vitrectomy with gas (C) in the treatment of PRD without encircling band (exploratory).

Trial design

VIPER is a multi-centre, randomised clinical trial with three parallel treatment arms (see figure 1); however, each comparison (superiority, non-inferiority) is based on two arms only (ie, E1 vs C, and E2 vs C, respectively). As the study treatments are different surgical procedures, blinding of the trial surgeons is not possible. Given the specific side effects of the additional encircling band such as myopic shift of about 2 D and possible complications such as infection, strabismus, explant intrusion and others, patient blinding is not possible either. The study protocol is available as supplementary file.

PARTICIPANTS AND METHODS

Study setting

Patients were enrolled at 14 trial centres specialised on retinal surgery. The participating institutions are university clinics that provide emergency care and treat the majority of regional cases of PRD.

Participating surgeons had to confirm that they had treated at least 100 cases of retinal detachments with primary vitrectomy using a 20 G approach of which at least 20 had to be combined surgery with vitrectomy plus encircling band. Moreover, for the secondary objective regarding 23/25 G vitrectomy selected surgeons were required to have performed at least 20 surgical procedures for retinal detachment with 23/25 G vitrectomy in addition to the 100 cases with 20 G vitrectomy, and the surgeon had to state that he or she felt safe and comfortable with the transconjunctival technique.

Eligibility criteria

Pseudophakic patients over 18 years of age were eligible if they suffered from a rhegmatogenous retinal detachment and gave written informed consent. Cataract surgery had to be done at least 3 months before the onset of symptoms of retinal detachment. The main exclusion criteria were manifest uveitis, uncontrolled glaucoma, active retinal vascular disease, malignant intraocular tumours, any history of intraocular surgery other than (distant) cataract surgery, giant retinal tears, proliferative vitreoretinopathy grade B or C, aphakia and any systemic disorder potentially preventing (i) local/general anaesthesia or (ii) participation in the control examinations.

Interventions

Control group (C): Patients who were randomly assigned to the control group received a 20 G vitrectomy without encircling band. Surgery was performed with an operating microscope and a wide field viewing system (contact/non-contact). The conjunctiva was opened at the limbus to expose the sclera. Three 20 G sclerotomies were made with a distance of 3–4 mm to the

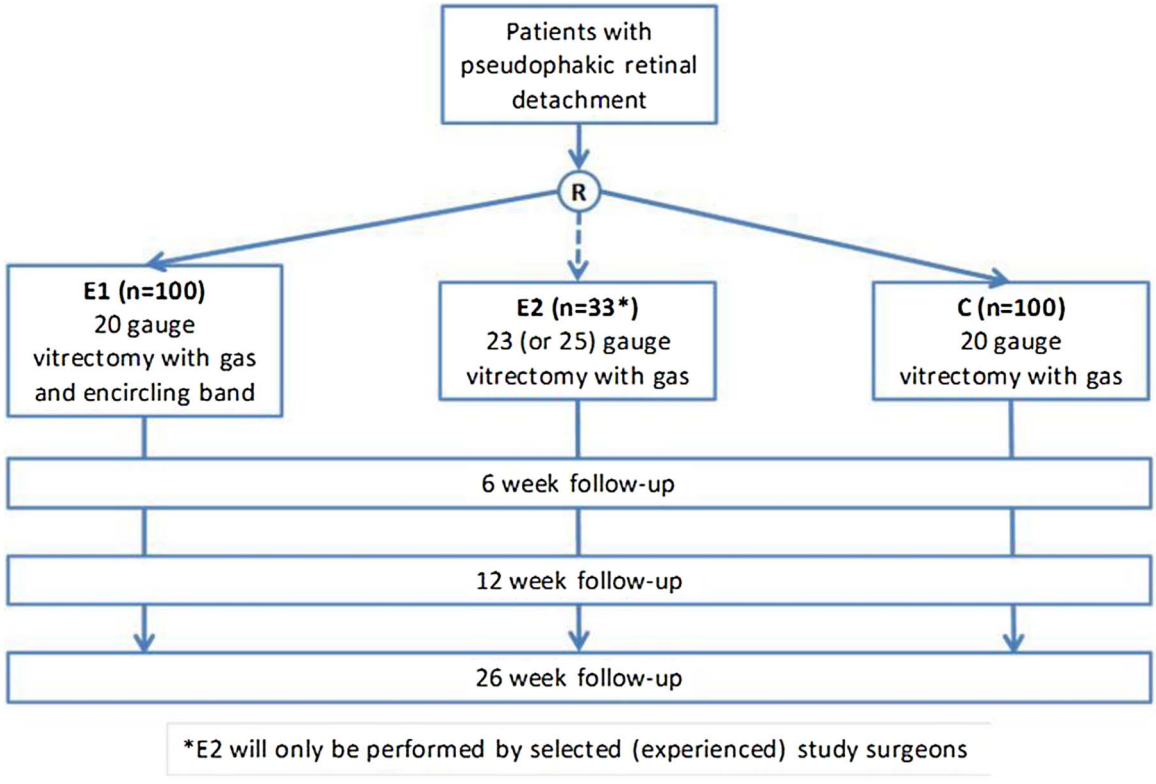

Figure 1 Design of the VIPER study.

limbus. A full vitrectomy was performed. If the vitreous was not fully detached, a complete vitreous detachment was achieved. Heavy liquids were allowed to drain subretinal fluid. After full re-attachment of the retina under heavy liquids or under air, each retinal break was treated with endolaser or transscleral cryopexy. Peripheral high-risk degenerations should be treated as well. A prophylactic circumferential laser treatment was not allowed. The surgery was completed with a gas fill using non-expandable air/gas mixtures such as SF6, C2F6 or C3F8 and closure of the sclerotomies and the conjunctiva. Ocular pressure had to be monitored at least once within 8 h after surgery and the day after surgery. If the intraocular pressure exceeded 40 mm Hg, gas should be released via the pars plana using sterile techniques.

Experimental group 1 (E1): Patients in this group received a 20 G vitrectomy with an encircling band. Surgery started with a circumferential opening of the conjunctiva at the limbus. A 2–4 mm encircling band was placed underneath the recti muscles and was fixated in all four quadrants. The encircling band was positioned onto the equator of the globe. At the end of surgery, sufficient buckling with no choroidal folds should be visible. The 20 G vitrectomy was performed as described above for the control group (C).

Experimental group 2 (E2): Patients in this group were treated with a 23 G or 25 G vitrectomy without an encircling band. A full vitrectomy was performed using valved or unvalved trans-conjunctival trocar systems. Trocars were inserted tangentially after displacement of the conjunctiva. If not yet present a full vitreous detachment should be achieved. Endodrainage of the subretinal fluid was achieved with the use of heavy liquids and/or air. After full re-attachment of the retina, breaks and high-risk degenerations were treated with the endolaser probe or with transconjunctival/transscleral cryopexy. A circumferential prophylactic laser treatment was not allowed. After full fluid-air exchange, the eye was filled with a non-expandable air/gas mixture. Trocars were removed. If the sclerotomies were leaking, they had to be sutured either transconjunctivally or after opening of the conjunctiva.

All groups (C, E1, E2): In none of the groups, the use of silicone oil, internal limiting membrane peeling or triamcinolone was allowed. Medical treatment could be given by the decision of the surgeon and according to institutional standards.

Outcomes

The primary endpoint was defined as the absence of an indication for any retina re-attaching procedure during the follow-up. Retina re-attaching procedures were additional gas injection, additional vitrectomy or additional buckling procedure. The presence of any such indication was regarded as treatment failure. Generally, functional (eg, visual acuity) or anatomic (as in this study) endpoints are possible to assess treatment success in retinal detachments. In our opinion, visual acuity is not a valid parameter because patients with retinal detachment present in emergency settings during the night or on weekends possibly with a dilated pupil which may affect exact preoperative EDTRS visual acuity testing. In fact almost all studies on retinal detachment use anatomical endpoints.[2–7] Further, supporting (secondary) endpoints on efficacy and safety are given in table 1.

After completion of the study follow-up, all documented clinical data (including fundus drawings and photographs) were evaluated by a clinical endpoint committee (SB, BM, PW) regarding the incidence of key study events.

Participant timeline

Following inclusion of a patient in the study, randomisation and surgery, patients were examined after 6, 12 and 26 weeks (see table 2).

Sample size

In the SPR study, 11.4% (=10/88) of pseudophakic patients who had received combined primary vitrectomy and scleral buckling suffered from a re-detachment, in contrast to 40.9% (=18/44) of pseudophakic patients who received primary vitrectomy only.[8] We calculated 82 patients per group (E1, C) (software PS V.3.0.43; http://biostat.mc.vanderbilt.edu/PowerSampleSize) for the continuity corrected χ^2 test to have 80% power at two-sided type I error rate of 5% assuming event proportion of 35% (E1) and 15% (C).[14] According to Donner (1984), about 10% inflation seems adequate to account for the stratification (ie, 91≈82/

Table 1 Key secondary endpoints evaluated in the VIPER study

Endpoint	Measurement variable	Analysis metric	Method of aggregation	Time
Visual acuity	LogMAR visus using ETDRS charts	Change from baseline	Means	At 26 weeks post-surgery
Refractive status	Sphere (D), cylinder (D), axis (°A)	Change from baseline	Means	At 26 weeks post-surgery
Intraocular pressure	Tonometry (mm Hg)	Change from baseline	Means	At 26 weeks post-surgery
Retina re-attachment	…	Value (yes/no)	Proportions	At surgery At 26 weeks post-surgery
Retina-specific procedures	… to achieve a stable retinal attachment	Value (yes/no) Count (>0)	Centiles Proportions	Within 26 weeks
Proliferative vitreoretinopathy grade C	… according to Machemer	Value (yes/no)	Proportions	Within 26 weeks
Operation time	Time between cut and suture	Value	Means	At surgery
Anatomical situation	… of lids, conjunctiva, cornea, anterior chamber, iris, intraocular lens or vitreous cavity	Value (yes/no) Count (>0)	Centiles Proportions	Within 26 weeks
Intraoperative complications	… as iatrogenic breaks, bleeding, sclera perforation	Value (yes/no) Count (>0)	Centiles Proportions	At surgery
Postoperative complications	… as macular pucker, macular oedema, ocular hypertony, diplopia	Value (yes/no) Count (>0)	Centiles Proportions	Within 26 weeks
Enucleation	…	Value (yes/no)	Proportions	Within 26 weeks
Death	…	Time to event Value (yes/no)	Centiles Proportions	Within 26 weeks

Table 2 Visit schedule

	Enrolment (day −2 to 0)	Surgery (day 0)	Week 6 (W5–7)	Week 12 (W10–14)	Week 26 (W23–29)	Additional visit* (W1–29)
Enrolment						
Screening for eligibility	X					
Informed consent	X					
Allocation	X					
Interventions						
Surgery (C, E1, E2)		X				
Assessment						
Demographic data, medical history	X					
Best corrected visual acuity (ETDRS)	X		X	X	X	X*
Refraction	X		X	X	X	X*
Intraocular pressure	X		X	X	X	X*
Indication for retina re-attaching procedure		X	X	X	X	X
Anatomical findings	X		X	X	X	X*
Slit lamp	X		X	X	X	X*
Funduscopy	X		X	X	X	X*
Fundus drawing	X		X	X	X	X*
Fundus photography					X	X*
Operation time		X				
Intraoperative complications		X				
Postoperative complications			X	X	X	X*
AEs/SAEs		X	X	X	X	X*
End of treatment/study					X	X*

*As required.
AE, adverse event; SAE, serious adverse event.

