Clinical Investigation Title:

Comparative study 27G vitrectomy vs larger gauge surgery

Two-arm, mono-center, prospective, interventional comparative case study to compare postoperative recovery between the 27G and larger gauge surgical approach.

Clinical Investigation Acronym: 27G vs larger gauge

Sponsor	*UZ Leuven*
Coordinating Investigator	*Prof. Dr. Peter Stalmans*
Sponsor Reference Number	*S 63610*
Version Number and Date	*27G compared to larger gauge* *Version 2* *Date: 20/04/2020*

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, regulatory authorities, and members of the Research Ethics Committee.

CLINICAL INVESTIGATION PLAN AUTHORISATION

Coordinating Investigator

Name: Peter Stalmans
Title: Prof. Dr.
Signature:
Date:
Site: UZ Leuven (Belgium)

Principle Investigator(s)

Name: Christiane Falkner-Radler
Title: Dr.
Signature:
Date:
Site: Rudolf Foundation Hospital (Austria)

Name: Chérif Mazit , Mounir Benzerroug
Title: Dr.
Site: Anjou Clinic – Centre Retine Anjou (France)

Name: Mitrofanis Pavlidis
Title: Prof. Dr.
Signature:
Date:
Site: Augencentrum Köln (Germany)

Name: Luigi Caretti
Title: Dr.
Signature:
Date:
Site: Caretti Rovigo (Italy)

Name: Virgilio Morales Canton
Title: Dr.
Signature:
Date:
Site: TBD (Mexico)

Name: Luis Arias
Title: Dr.
Signature:
Date:
Site: Bellvitge University Hospital (Spain)

Name: Renardel de Lavalette
Title: Prof. Dr.
Signature:

Date: Site: UMC Groningen (The Netherlands) Name: Aysegul Mavi Title: Dr. Signature: Date: Site: Retina Göz Hastanesi (Turkey) Name: Zac Koshy Title: Dr. Signature: Date: Site: University Hospital Ayr (United Kingdom)
Statistician Name: Ars Statistica, Jean-Francois Fils Title: Medical statistician Signature: Date:
Sponsor Name: UZ Leuven Title: Signature: Date:

TABLE OF CONTENTS

Contents

This CIP describes the 27G vs larger gauge clinical investigation and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the clinical investigation. Problems relating to this clinical investigation should be referred, in the first instance, to the Principal Investigator.

This clinical investigation will adhere to the principles outlined in the ISO 14155:2011. It will be conducted in compliance with the CIP, the Data Protection Act and other regulatory requirements as appropriate.

1. AMENDMENT HISTORY

Amendment No.	CIP Version No.	Date Issued	Author(s) of Changes	Details of Changes

2. LIST OF APPENDICES

Appendix A	Assessment of eye reddishness – Reference photographs
Appendix B	Investigator's Brochure
Appendix C	Case Report Form
Appendix D	Case Report Form (S)AEs reporting
Appendix E	Inform Consent Form

3. ABBREVIATIONS

AE	Adverse Event
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee
GCP	Good Clinical Practise
IB	Investigator Brochure
ICF	Informed Consent Form
PI	Principle Investigator
SAE	Serious Adverse Event

4. CLINICAL INVESTIGATION SUMMARY

Title	Comparative study 27G to larger gauge vitrectomy
Reference Number (Acronym)	*27G compared to larger gauge sizes*
Clinical Phase	Post-Market stage
Objectives	To perform a prospective randomized comparison of postoperative recovery between 27G and larger gauge surgical approaches
Endpoints	Primary endpoint: determine whether ultra-small gauge surgery (27G) improves postoperative outcome and patient morbidity
Design	Investigator-initiated, comparative double-arm, mono-center, prospective, interventional case study

Data Collection	Total duration of study for each patient will be 1 week or less (from surgery to last follow-up). See Study Flow Chart 7.3
Planned Clinical investigation Period	2020-2021
Clinical investigation population	Patients that are scheduled for a vitrectomy surgery for either floater removal or macular surgery, with or without combined cataract (phaco) surgery.
Number of Participants	Target 500 patients
Inclusion/Exclusion Criteria	<u>Inclusion criteria</u> • Patients aged over 18 • No prior vitrectomy surgery in the study eye (for the same eye) • No prior inclusion in this trial • Scheduled for vitrectomy for floater removal or macular surgery (including macular holes) without endotamponades such as PFCL, Gas or Silicone oil. Air tamponade is allowed. <u>Exclusion criteria</u> • Patients with serious heart, lung, liver, or kidney dysfunction • Patients with proliferative diabetic retinopathy, endophthalmitis, uveitis, eyes with refraction >+5D or <-8D , or other eye disease that impacts the outcome of vitrectomy surgery • Patient with HIV • Patients with history of drug abuse or alcoholism • Patients participating in other drug or medical device clinical trials before screening for this trial • Pregnancy, preparation for pregnancy during clinical trial, or breast-feeding • Belief by the investigator that a patient's condition would hinder the clinical trial, such as a patient prone to mental stress, loss of control of mood, or depression
Device Name	EVA used in combination with a trocar system