0.9 per group).[15] Another 10% was added to account for inevaluable patients (ie, 100≈91/0.9). After reaching this target, recruitment to the whole trial was stopped, that is, when, according to expectation, about 33 patients would have been allocated to group E2.

Expecting an event percentage of 35% for treatment C, we considered a difference smaller than 5 percentage points clinically non-inferior. This corresponds to an OR of about 1.25 which was used as the non-inferiority margin for the comparison of treatments C and E2. Assuming event percentages of 35% in both arms and a non-inferiority bound of 5 percentage points, 1427 patients per treatment arm are required to reach 80% power at 2.5% one-sided type I error rate (calculated with R V.3.0.3, package gsDesign, function nBinomial). Such a big trial seems unfeasible, thus the comparison of C and E2 can be explorative only.

The issue of an 'underpowered comparison' was also raised by the local ethics committee. We argued that little evidence of high quality (ie, based on a small number of randomised patients) (i) is better than no evidence at all, at least for the time being, and (ii) may later be incorporated in a meta-analysis of similar cases. This argumentation was approved upon by the local ethics committee. Note also that E2 has already become popular (eg, due to shorter operation time, less postoperative discomfort and logistics) without any evidence from randomised trials.

Allocation

Patients were consecutively screened and eligible patients were included in the trial. After written informed consent, patients were assigned to one of three treatment groups. In order to achieve comparable intervention groups, patients will be allocated concealed by preoperative randomisation at the day of surgery using a 24/7-internet-service (ALEA, FormsVisions BV, Abcoude, the Netherlands).

Randomisation was stratified by surgeon (permuted blocks of varying length, ie, either two or three occurrences per block). In case of inavailability of the service, patients could be centrally assigned using a prepared sequence of random numbers (ie, by fax, phone or email). The randomisation ratio was either 1:1:1 or 1:1 depending on individual experience/training in 23/25 G vitrectomy (E2).

We planned to enrol patients at 14 centres with two participating surgeons per centre on average. From a survey among interested surgeons, we estimated that about one-third would be eligible to do E2. Thus, we expected 19 surgeons to enrol for C, E1 and 9 surgeons to enrol for C, E1, E2. Assuming equal enrolment per surgeon (ie, about three per arm), we estimated that overall patients would be assigned to treatment arms in a ratio of 3:3:1 (C:E1:E2).

Methods against bias

Selection bias is minimised by central 24/7 internet randomisation. Performance bias is minimised by standardisation of trial treatments and including only experienced surgeons. Note that masking of patients or surgeons is not possible. Attrition bias is minimised by provision of excellent care and dedicated follow-up efforts. Detection bias is minimised by using standardised outcome assessment, for example, based on ETDRS visus charts. Note that masking of outcome assessors (ie, the clinical endpoint committee) is generally not possible (eg, due to fundus drawings/photographs).

Data collection and management

All patient data were remotely entered by clinical centre staff into a validated (ie, US Food And Drug Administration 21 Code

of Federal Regulations Part 11 compliant) electronic database and checked for plausibility and completeness (central monitoring). Moreover, fundus drawings and 9-field fundus photographs were sent to the coordinating investigator. On-site monitoring could not be performed due to limited funding. Access to the database was restricted to the participating surgeons and monitors. The access of the surgeons was restricted to their own patients. Patient data were pseudonymised.

Statistical methods

Three trial populations are evaluated: (i) intention-to-treat (ITT) population (all trial subjects enrolled and randomised; analysis as assigned), (ii) per-protocol (PP) population (all trial subjects treated and observed according to protocol) and (iii) the as-treated (AT) population (all trial subjects enrolled and randomised; analysis as treated). The primary analysis of E1 versus C (superiority) is derived from the ITT principle, that is, all patients randomised are analysed as assigned. A missing primary endpoint is considered a treatment failure. Otherwise (secondary) the last observation may be carried forward and/or multiple imputation may be done. For the exploratory comparison of E2 versus C (non-inferiority), the analyses based on the ITT analysis set and the PP analysis set are considered equally important.[16] Further details are laid out in the statistical analysis plan (see Supplementary file).

The primary target variable is the number of patients with 'absence of an indication for any retina re-attaching procedure within 26 weeks after surgery'. The treatment comparison E1 versus C is evaluated for superiority by the Cochran–Mantel–Haenszel test stratified by surgeon and the corresponding common OR.[17] Heterogeneity due to surgeon (ie, treatment by surgeon interaction) is tested by the Breslow–Day test. Any significant heterogeneity is attempted to be explained by relevant covariates. For the exploratory comparison of E2 versus C, a non-inferiority margin of 1.25 (OR) is employed. Logistic regression and multiple imputation methods are used for sensitivity analysis.

The secondary endpoints are evaluated by Cochran–Mantel–Haenszel methods (nominal variables) or linear models (metric variables), respectively, stratified by surgeon. Mixed models for repeated measures, generalised estimating equations and multiple imputations methods are used for sensitivity analysis. Safety data, that is, adverse events and/or complications, are summarised by type, seriousness, intensity, relatedness and the treatment performed. A subgroup analysis is done with respect to sex (the expected proportion of men is 73%). No formal interim analysis was planned.

Ethical and legal aspects

The study was designed and conducted according to the principles of Good Clinical Practice (GCP, ICH E6) and data protection laws. Important protocol modifications can only be made if agreed by the coordinating investigator, the project manager and the statisticians and all authors of the trial protocol. Any changes must be made in writing and must be documented with reasons. They will be signed by all authors of the original trial protocol. Amendments that require approval are submitted to the ethics committee and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

The study was prospectively registered in the German Clinical Trials Register under DRKS00003158.

It is planned to publish the trial results, in mutual agreement with the Principal Coordinating Investigator (PCI), in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors)'.[18]

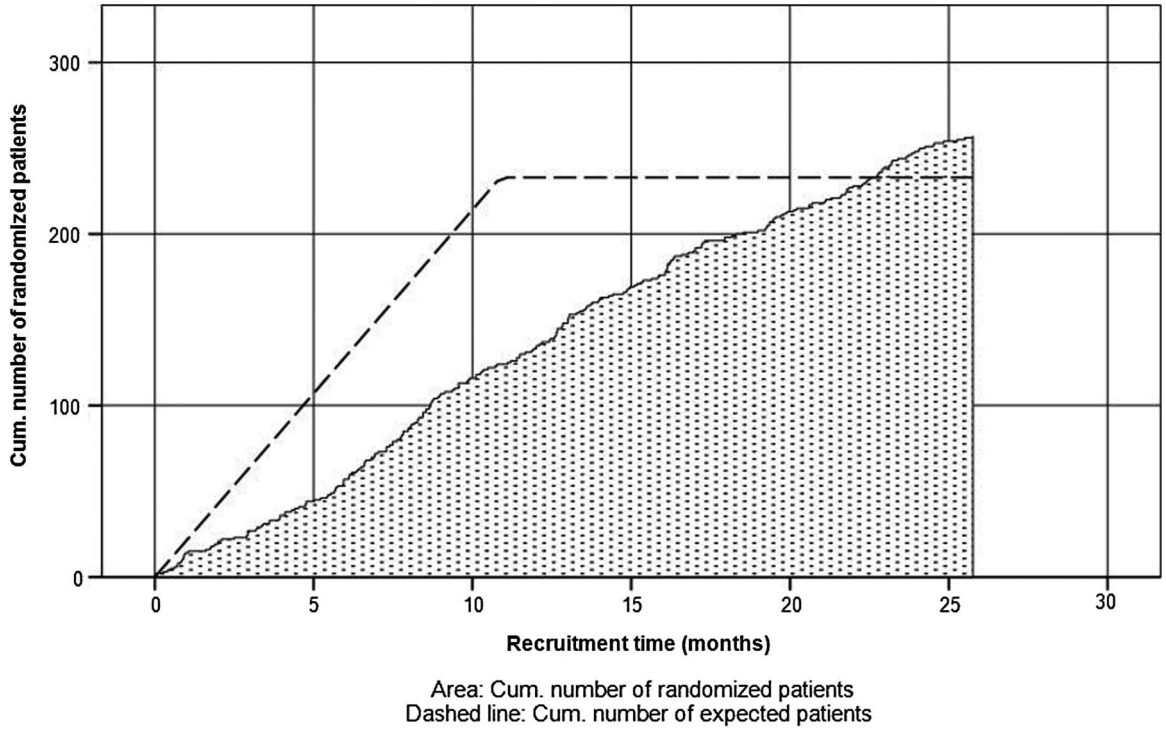

Figure 2 Enrolment of patients over time.

Trial status

Overall, 14 centres and 34 surgeons participated in the study, 18 surgeons enrolled only in arms E1 and C with allocation ratio 1:1 and 16 surgeons enrolled in all three arms, including 23/25 G vitrectomy with gas (E2) with ratio 1:1:1. During the enrolment phase from June 2011 to August 2013, a total of 257 patients with PRD were included (see figure 2), 100 patients were randomly assigned to arm E1, 57 patients to arm E2 and 100 patients to arm C, respectively. Because the surgeons who were proficient in all three techniques tended to recruit more patients than expected, that is, eventually 57 instead of 33 patients as given in the protocol, the local ethics committees were timely asked for reapproval which they granted.

SUMMARY AND CONCLUSION

The additional implantation of a scleral buckle in the treatment of retinal detachments with vitrectomy implies an additional trauma. The 360° incision of the conjunctiva and exposition of the sclera lead to consecutive scarring and surface alterations and the impact of the buckle on the shape of the eye results in a significant myopisation. The VIPER study will demonstrate whether the additional risks of a circumferential scleral buckle combined with vitrectomy are justified by a superior success rate. Moreover, in view of the increasing use of transconjunctival vitrectomy to treat retinal detachments, it seems mandatory to investigate whether patients benefit from an additional buckle before this technique is, possibly prematurely, abandoned due to technical progress.

Trial organisation

Coordinating investigator is Peter Walter, Department of Ophthalmology, University of Aachen (RWTH). Project coordination, correspondence with regulatory authorities, data management and central monitoring were performed by the Clinical Trials Centre Cologne (ZKS Köln), University of Cologne. Statistical design, randomisation and data analysis were performed by the Institute of Medical Statistics, Informatics and Epidemiology (IMSIE), University of Cologne. Trial procedures were implemented according to the standard operating procedures of ZKS Köln and IMSIE.

Collaborators VIPER Study Group *Surgeons, in alphabetical order:* Agostini H (Freiburg), Aisenbrey S (Tübingen), Bartz-Schmidt U (Tübingen), Bornfeld N (Essen), Clemens C (Münster), Dahlke C (Cologne), Eter N (Münster), Fauser S (Cologne), Feltgen N (Göttingen), Gamulescu MA (Regensburg), Gök M (Essen), Helbig H (Regensburg), Hillenkamp J (Kiel), Holz F (Bonn), Jochmann C (Leipzig), Joussen A (Berlin), Junker B (Freiburg), Kirchhof B (Cologne), Lappas A (Cologne), Lommatzsch A (Münster), Lüke M (Lübeck), Mazinani B (Aachen), Meier P (Leipzig), Neß T (Freiburg), Nestler A (Leipzig), Partsch M (Tübingen), Pielen A (Freiburg), Rasche W (Leipzig), Ritzau-Tondrow U (Göttingen), Rössler G (Aachen), Roider J (Kiel), Rudolf M (Lübeck), Uhlig C (Münster), Walter P (Aachen), Wiedemann P (Leipzig). *Data management, central monitoring:* Pfeiffer A (Cologne). *Medical statistics:* Hellmich M (Cologne), Schiller P (Cologne). *Project management:* Limburg E (Cologne), Weiß C (Cologne).

Contributors The following persons have contributed to the planning, conduct and reporting of the study: BM, SB, PS, HA, HH, EL, MH and PW.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval The local ethics committees of all participating institutions.

Provenance and peer review Not commissioned; externally peer reviewed.

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TRIAL PROTOCOL

VIPER STUDY: **VI**TRECTOMY **P**LUS **E**NCIRCLING BAND VS. VITRECTOMY ALONE FOR THE TREATMENT OF PSEUDOPHAKIC **R**ETINAL DETACHMENT

Principal Coordinating Investigator:

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Trial protocol code: VIPER

ISRCTN: wird nachgetragen

EudraCT number: n/a

VIPER Study Protocol, Version V5-11 of 24.03.2011

The information in this trial protocol is strictly confidential. It is for the use of the Principal Coordinating Investigator, investigators, trial personnel, ethics committees, the authorities, and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the Principal Coordinating Investigator.

This protocol was written based on the template provided by G. Grass (Ethics Committee University of Cologne, guido.grass@uni-koeln.de) and C. Weiß (Center for clinical trials Cologne / Retina.net Coordination, claudia.weiss@zks-koeln.de)

Signatures

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Statistician	Signature	Date
Institute for Medical Statistics, Informatics and Epidemiology, University of Cologne		
Dr. Claudia Weiß		
Scientific Advice	Signature	Date
Dr. Endrik Limburg		
Scientific Advice / support of trial management	Signature	Date
Clinical Trials Center, University of Cologne		

I. Synopsis

Sponsor:	Not applicable
Principal Coordinating Investigator:	Prof. Dr. P. Walter Department of Ophthalmology University Hospital Aachen RWTH Aachen University Pauwelsstr. 30 D-52074 Aachen
Title of the clinical trial:	VIPER Study: Vitrectomy plus encircling band vs. vitrectomy alone for the treatment of pseudophakic retinal detachment
Indication:	Treatment of pseudophakic retinal detachment
Phase:	Phase IIb/III (non AMG / non MPG)
Type of trial, trial design, methodology:	Multicentre, multinational randomised controlled trial: (C) 20 gauge vitrectomy with encircling band versus (E1) 20 gauge vitrectomy without encircling band versus (E2) 23/25 gauge vitrectomy.
Number of subjects:	100 patients in groups (C) and (E1), 33 in group (E2).

Primary trial objective:	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 primary endpoint is the absence of any situation leading to an additional retina re-attaching surgical procedure during the follow-up.
Study endpoints:	Primary endpoint: • 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 Secondary endpoints: • Visual acuity at the end of follow-up as measured by ETDRS charts • Refractive status • Anatomical situation of the anterior and posterior segment • Retina reattachment rate • Occurrence of PVR • Occurrence of adverse events • Number of retina specific procedures to achieve a stable retinal attachment Other variables: • Operation time (time between cut and suture) • Postoperative pain

Criteria for evaluation:

Efficacy:

- Documentation of surgical procedures, visual acuity, refraction status, slitlamp examination and fundus appearance as documented by fundus photography.

Safety:

- Iatrogenic breaks / macular hole, macular edema, macular pucker, ocular hypertony (at week 26), diplopia, choroidal hemorrhage, pain medication, enucleation, death.
- Other adverse events reported by the patients or observed by the investigators.

Medical condition and principal inclusion criteria:	Medical condition or disease to be investigated: • Pseudophakic retinal detachment Principal inclusion criteria: • Age: 18 years or older • Pseudophakic rhegmatogenous retinal detachment not suitable for buckling surgery • Agreement of the patient to participate in the trial • Written informed consent of the patient Principal exclusion criteria: • Manifest uveitis • Uncontrolled glaucoma • Active retinal vascular disease • Malignant intraocular eye tumours • History of cataract surgery less than 3 months ago • History of any other intraocular surgery other than cataract surgery • Giant retinal tears • PVR grade B or C • Inability to understand the rationale of this trial or the study aim • Participation in another clinical trial (less than 3 months ago) • Aphakia • Systemic disorders preventing the participation of control examinations during the follow-up • Systemic disorders not compatible with the local periocular or general anesthesia

Treatments under investigation:	(E1) Surgical therapy of pseudophakic retinal detachment with encircling band and 20 gauge vitrectomy with gas; (E2) Comparison with small gauge (23 or 25G) vitrectomy.
Comparator:	(C) Surgical therapy of pseudophakic retinal detachments by 20 gauge vitrectomy with gas without encircling band
Duration of treatment:	The treatments under investigation have a mean duration of 70 minutes, the comparator a mean duration of 60 minutes.
Time plan:	First patient first visit (FPFV): *03/2011* Last patient first visit (LPFV): *03/2012* Last patient last visit (LPLV): *9/2012* Final study report: *12/2012*
Statistician:	PD Dr. Martin Hellmich Institute for Medical Statistics, Informatics and Epidemiology University of Cologne Kerpener Str. 62 50937 Cologne Germany

Statistical methods:	*Randomisation will be 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.*The primary (superiority) and secondary (non-inferiority) objectives will be evaluated by Cochran-Mantel-Haenszel methods stratified by surgeon. For the exploratory comparison of (C) and (E2) a non-inferiority margin of 1.25 (odds ratio) will be employed. All randomised patients will be analysed (intention-to-treat principle). A missing primary endpoint is considered a treatment failure.
GCP conformance:	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.
Financing:	The present trial is performed under the auspices of the retina.net and therefore supported by the retina.net coordination office at the Clinical Trials Center Cologne. Financial support for the retina.net coordination office is given by Jackstaedt Stiftung, Retinologische Gesellschaft and Deutsche Ophthalmologische Gesellschaft. There is no financial support for the trial.

II. Table of contents

II.a) List of tables

II.b) List of figures

III. Abbreviations

abbreviation	meaning
AE	Adverse Event
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BSS	Balanced salt solution
C	Control Group
CRF	Case Report Form
DMC	Data Monitoring Committee
E1	Experimantal Group 1
E2	Experimantal Group 2
ETDRS	Early treatment of diabetic retinopathy study
GCP	Good Clinical Practice
IOL	Intraocular lens
IOP	Intraocular pressure
LKP	Principal Coordinating Investigator (PCI, Leiter der klinischen Prüfung)
n/a	Not applicable
PEI	Paul-Ehrlich-Institut
PPV	Pars plana vitrectomy
PVR	Proliferative vitreoretinopathy
PRD	Pseudophacic retinal detachment
RD	Retinal Detachment

RPE	Retinal pigment epithelium
RWTH	Rheinisch Westfälische Technische Hochschule
SAE	Serious Adverse Event
SPR trial	Primary vitrectomy vs. scleral buckling for rhegmatogenous RD
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Introduction

Pseudophakic retinal detachment (PRD) can be treated either by scleral buckling alone or by primary vitrectomy. The SPR trial showed that the outcome of patients with PRD treated with primary vitrectomy is better than those treated with scleral buckling. However, it remains unclear whether the use of an additional encircling band improves the outcome of the vitrectomy for PRD. With the broader use of transconjunctival small incision vitrectomy techniques an encircling band is not anymore possible. It is not known if the outcome of small gauge vitrectomy in the treatment of patients with PRD is comparable to the “older” technique. These two questions are addressed in this multicentre randomised controlled trial. The control group (C) consists of PRD patients treated with 20 gauge vitrectomy alone whereas the experimental group 1 (E1) consists of PRD patients treated with 20 gauge vitrectomy plus encircling band. The experimental group 2 (E2) consists of PRD patients treated with 23 or 25 gauge vitrectomy without encircling band. The outcome of both experimental groups will be compared with the outcome of the control group. Primary outcome parameter is the absence of any situation leading to further retina re-attaching procedures during the follow up of 26 weeks. Secondary outcome parameters are visual acuity, retinal re-attachment rates, complications, and adverse events.

2. Objectives of the clinical trial

2.1. Rationale for the clinical trial

The incidence of retinal detachment in pseudophakic eyes after phacoemulsification is on average about 1% in the first year (*Lois & Wong*: Surv Ophthalmol 48; 467-87, 2003). With 600,000 cataract procedures per year in Germany it could be estimated that 6,000 cases of retinal detachment do occur. Three treatment options are currently used: Scleral buckling, primary vitrectomy or a combination of both. These methods have their specific risk and complication profiles and have mostly been compared in retrospective non-randomised trials. Brazitikos and co-authors published data of a prospective randomised trial comparing vitrectomy alone with scleral buckling for pseudophakic retinal detachment in 150 patients with a postoperative follow-up of 1 year (*Brazitikos et al*: Retina 25; 957-64, 2005). They found that with vitrectomy alone the retina was attached in 94% after one procedure and with scleral buckling in 82%. The difference was statistically significant. In a large retrospective series of 524 cases the success rate of scleral buckling was significantly worse for pseudophakic detachments compared to phakic patients (*Haritoglu et al*: Ophthalmologica 224(5); 312-318, 2010). The SPR trial (Primary vitrectomy vs. scleral buckling for rhegmatogenous retinal detachment) was a multicentre randomised trial funded by the German Research Council (DFG) in which both methods were compared with respect to efficacy. The re-attachment rate in pseudophakic eyes after one procedure was 73% in the vitrectomy group and 56% in the scleral buckling cohort which was statistically significant. It has been further shown that the risk to develop proliferative vitreoretinopathy (PVR) as a typical negative outcome of the disease is statistically less after primary vitrectomy than after scleral buckling in this condition (*Heimann et al*: Ophthalmology 114; 2142-54, 2007). However, in the SPR trial primary vitrectomy was sometimes combined with a circumferential scleral buckle (encircling band) depending on the choice of the surgeon. A subgroup analysis of the data did not show conclusive results (i.e. non-randomised comparison): In pseudophakic eyes 10/88 showed a re-detachment when vitrectomy was combined with a circumferential buckle whereas in 18/44 eyes a re-detachment occurred when no buckle was placed. In contrast, in phakic eyes this difference was not seen. In case series it was

reported that with primary vitrectomy without scleral buckling retinal re-attachment is achieved in 64 – 94 % of cases. In series where vitrectomy was combined with an encircling band the primary re-attachment rates vary between 89% and 100% suggesting also a superiority of the combined method. In several non-randomised studies vitrectomy was compared with vitrectomy plus encircling band as treatment for pseudophakic retinal detachment. In the series of Pournaras and Kapetanios with both techniques excellent reattachment rates were reported which were statistically not different suggesting that the encircling band is not necessary (*Pournaras & Kapetanios*: Eur J Ophthalmol 13; 298-306, 2003). Wickham and co-authors retrospectively compared vitrectomy alone with vitrectomy and scleral buckling in cases with inferior breaks. In both groups about half of the patients were pseudophakic. The primary re-attachment rate was 89% in the vitrectomy alone group and 73% in the vitrectomy plus buckle group. The difference was statistically not significant (*Wickham et al*: Br J Ophthalmol 88; 1376-9, 2004). Stangos and co-authors published a prospective non-randomised trial in which they compared vitrectomy alone with vitrectomy plus scleral buckling for pseudophakic retinal detachment. The reattachment rate was 97% in the vitrectomy alone group and 92% in the vitrectomy plus buckle group. However, the groups differed considerably in size and the choice of the treatment was assigned to the patient (*Stangos et al*: Am J Ophthalmol 138; 952-8, 2004).

Up to now there is no randomised controlled trial comparing vitrectomy alone with vitrectomy plus encircling band in a sufficient number of patients for the treatment of pseudophakic retinal detachment, leaving the decision on the best technique to treat the pseudophakic retinal detachment up to the surgeon and his individual experience. The success rate of retinal detachment surgery is not getting better. Success rates of about 70-80% were already achieved 30 years ago. A subgroup analysis of the SPR trial in which the results of vitrectomy alone were compared with vitrectomy plus encircling band was inconclusive however contrary to the expectations of many surgeons. Because the use of an encircling band strongly effects the outcome of the surgery at least in inducing a myopic shift of about 2 D but also by possibly causing complications such as infection, prolonged surgical time, strabism, explant intrusion, and others, it is important to determine whether the use of it is of any benefit.

2.2. Primary 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.

2.3. Secondary and other objectives

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.

3. Organisational and administrative aspects of the trial

3.1. Sponsor

Sponsor : n/a

Represented by: n/a

3.2. Principal Investigator

Principal Coordinating Investigator:

Prof. Dr. P. Walter
Department of Ophthalmology
University Hospital Aachen
RWTH Aachen University
Pauwelsstr. 30

3.3. Statistics

Statistician:

PD Dr. Martin Hellmich
Institute for Medical Statistics, Informatics and Epidemiology
University of Cologne
Kerpener Str. 62
50937 Cologne
Germany

Data Monitoring Committee:

For this clinical trial, no Data Monitoring Committee will be set up.

3.4. Further committees

3.4.1. Steering Committee

For this clinical trial, no Steering Committee will be set up.

3.4.2. Advisory Committee

For this clinical trial, no Advisory Committee will be set up.

3.4.3. Review Board

For this clinical trial, no Review Board will be set up.

Decisions concerning evaluation of potential protocol violations in the context of definition of the study populations (intention-to-treat, ITT; per-protocol, PP, as treated / valid for safety, VFS / full analysis set, FAS) will be agreed between the Principal Coordinating Investigator and the responsible Statistician. Further clinical experts will be involved if necessary.

3.5. Study laboratories and other technical services

There are no further tasks that will be performed by other service providers.

3.6. Central organisation units

Trial and safety management:	Prof. Dr. P. Walter Department of Ophthalmology University Hospital Aachen RWTH Aachen University Pauwelsstr. 30
Monitoring:	central quality assurance (see also 4.8.1) will be perfomed by Data Management

Data management: Andrea Pfeiffer
Cologne Centre for Clinical Trials (ZKS Köln)
Gleueler Strasse 269
50935 Cologne
Germany
Tel.: +49 221 478 88133
Fax: +49 221 478 7983
Email: Andrea.Pfeiffer@zks-koeln.de

Scientific advice and support of trial management: Dr. Endrik Limburg
Dr. Claudia Weiß
Cologne Centre for Clinical Trials (ZKS Köln)
Gleueler Strasse 269
50935 Cologne
Germany
Tel.: +49 221 478 88135
Fax: +49 221 478 88209
Email: Endrik.limburg@zks-koeln.de

3.7. Investigators and trial sites

This clinical trial will be carried out as a multicentre trial in Germany and the United Kingdom. If necessary, further qualified trial sites may be recruited to the trial.

A list of trial sites involved, including information on the principal investigators, further investigators, and trial staff, will be continuously updated. A list of the trial sites with names of the principal investigators is given in Appendix 11.1.

Requirements for investigators and trial sites

Surgeons must confirm that they had treated at least 100 cases of retinal detachment with primary vitrectomy using a 20 gauge approach of which at least 20 must be combined

surgery vitrectomy plus encircling band. For surgeons included in the 1:1:1 randomisation scheme, 20 surgical procedures for retinal detachment with 23 or 25 gauge vitrectomy are required in addition to the 100 cases with 20 gauge vitrectomy and the surgeon has to state that he or she feels safe and comfortable with the transconjunctival technique.

3.8. Financing

The present trial is performed under the auspices of the retina.net and therefore supported by the retina.net coordination office at the Clinical Trials Center Cologne. Financial support for the retina.net coordination office is given by Jackstaedt Stiftung, Retinologische Gesellschaft and Deutsche Ophthalmologische Gesellschaft. There is no financial support for the trial.

4. Trial conduct

4.1. General aspects of trial design

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

4.1.1. Time plan

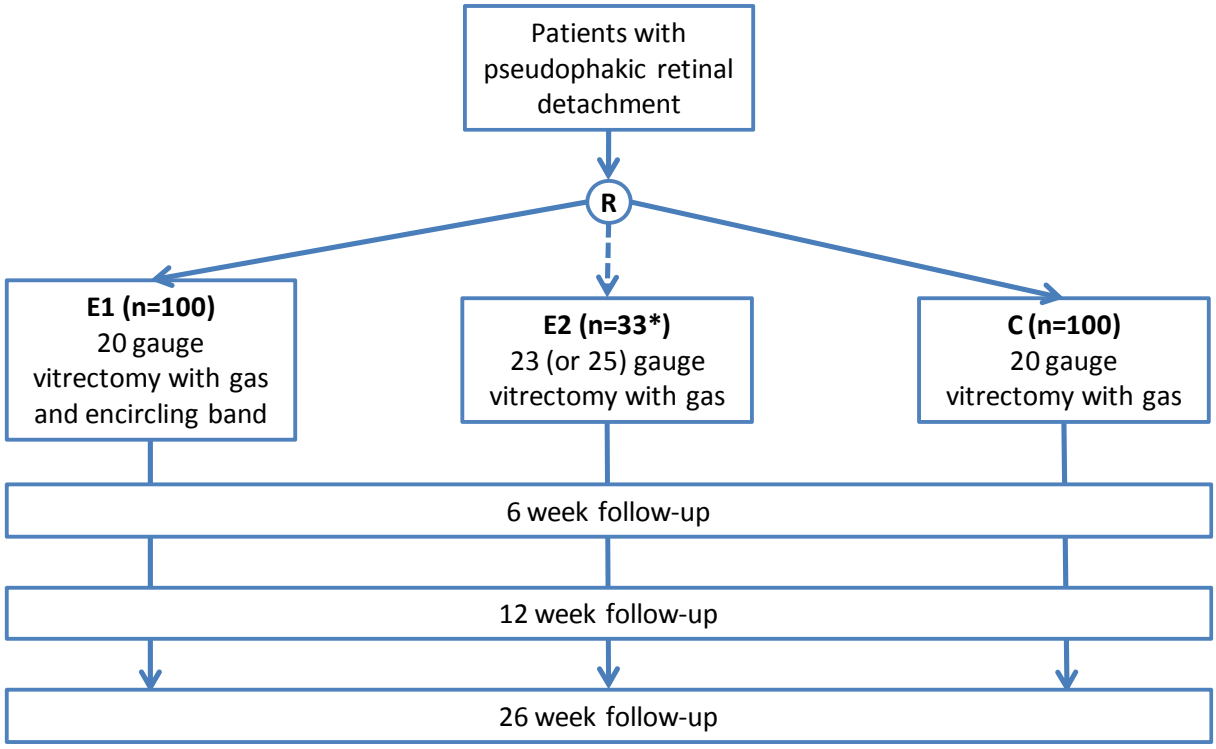
Table 1: Time plan of the trial

First patient first visit (FPFV):	*03/2011*
Last patient first visit (LPFV):	*03/2012*
Last patient last visit (LPLV):	*9/2012*
Final study report:	*12/2012*

End of the clinical trial

The end of this clinical trial is defined as the last visit of the last patient (LPLV).

Figure 2: Trial Flowchart



*E2 will only be performed by selected (experienced) study surgeons

4.2. Discussion of trial design

Pseudophakic retinal detachment can be treated either by scleral buckling alone or by primary vitrectomy. The SPR trial showed that the outcome of patients with PRD treated with primary vitrectomy is better than those treated with scleral buckling. However, it remains unclear whether the use of an additional encircling band improves the outcome of the vitrectomy for PRD. With the broader use of transconjunctival small incision vitrectomy techniques an encircling band is not anymore possible. It is not known if the outcome of small gauge vitrectomy in the treatment of patients with PRD is comparable to the “older” technique. These two questions are addressed in this multicentre randomised controlled trial. The control group (C) consists of PRD patients treated with 20 gauge vitrectomy alone whereas the experimental group 1 (E1) consists of PRD patients treated with 20 gauge

vitrectomy plus encircling band. The experimental group 2 (E2) consists of PRD patients treated with 23 or 25 gauge vitrectomy without encircling band. The outcome of both experimental groups will be compared with the outcome of the control group.

Randomisation will be stratified by surgeon. The ratio is either 1:1:1 or 1:1 depending on individual experience/training in 23/25 G vitrectomy (E2). The individual ratio may be switched (i.e. from 1:1 to 1:1:1) while the trial is ongoing (i.e. when sufficient experience/training has been gained outside the trial).

4.3. Selection of trial population

4.3.1. Inclusion criteria

- Pseudophakic retinal detachment
- pseudophakic rhegmatogenous retinal detachment not suitable for buckling surgery
- Age: 18 years or older
- Agreement of the patient to participate in the trial
- Written consent of the patient

4.3.2. Exclusion criteria

- Manifest uveitis
- Uncontrolled glaucoma
- Active retinal vascular disease
- Malignant intraocular eye tumours
- History of cataract surgery less than 3 months ago
- History of any other intraocular surgery other than cataract surgery
- Giant retinal tears
- PVR grade B or C

- Inability to understand the rationale of this trial or the study aim
- participation in another, potentially interfering interventional clinical trial (less than 3 months ago)
- Aphakia
- Systemic disorders preventing the participation of control examinations during the follow-up
- Systemic disorders not compatible with the local periocular or general anesthesia
- legally incapacitated

4.4. Withdrawal of trial subjects after trial start

An individual patient will only be withdrawn from the trial in case of withdrawal of consent to the trial (nonretention). In case of withdrawal it has to be clarified whether the patient only refuses study treatment and / or additional treatment or if he refuses follow-up investigation and documentation as well. This has to be documented in the eCRF and patients original chart.

In order to assure analysis of the intention-to-treat (ITT) population, it is intended to complete follow-up of all patients, even in case of occurrence of protocol violations which will be documented as well.

No replacement of drop-out patients is planned.

4.4.1. Procedures for premature withdrawal from treatment during the trial

Premature withdrawal from study treatment is not applicable. Study treatment consists of the initial surgery only. Further surgeries as well as any modification of the randomised treatment are to be performed in case of medical indication only.

4.5. Closure of trial sites/Premature termination of the clinical trial

4.5.1. Closure of trial sites

Closure of a trial site will be considered by the Principal Coordinating Investigator in case of serious concerns regarding safety of the patients or data validity (plausibility, completeness). Decisions will be made after consulting the retina.net board.

4.5.2. Premature termination of trial

The PCI has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which has to be documented. The PCI must be informed without delay if any investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly
- other reasons reducing ethical justification
- an unacceptable high number of serious adverse events
- The PCI considers that the trial must be discontinued for safety reasons
- relevant superiority of one group (therapy) in a comparable clinical trial
- a novel therapy, developed in the meantime, superior to the investigated therapy modalities
- It is no longer practicable to complete the trial
- a high number of drop-outs (> 20 %)

The PCI decides on whether to discontinue the trial in consultation with the ZKS project manager, the advisory board of retina.net and the trial statistician.

4.6. Treatment

4.6.1. Treatments to be given

Control group (C): Patients who are randomised to the control group will receive 20 gauge vitrectomy without encircling band.

Surgery is performed with an operating microscope and a wide field viewing system. The conjunctiva is opened at the limbus to expose the sclera. Three sclerotomies are made with a distance of 3-4 mm to the limbus. The sclerotomies are 20 gauge wide. A full vitrectomy is performed. If the vitreous is not fully detached a complete vitreous detachment should be obtained. Heavy liquids may be used to drain subretinal fluid. After full re-attachment of the retina under heavy liquids or under air, each retinal break is treated with endolaser or cryopexy. High risk degenerations should be treated as well. A prophylactic circumferential laser treatment is not allowed. The surgery is completed with a gas fill using non expandable gases such as SF6 20%,C2F6 14% or C3F8 14% and the closure of the conjunctiva. Ocular pressure must be monitored at least once within 8h after surgery and the day after surgery. If the intraocular pressure rises to more than 40 mmHg, gas should be released via the pars plana using sterile techniques.

Experimental group 1 (E1): Patients in this group receive 20 gauge vitrectomy with encircling band.

Surgery starts with a circumferential opening of the conjunctiva at the limbus. A 2 to 4 mm encircling band is placed underneath the recti muscles and fixated in all four quadrants. The encircling band is positioned onto the equator of the globe. At the end of surgery no folding of choroidal tissue adjacent to the impression of the encircling band should be visible. The 20 gauge vitrectomy is perfomed as described for the control group (C).

Experimental group 2 (E2): Patients in this group receive 23 or 25 gauge vitrectomy without encircling band.

A 23 or 25 gauge vitrectomy is performed using transconjunctival trokar systems. Trokars are inserted tangentially after displacement of the conjunctiva. A full vitrectomy is performed. If not yet present a full vitreous detachment should be achieved. Endodrainage of the subretinal fluid is achieved with the use of heavy liquids and/or air. After full re-attachment of the retina, breaks and high-risk degenerations are treated with the endolaser probe or with exocryo. A circumferential prophylactic laser treatment is not allowed. After full fluid air exchange the eye is filled with a non expandable air/gas mixture. Trokars are removed. If the sclerotomies are not tight they have to be sutured either transconjunctivally or after opening of the conjunctiva.

4.6.2. Treatments not allowed:

- Use of Triamcinolone or other means to visualize the vitreous
- Use of silicone oil
- Prophylactic circumferential laser/cryo
- Peeling of the internal limiting membrane

4.6.3. Description of investigational medicinal product

not applicable

4.6.4. Compliance with treatment / Dispensing and return of investigational medicinal product

Surgical procedures will be performed following a center specific standard procedure (for all of the three or for two out of three procedures) which will be documented and handed out to the PCI before start of recruitment.

4.6.5. Assignment of trial subjects to treatment groups

Rhegmatogeneous retinal detachment is an emergency situation. Therefore sophisticated screening examinations are not possible. During the initial examination, inclusion and exclusion criteria are considered, the patient is informed in detail and written consent of the patient to participate in the trial is obtained. The results of this initial examination are documented as the first examination of the trial. After including the patient, he will be randomised to one of three treatment groups. Randomisation is 1:1:1 or 1:1, depending on experience/training of the surgeon. A central Internet 24/7 randomisation service is used for randomisation. Sealed opaque envelopes containing allocation details may be prepared as a fallback procedure.

Control group (C): Patients, assigned to the control group, will receive 20 gauge vitrectomy without encircling band.

Experimental group 1 (E1): Patients assigned to receive 20 gauge vitrectomy with encircling band.

Experimental group 2 (E2): Patients assigned to receive 23 or 25 gauge vitrectomy without encircling band.

4.6.6. Selection of dosage of investigational medicinal product

not applicable

4.6.7. Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject

not applicable

4.6.8. Blinding

As the study treatments are different surgical procedures, blinding of the study surgeons is not possible. Taking into account the described possible effects of the additional encircling

band, such as myopic shift of about 2 D and possible complications such as infection, strabism, explant intrusion, and others, patient blinding it is not possible either.

4.6.8.1. Unblinding

not applicable

4.6.9. Previous and concomitant medication

4.6.9.1. Rescue therapy for emergencies

not applicable

4.7. Efficacy and safety variables

4.7.1. Measurement of efficacy and safety variables

4.7.1.1. Primary target variable

The primary endpoint is defined as the absence of an indication for any retina reattaching procedure during the follow-up.

Retina re-attaching procedures are additional gas injections, additional vitrectomy or additional buckling procedure.

4.7.1.2. The release of gas after a gas fill with a postoperative intraocular pressure of more than 40 mmHg, laser- or cryotreatment for new or overseen breaks or to demarcate persistant areas of retinal detachment anterior to the equator are not regarded as failure indicating procedures.Secondary and other target variables

- Visual acuity at the end of follow-up as measured by ETDRS charts
- Refractive status
- Retina reattachment rate
- Rate of occurrence of PVR, Grade C according to Machemer

- The number of retina specific procedures to achieve a stable retinal attachment
- Operation time (time between cut and suture)
- Postoperative pain will be evaluated
- Anatomical situation of the anterior and posterior segment

4.7.1.3. Safety data

- Iatrogenic breaks / macular hole
- Macular edema
- Macular pucker
- Ocular hypertony (at week 26)
- Diplopia
- Choroidal hemorrhage
- Pain medication
- Enucleation
- Death

4.7.1.4. Description of visits

Visits will be conducted at the following times and must fall between the ‘first day possible’ and the ‘last day possible’ (measured in trial weeks) given in Table 2.

Table 3: Overview on data acquisition and timing of examination

Time (weeks)	0	6	12	26
first and last week possible	0	5-7	10-14	23-29
Inclusion and exclusion criteria	X			
Informed consent	X			
Medical history	X	X	X	X
AEs/SAEs		X	X	X
Best corrected visual acuity (ETDRS)	X	X	X	X
Refraction	X	X	X	X
Tonometry	X	X	X	X
Slitlamp	X	X	X	X
Funduscopy	X	X	X	X
Fundus drawing	X	X	X	X
Fundus photography				X
End of study				X

Duration of the clinical trial in the individual subject

Trial duration of an individual patient consists of the initial surgery and a follow-up of 26 weeks.

4.7.2. Pharmacokinetics/Determination of drug levels

not applicable

4.8. Data quality assurance

4.8.1. Monitoring

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 riscs. 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.

4.8.2. Audits/Inspections

As part of quality assurance, the PCI has the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The PCI may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

The PCI and all trial sites involved undertake to support auditors at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits undertake to keep all trial subject data and other trial data confidential.

4.9. Documentation

All data relevant to the trial are documented soon after measurement by the investigator responsible in the electronic case report form supplied. Entering data may be delegated to members of the trial team. The eCRFs are electronically signed by the investigator.

4.9.1. Data management

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 will be specified in the data management manual.

4.9.2. Archiving

All CRFs, informed consent forms and other important trial materials will be archived for at least 10 years in accordance with §13 Sec. 10 of the GCP Regulations. Trial subject identification lists at each trial site will be stored separately from trial documentation.

5. Ethical and regulatory aspects

5.1. Independent ethics committee

In each trial site, the clinical study will not be started before approval of the competent local ethics committee concerning the suitability of the trial site and the qualifications of the investigators.

5.2. Ethical basis for the clinical trial

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki in the version of October 1996 (48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa).

5.2.1. Legislation and guidelines used for preparation

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation (especially the GCP-V). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, trial subjects' medical records (source documents), documentation and reporting of adverse events (AEs), preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the competent federal authorities and authorised representatives of the sponsor have the right to review trial documentation and the trial subjects' medical records at any time.

5.3. Notification of the authorities, approval and registration

As the regulations of federal drug law (Arzneimittelgesetz, AMG) or Medical Products Act (Medizinproduktegesetz, MPG) do not apply to this trial, notification is not applicable.

Before the trial is started, it will be registered under Current Controlled Trials (www.controlled-trials.com) or another trial register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/). The trial protocol will be submitted for publication.

5.4. Obtaining informed consent from trial subjects

Trial subjects may not be enrolled into the present trial unless they have consented to take part in the trial after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences by a trial investigator. Together with the consent to take part in the trial, the trial subject must also agree to representatives of the sponsor (e.g. monitors or auditors) or the competent supervisory or federal authorities having access to the data recorded within the framework of the clinical trial. The trial subject will be informed of the potential benefit and possible side effects of the study therapy. It must be clear to trial subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment.

The originally signed consent form is archived in the investigator site file. Trial subjects receive copies of the written information sheet, confirmation of insurance with conditions, and the signed informed consent form. A copy of the written information sheet and the signed informed consent form will be filed in the patient's record.

The patient information sheet and informed consent form are supplied in Appendix 11.3.

The patient information sheet, informed consent form, all other documents handed out to the trial subject and any recruitment advertisements must be submitted for approval before use to the ethics committee

5.5. Insurance of trial subjects

The insurance of trial subjects is provided by the general insurance company of the respected study centre. For the centre of the PCI in Aachen this is Zürich Versicherungs AG No. 813.380.000.270. The

administration of the insurance documents for the PCI centre is provided by Ecclesia Mildenberger Hospital GmbH, Klingenbergstr. 4, 32758 Detmold. The insurance of trial subjects for other participating centers has to be provided by the respective study centers.

5.6. Data protection

The provisions of data protection legislation will be observed. It is assured by the PCI that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing.

Trial subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial.

6. Statistical methods and sample size calculation

6.1. Statistical and analytical plan

The primary analysis will be according to intention to treat, i.e. all patients randomised will be analysed as assigned. A missing primary endpoint is considered a treatment failure. Otherwise (secondary) the last observation may be carried forward and/or multiple imputation may be done. Further details will be layed out in the statistical analysis plan.

6.1.1. Trial populations

All analyses will be conducted in three trial populations:

Intention-to-treat (ITT) population. This dataset includes all trial subjects enrolled into the trial and randomised. Analysis will be as assigned

Per-protocol (PP) population. This dataset includes all trial subjects who were treated and observed according to protocol.

As-treated (AT) population: This dataset includes all trial subjects enrolled into the trial and randomised. Analysis will be as treated.

6.1.2. Description of trial subject groups

Demographic data and baseline values of target variables will be summarised using mean, standard deviation, count and percentage etc.

6.1.3. Primary target variable

Primary endpoint:

The primary target variable is obtained as the number of patients for which is stated

“absence of an indication for any retina reattaching procedure during the follow-up”.

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.

Logistic regression, GEE and multiple imputation methods will be used for sensitivity analysis.

6.1.4. Secondary target variables

Secondary endpoints:

- Visual acuity at the end of follow-up as measured by ETDRS charts
- Refractive status
- Retina reattachment rate
- The occurrence of PVR, Grade C according to Machemer
- The number of retina specific procedures to achieve a stable retinal attachment
- Operation time (time between cut and suture)
- Postoperative pain (medication)
- Anatomical situation of the anterior and posterior segment

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.

6.1.5. Subgroup analyses

Men (expected 73%) and women will be analysed together as well as separately.

6.1.6. Interim analysis

No formal interim analysis is planned in this study.

6.2. Sample size calculation

In the SPR study 11.4% (=10/88) of pseudophakic patients who had recieved combined primary vitrectomy and scleral bluckling suffered from a redetachment, 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.

7. Safety

7.1. Definitions of adverse events and adverse drug reactions

7.1.1. Adverse event

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment.

The term 'adverse event' covers any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the well being of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). The adverse event may be:

- a new illness
- worsening of a sign or symptom of the condition under treatment, or of a concomitant illness
- an effect of the study intervention
- a combination of two or more of these factors.

No causal relationship with the study intervention or with the study itself is implied by the use of the term "Adverse Event". Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event.

Possible AE's for example are any newly diagnosed systemic diseases, conjunctivitis, headache, infection of the fellow or of the study eye, late macular edema, macular pucker, optic atrophy, persistent postoperative elevated intraocular pressure (IOP > 22 mmHg), retinal traction detachment, sicca syndrome, unscheduled reoperation of the study eye, uveitis or other diagnoses.

All adverse events that occur after the subject has signed the informed consent document must be documented on the pages provided in the electronic case report form (eCRF) online. Every attempt should be made to describe the adverse event in terms of diagnosis. If only non-specific signs or symptoms are present, then these should be recorded as a diagnosis.

All subjects who have adverse events, whether considered associated with the study intervention or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.

Concomitant diseases

The deterioration of a preexisting illness is also an AE in the context of a clinical trial. The following, however, is not regarded as an AE: a preexisting disease that led to a planned treatment measure before the start of the clinical trial, e.g. admission to hospital as an inpatient. This should be made clear in the trial subject's medical records and should also be documented in the CRF (see Section 7.1.3).

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an AE.

7.1.2. Adverse reaction

The term "adverse drug reaction, ADR" is not applicable. However, adverse events regarded to be related to the study treatment (initial surgery) will be regarded as adverse reaction (AR).

7.1.3. Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious AR (SAR) is any untoward medical occurrence that at any dose

1. Results in death,

2. Is life-threatening at the time of the event
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly or birth defect (1.-4.: § 3(8) GCP Regulations)
6. In the opinion of the investigator, fulfils any other criteria similar to 1.–4.

Inpatient hospitalisation is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the IMP are not SAEs, but must be documented in the proper manner in the trial subject's medical records and CRF (see Section 7.1.1).

If an AE is classified as an SAE, this is documented on a separate SAE eform in addition to the standard AE documentation. The PCI must be notified of SAEs (for procedure, see 7.3)

7.1.4. Unexpected adverse reaction

An unexpected AR is an AR which, the nature or severity of which is not consistent with the following:

- iatrogenic breaks

7.1.5. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

7.2. Documentation and follow-up of adverse events

The PCI ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be

asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the eCRF.

For the procedure of SAE-reporting see section 7.3, and section 4.7.1.3 for safety analyses.

7.2.1. Documentation of adverse events and adverse drug reactions

All AEs will be documented in the CRF including all information listed below.

The AE is documented in the CRF including the following information:

- Date and time of onset and resolution
- Severity
- Causal relationship with study treatment
- Seriousness
- measures taken

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events will be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, or the study has been terminated for the trial subject concerned.

Preexisting diseases are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

7.2.2. Severity of the adverse event

The investigator will classify the severity of AEs as follows:

- Mild: clinical symptoms or signs that are well tolerated
- Moderate: clinical symptoms or signs that are enough to impair everyday activities
- Severe: clinical symptoms or signs that markedly impair the trial subject and result in inability to work or go about everyday activities

7.2.3. Causal relationship between adverse event and investigational medicinal product

The investigator will assess the for every AE whether a causal relationship with the study treatmentcan be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the study treatment, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed.

The following definitions are used to assess the causal relationship between all AEs and the IMP (for documentation in CRF, see also Section 7.2.2) (WHO Causality Assessment of Suspected Adverse Reactions):

- Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

- Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

  Unassessable/unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

An AR is suspected if the causal relationship is at least 'possible' or 'conditional/unclassified' or 'unassessable/unclassifiable'. Events assessed as 'unlikely' are not suspected ARs.

7.3. Reporting of serious adverse events and changes in risk-benefit assessment

Regardless of the assumed causal relationship, every SAE that occurs during a trial must be documented in the appropriate part of the eCRF. With immediate online-documentation without unreasonable delay, the investigators fulfill their obligation of reporting SAEs to the PCI.

The principle investigator of each study Centre is responsible for reporting SAEs to the local ethics committee if required.

7.3.1. Reports from the investigator to the PCI

The investigators ensure immediate online-documentation of the occurrence or receipt of knowledge of the occurrence of an SAE without delay, at the latest within 24 hours of being made aware of the SAE. Herewith the investigators fulfill their obligation of reporting SAEs to the PCI.

All cases of suspected SAEs are assessed by the PCI with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments.

7.3.2. Unblinding when treatment is blinded

Not applicable: not a blinded study

7.3.3. Notification of ethics committee

SUSARs that become known in this clinical trial will be reported by the PCI to the ethics committee.

The principle investigator of each study Centre is responsible for reporting SUSARs to the local ethics committee if required.

Over and above this, reporting responsibilities and deadlines for Great Britain have to be respected for the trial site in Great Britain. All reporting requirements will be cleared and regulated by the responsible PI before the trial site starts recruitment to ensure that appropriate organisational measures can be taken.

Fatal and life-threatening SUSARs

The ethics committee responsible must be informed by the PCI of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the ethics committee within a further 8 days. Furthermore, if a trial subject dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

SUSARs that are not fatal or life-threatening

The ethics committee responsible will be informed without delay by the PCI of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

7.3.4. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the PCI will inform the ethics committee responsible of any events or factors that mean that the risk-benefit ratio of the study has to be reviewed. These consist of especially:

- Individual reports of expected serious ARs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SARs
- Factors emerging in connection with trial conduct that may affect the safety of persons concerned.

7.3.5. Informing the Data Monitoring Committee

No DMC is installed for this study

7.3.6. Informing the investigators

The PCI will inform investigators of all SUSARs including all relevant further information.

If new information becomes known that is different from the scientific information given to the investigator, all investigators will be informed of this by the PCI.

7.3.7. Informing the marketing authorisation holder

not applicable

7.4. Annual safety report of trial subjects

not applicable

8. Use of trial findings and publication

8.1. Reports

8.1.1. Interim reports

No interim analysis is planned, so interim reports will only be provided in case of premature termination of the study.

8.1.2. Final report

The ethics committee will be informed within 90 days that the trial has officially ended.

Within one year of the completion of the trial, the ethics committee will be supplied with a summary of the final report or an adequate publication on the clinical trial containing the principle results.

8.2. Publication

It is planned to publish the trial results, in mutual agreement with the PCI, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997;277:927-34]).

The trial will also be registered in a public register in accordance with the recommendations of the ICMJE (see also Section 5.3).

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the PCI in advance, and the PCI reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organisations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

The support by the ZKS is to be mentioned in any publication. ZKS staff will be included as coauthors as applicable and the Grant number oft the ZKS (01KN0706) is mentioned in an acknowledgement. A copy of all publications will be sent to the ZKS.

9. Amendments to the trial protocol

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the PCI, the ZKS project manager and the biometrician, and all Authors of this trial protocol. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by all Authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

10. References

1. The European Agency for the Evaluation of Medicinal Product. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
2. The European Agency for the Evaluation of Medicinal Product. Note for Guidance Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).
3. National Cancer Institute. Protocol Templates, Applications and Guidelines http://ctep.cancer.gov/guidelines/templates.html.
4. EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr
5. The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22
6. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Accessed at http://www.icmje.org/clin_trial.pdf on 22 May 2007.
7. WHO. Causality Assessment of Suspected Adverse Reactions. http://www.who-umc.org/DynPage.aspx?id=22682
8. *Heimann et al: Ophthalmology 114; 2142-54, 2007.*. „Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment: a prospective randomized multicenter clinical study.“ Heimann H, Bartz-Schmidt KU, Bornfeld N, Weiss C, Hilgers RD, Foerster MH; Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study Group.
9.

11. Appendices

11.1. Trial sites and principle investigators

11.2. Protocol Agreement Form

11.3. Patient information sheet and informed consent form

11.4. Confirmation of insurance

11.5. Conditions of insurance

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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VIPER-STUDIE

Vitrektomie mit Cerclage oder Vitrektomie allein zur Behandlung der Pseudophakieamotio

Vitrectomy with encircling band or vitrectomy alone for the treatment of pseudophakic retinal detachment

Eine randomisierte multizentrische Studie

A randomised multicentre trial

Patientenaufklärung

zur Vorbereitung und Dokumentation des mündlichen Aufklärungsgesprächs durch den Arzt

Koordinierender Prüfarzt der Studie:

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Prüfarzt an Ihrem Prüfzentrum:

(bitte für jedes Studienzentrum eintragen

Univ.-Prof. Dr. Peter Walter
Direktor der Universitäts-Augenklinik aachen
s.o.)

Sehr geehrte Patientin, sehr geehrter Patient!

Bei Ihnen liegt eine Netzhautablösung vor. Es handelt sich dabei um eine Erkrankung, die nur operativ behandelt werden kann. Es handelt sich bei dieser Erkrankung um eine schwere Erkrankung, die unbehandelt zur Erblindung führt. Gleichzeitig wurde bei Ihnen bereits früher eine Operation am grauen Star durchgeführt. Es ist bei Ihnen eine Kunstlinse eingepflanzt worden.

Es gibt mehrere Möglichkeiten zur Behandlung der Netzhautablösung. Eine große klinische Studie hat ergeben, dass die Ergebnisse der operativen Glaskörperentfernung (Vitrektomie) in Ihrer Situation besser sind als nur eine Chirurgie mit eindellenden Elementen (Plombe, Cerclage). Das bedeutet, dass die operative Glaskörperentfernung häufiger zur Wiederanlegung der Netzhaut führt als die alleinige eindellende Buckelchirurgie.

Es ist aber derzeit unbekannt, ob die Kombination aus eindellender Chirurgie und Vitrektomie der alleinigen Vitrektomie überlegen ist oder nicht. Weiterhin ist derzeit nicht bekannt, ob eine neuere Technik der Vitrektomie, bei der die Instrumente direkt durch die Bindehaut in das Auge eingeführt werden, der herkömmlichen Technik gleichwertig ist.

Diese Fragen sollen in der VIPER Studie beantwortet werden. Da Sie die Kriterien zur Teilnahme an der Studie erfüllen, möchten wir Sie bitten, an dieser Studie teilzunehmen. Durch Ihre Teilnahme an der Studie würden Sie erheblich zum medizinischen Kenntnisgewinn und Fortschritt beitragen ohne dass Nachteile für Sie entstehen.

Die VIPER Studie soll klären, welches das beste Verfahren zur Behandlung der Netzhautablösung nach Cataractoperation ist. Sie würden dazu beitragen, dass in Zukunft medizinische Verfahren besser und schonender für künftige Patienten eingesetzt werden können. Derzeit ist es dem Operateur und seiner Erfahrung überlassen, welches Verfahren er in Ihrer Situation einsetzt.

Welche Operationsverfahren werden in der Studie eingesetzt?

1. Operative Glaskörperentfernung mit Legen eines den Augapfel umschnürenden Bandes (Cerclage).
2. Operative Glaskörperentfernung ohne Legen des Cerclagebandes.
3. Operative Glaskörperentfernung durch Bindehautzugänge, die in der Regel keinen Nahtverschluss benötigen.

Was ist bei allen Behandlungen gleich?

In allen Fällen erfolgt eine operative Ausräumung des Glaskörpers. Dieses Verfahren hat sich in früheren Studien alten Techniken gegenüber als überlegen herausgestellt. Es erfolgt dann das Anlegen der Netzhaut mit einer Flüssigkeit, die schwerer als Wasser ist. Die auslösenden Netzhautlöcher werden mittels Laserbehandlung oder Kälteanwendung abgedichtet. Dann wird die schwere Flüssigkeit entfernt und gegen ein Luft/Gasgemisch ausgetauscht. Durch dieses Luft/Gasgemisch können Sie die ersten Tage nicht hindurch sehen.

Wodurch unterscheiden sich die Behandlungen?

Das Legen des Cerclagebandes führt zu einer größeren Wundfläche. Patienten haben geringfügig stärkere Beschwerden nach der Operation. Da das Band unter den Augenmuskeln gelegt wird, kann es vor allem in den ersten Wochen nach der Operation zu Bewegungsstörungen des Augapfels kommen, was sich unter Umständen auch in Doppelbildern bemerkbar machen kann. Das Cerclageband führt zu einer Verlängerung des Augapfels, so dass die Brillenwerte nach der Operation angepasst werden müssen.
Bei der dritten Methode wird die Bindehaut nicht eröffnet, d.h. es treten keine äußeren Wundflächen auf, was prinzipiell dazu führt, dass Patienten sehr wenig Schmerzen nach der Operation haben. In älteren Berichten gab es Hinweise auf eine erhöhte Entzündungsrate bei dieser Operationstechnik. Das hat sich aber in neueren Studien nicht bestätigen lassen.

Worin liegen die theoretischen Vor- und Nachteile des ein oder anderen Verfahrens?

Es könnte möglich sein, dass das Legen des zusätzlichen Cerclagebandes die Operation sicherer macht und das Risiko für eine Wiederablösung der Netzhaut reduziert. Das Legen des Bandes ist aber Ursache für stärkere Nebenwirkungen der Operation. Wenn es sich herausstellt, dass das Legen des Cerclagebandes nicht zu einem besseren Erfolg führt, sondern nur mit stärkeren Nebenwirkungen einhergeht, würden wir in Zukunft das Band gar nicht mehr legen.

Der Einsatz der Vitrektomie durch Hülsensysteme mithilfe derer eine Eröffnung der Bindehaut nicht mehr nötig ist und die theoretisch auch ohne Naht der Zugänge erfolgen kann, ist wahrscheinlich mit geringeren postoperativen Beschwerden für den Patienten verbunden. Möglicherweise kann aber der Glaskörper nicht wie bei den anderen Techniken ähnlich vollständig entfernt werden, was einen gewissen Risikofaktor für das Auftreten einer Wiederablösung darstellt. Andererseits schützen die Hülsen aber wahrscheinlich vor dem Auftreten von Netzhautlöchern in dem Bereich, wo die Instrumenten eingeführt werden, was eventuell mit einem besseren Ergebnis einhergehen könnte.

Warum wird die Studie durchgeführt?

Netzhautoperateure weltweit entscheiden zur Zeit alleine nach ihrer Erfahrung, welches Operationsverfahren sie in einer Situation, wie sie bei Ihnen vorliegt, einsetzen. Es gibt für jedes Verfahren theoretisch Vor- und Nachteile. Genau weiß man es aber nicht. Das Ergebnis dieser Studie wird eindeutig klären, welches Verfahren das Beste ist. Dabei geht es vor allem darum festzustellen, mit welchem Verfahren am sichersten eine Wiederanlage der Netzhaut erreicht werden kann.

Welchen Vorteil habe ich, wenn ich an der Studie teilnehme?

Sie werden innerhalb der Studie sehr genau nachkontrolliert. Man kann davon ausgehen, dass wenn bei Ihnen Probleme im Heilungsverlauf nach der Operation auftreten, diese sofort

auffallen und Gegenmaßnahmen ergriffen werden können. Sie tragen mit Ihrer Teilnahme an der Studie erheblich zum medizinischen Fortschritt bei.

Welche Maßnahmen erfolgen im Rahmen der Studie und welchen Belastungen bin ich dabei ausgesetzt?

Einschlussuntersuchung:

Maßnahme	Belastung	Zeitdauer
Anamnese	Keine	10 Minuten
Refraktion, Visus	Keine	10 Minuten
Augendruck	Augentropfen	2 Minuten
Spaltlampe	Beleuchtung	5 Minuten
Fundus	Pupillenerweiterung, Beleuchtung, Kontaktglas	10 Minuten

Operation (es wird eines dieser Verfahren durchgeführt)

Maßnahme	Belastung	Zeitdauer
Operation 1	Vitrektomie mit Cerclage	70 Minuten
Operation 2	Vitrektomie ohne Cerclage	60 Minuten
Operation 3	Vitrektomie mit Hülsensystem	60 Minuten

Postoperative Untersuchungen nach 6, 12 und 26 Wochen:

Maßnahme	Belastung	Zeitdauer
Anamnese	Keine	10 Minuten
Refraktion, Visus	Keine	10 Minuten
Augendruck	Augentropfen	2 Minuten
Spaltlampe	Beleuchtung	5 Minuten
Fundus	Pupillenerweiterung, Beleuchtung	10 Minuten
Fundusphotografie (nur 26. Woche)	Pupillenerweiterung, Beleuchtung	15 Minuten

Gibt es Risiken, mögliche Komplikationen, Beschwerden und Begleiterscheinungen?

Jede Operation der Netzhautablösung hat ein typisches Risiko- und Nebenwirkungsprofil unabhängig davon, ob diese Verfahren in klinischen Studien angewendet werden oder nicht.

Nach der Operation wird das Auge etwas schmerzhaft sein, es wird ein Fremdkörpergefühl da sein, das Auge wird gerötet sein. In manchen Fällen kann die oberste Hornhautschicht (Hornhautepithel) aufgekratzt sein (<10 %). Diese Beschwerden werden mit Augentropfen und –salben oder mit schmerzstillenden Medikamenten aufgefangen werden.
Nach der Operation kann der Augendruck ansteigen (<20 %). Das wird der Augenarzt durch eine entsprechende Messung erkennen. In solchen Fällen kann der Augendruck durch Medikamente gesenkt werden.
Nach der Operation ist das Sehvermögen wegen der Gasfüllung zuerst sehr schlecht. Das Gas löst sich aber auf und dann wird die Sehschärfe schrittweise besser.
Eine Blutung im Augeninneren kann auftreten (< 5 %). Solche Blutungen lösen sich in der Regel von alleine auf. Falls das nicht der Fall ist, kann man das Blut auch in einem operativen Eingriff wieder absaugen.
Entzündungen im Auge können ebenfalls auftreten. Sie sind extrem selten (< 1 %), erfordern aber einer medikamentöse in sehr seltenen Fällen auch eine operative Therapie. Solche Entzündungen können im Fall von Infektionen bis zur Erblindung des Auges und zum Verlust des Augapfels führen. Ein solches Ereignis ist extrem unwahrscheinlich (< 0,01 %) und tritt auch unabhängig vom Rahmen einer klinischen Studie auf.
Ziel der Operation ist die dauerhafte Wiederanlegung der Netzhaut. Man rechnet heute damit, dass in bis zu 15 % der Fälle eine Wiederablösung der Netzhaut auftritt. Ziel der Studie ist es herauszufinden, mit welchem Verfahren dieses Risiko am geringsten ist. Sollte es zu einer Wiederablösung der Netzhaut kommen, so sind weitere operative Maßnahmen erforderlich.
Wenn eine Cerclage gelegt wird, kann es in seltenen Fällen zu Bewegungsstörungen des Auges und zu Doppelbildern kommen (< 5 %). Darüberhinaus werden sich die Brillenwerte ändern.

Was ist bei Auftreten von Symptomen, Begleiterscheinungen oder unklaren Situationen zu tun?

Treten solche Beschwerden während des stationären Aufenthaltes auf, so werden sie von unserem Personal erkannt und es können Gegenmaßnahmen eingeleitet werden. Nach der Phase des stationären Aufenthaltes nehmen Sie bitte Kontakt mit dem Studienzentrum auf, in dem Sie operiert worden sind.

Ist die Studie durch eine Ethikkommission überprüft worden?

Die VIPER Studie ist von der Ethikkommission der Medizinischen Fakultät der RWTH Aachen geprüft worden. Es bestehen aus Sicht dieser Ethikkommission keine Bedenken, diese Studie durchzuführen. Sämtliche Studienzentren haben diese Genehmigung der für sie zuständigen Ethikkommissionen vorgelegt und auch von diesen Ethikkommissionen wurden keine Bedenken geäußert.

Bin ich versichert?

Sie sind im Rahmen der Haftpflichtversicherung des Krankenhauses abgesichert. Die Haftpflichtversicherung des UK Aachen wurde bei der Zürich Versicherungs AG mit der Versicherungsschein Nr. 813.380.000.270 abgeschlossen. Für nähere Angaben wenden Sie sich bitte an den Geschäftsbereich Recht des Universitätsklinikums Aachen, Pauwelsstr. 30, 52074 Aachen, Tel.: 0241-8088010 oder 0241-8089717. Der Versicherungsschutz des Aachener Klinikums wird über die Ecclesia Mildenberger Hospital GmbH, Klingenbergstr. 4, 32758 Detmold verwaltet.

Können mir Nachteile aus der Teilnahme an der Studie entstehen oder gehe ich ein Risiko ein?

Da im Rahmen der Studie nur etablierte Operationsverfahren eingesetzt werden und sie von erfahrenen Netzhautchirurgen operiert werden, entstehen Ihnen keine Nachteile. Da es sich

ja um eine Notfallsituation handelt, muss eine der drei Operationen sowieso durchgeführt werden. Der einzige Unterschied für Sie ist, dass das Los darüber entscheidet, welches Verfahren zum Einsatz kommt. Der Operateur beherrscht jedes der Verfahren gleichermaßen. Die Entscheidung per Los ist erforderlich, damit die mit den verschiedenen Verfahren operierten Patientengruppen miteinander vergleichbar sind.
Es wird sichergestellt, dass Sie als Teilnehmer diese Studie zeitnah über neue Behandlungsverfahren oder neu aufgetretene Nebenwirkungen informiert werden.

Wann wird die klinische Studie vorzeitig beendet?

Die Teilnahme an der Studie ist für Sie ganz und gar freiwillig. Sie können die Teilnahme an der Studie jederzeit und ohne Angabe von Gründen abbrechen.
Der Prüfarzt Ihres Studienzentrums wird Sie informieren, sollten aus dem Verlauf der Studie Gründe hervorgehen, die Studie abzubrechen. Solche Gründe könnten sein, dass es bereits vor Ablauf der Studie deutlich wird, dass ein Verfahren dem anderen klar überlegen oder unterlegen ist. Sollte sich im Verlauf der Studie herausstellen, das andere medizinische Fortschritte dazu führen, dass die eingesetzten Verfahren nicht mehr dem Stand der Wissenschaft entsprechen, wird der leitende Prüfarzt die Studie abbrechen und Sie hierüber informieren.

Wie werden die im Rahmen der Studie gesammelten Daten verwendet?

Bei wissenschaftlichen Studien werden persönliche Daten und medizinische Befunde über Sie erhoben. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen ohne Namensnennung.

Die Daten, die im jeweiligen Prüfzentrum erhoben und archiviert werden, stehen dem Koordinierungszentrum für Klinische Studien an der Universität zu Köln zur Auswertung und Studienüberwachung zur Verfügung, der zuständigen Überwachungsbehörde (Bezirksregierung Köln) zur eventuellen Überprüfung der ordnungsgemäßen Durchführung der Studie. Autorisierte und zur Verschwiegenheit verpflichtete Beauftragte des

Koordinierungszentrum für klinische Studien der Universität Köln können in dem jeweiligen Studienzentrum Akteneinsicht nehmen.

Kostenerstattung

Alle Maßnahmen im Rahmen der Studie sind notwendige Behandlungen und Untersuchungen, die von Ihrer Krankenversicherung gedeckt sind.

Wem kann ich weitere Fragen stellen?

Für weitere Fragen im Zusammenhang mit der VIPER Studie steht Ihnen Ihr Prüfarzt im jeweiligen Zentrum jederzeit zur Verfügung.

Prüfarzt: _____

Zentrum: _____

Adresse: _____

Ort: _____

Telefon: _____

Oder wenden Sie sich an den Koordinierenden Leiter der Studie:

Univ.-Prof. Dr. Peter Walter
Direktor der Univ.-Augenklinik Aachen
Pauwelsstr. 30
52074 Aachen
Tel.: 0241-8088191

Die mündliche Aufklärung wurde durchgeführt von _____

_____ _____ _____

Ort Datum Unterschrift

Einwilligungserklärung

Zur Teilnahme an der klinischen Studie VIPER

Vitrektomie mit Cerclage oder Vitrektomie allein zur Behandlung der Pseudophakieamotio

Prüfarzt:

Name: _____

Anschrift: _____

_____

_____

Tel.: _____

FAX: _____

Name des Patienten: _____

Geburtsdatum: _____

Code: _____

Bereitschaft zur Teilnahme:

Ich bin von _____ in einem persönlichen Gespräch ausführlich und verständlich über Wesen, Bedeutung und Tragweite der klinischen Studie sowie über mögliche Belastungen und Risiken aufgeklärt worden. Ich habe darüber hinaus den Text der Aufklärungsschrift erhalten, gelesen und verstanden. Meine Fragen wurden beantwortet. Ich hatte ausreichend Zeit, um die Entscheidung zur Studienteilnahme zu treffen.

Ich werde den ärztlichen Anordnungen, die für die Durchführung der klinischen Studie notwendig sind Folge leisten. Ich behalte mir das Recht vor, die Teilnahme an der Studie jederzeit zu beenden, ohne das mir dadurch Nachteile in der medizinischen Betreuung entstehen. Sofern ich unerwartete und ungewöhnliche Gesundheitsstörungen während dieser Studie bemerke, werde ich meinen Prüfarzt sofort kontaktieren. Für die Studiendauer werde ich den Prüfarzt über jede zusätzlich notwendige Behandlung, der ich mich unterziehen muss, informieren. Ich habe den Prüfarzt über bestehende Vorerkrankungen und über die Medikamente, die ich einnehmen muss informiert.

Ich werde über Erkenntnisse, die im Verlauf der Studie bekannt werden und die meine Teilnahme an der Studie beeinflussen könnten unmittelbar informiert.

Ich habe eine Kopie der Aufklärung und der Einverständniserklärung erhalten.

Ich habe verstanden, dass bei wissenschaftlichen Studien persönliche Daten und medizinische Befunde erhoben werden. Die Weitergabe, Speicherung und Auswertung dieser studienbezogenen Daten erfolgt nach gesetzlichen Bestimmungen und setzt vor Teilnahme an der Studie meine freiwillige Einwilligung voraus:

Patient:

Prüfarzt:

Datenschutzerklärung:

Alle im Rahmen der Studie erhobenen Daten des Studienteilnehmers werden auch im Fall der Veröffentlichung der Studienergebnisse geheim gehalten.
Ich erkläre mich damit einverstanden, dass im Rahmen dieser Studie erhobene Daten/Krankheitsdaten auf Fragebögen und elektronische Datenträger aufgezeichnet und ohne Namensnennung weitergegeben werden an

a) das Koordinierungszentrum für klinische Studien der Universität zu Köln, Gleueler Str. 269, 50935 Köln, Tel.: 0221-47888121 zur wissenschaftlichen Auswertung;

b) die zuständige Überwachungsbehörde (Bezirksregierung) oder Bundesoberbehörde (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn) zur Überprüfung der ordnungsgemäßen Durchführung der Studie;

c) an den koordinierenden Leiter der Studie, Herrn Prof. Dr. Peter Walter, Univ.-Augenklinik Aachen, Pauwelsstr. 30, 52074 Aachen, Tel.: 0241-8088191 zur wissenschaftlichen Auswertung (verantwortlich für alle Aspekte der Datenverarbeitung).

Außerdem erkläre ich mich damit einverstanden, dass ein autorisierter und zur Verschwiegenheit verpflichteter Beauftragter des Koordinierungszentrums für klinische Studien, der zuständigen inländischen (und ausländischen) Überwachungsbehörde oder der zuständigen Bundesoberbehörde in meine beim Prüfarzt vorhandenen personenbezogenen Daten Einsicht nimmt, soweit dies für die Überprüfung der Studie notwendig ist. Für diese Maßnahme entbinde ich den Prüfarzt von der ärztlichen Schweigepflicht.

Ich habe verstanden, dass bei klinischen Studien Daten und medizinische Befunde erhoben werden, die in pseudonymisierter Form an Dritte weitergegeben werden. Empfänger dieser pseudonymisierten Daten sind das Koordinierungszentrum für klinische Studien der Universität Köln und der koordinierende Prüfarzt der Studie, Prof. Dr. Walter, Direktor der Univ.-Augenklinik Aachen. Unter Umständen kann die Bezirksregierung Köln als Überwachungsbehörde die Daten einsehen, um den ordnungsgemäßen Ablauf der Studie

zu überprüfen. Die Pseudonymisierung erfolgt durch eine automatische Vergabe von Identifikationsnummern beim Einschluss des Teilnehmers in die Studie.

Ich erkläre mich damit einverstanden, dass im Rahmen der VIPER Studie von mir erhobene Daten vom Prüfarzt in pseudonymisierter Form an das Koordinierungszentrum für klinische Studien der Universität zu Köln weitergegeben werden und von autorisierten und zur Verschwiegenheit verpflichteten Mitarbeitern dieser Institution eingesehen werden können. Ich erkläre mich außerdem damit einverstanden, dass meine Daten in pseudonymisierter Form von der Bezirksregierung Köln als Überwachungsbehörde zum Zweck der Überprüfung des ordnungsgemäßen Ablaufs der Studie eingesehen werden können. Ich erkläre mich damit einverstanden, dass der koordinierende Leiter der Studie, Herr Univ.-Prof. Dr. Walter die Daten in pseudonymisierter Form einsehen kann.
Ich erkläre mich damit einverstanden, dass Beauftragte der Ethikkommission Einblick in die Originalakten nehmen dürfen.
Der Teilnehmer hat das Recht auf Auskunft und Berichtigung fehlerhaft gespeicherter Daten.

Wenn ich meine Einwilligung zur Teilnahme an der Studie widerrufe, werden meine Daten gelöscht.

Ich erkläre mich bereit an der Studie VIPER teilzunehmen.

Patient:

Nachname: _____ Vorname: _____

Geburtsdatum: _____

Unterschrift: _____ Datum & Ort: _____

Prüfarzt:

Nachname: _____ Vorname: _____

Unterschrift: _____ Datum & Ort: _____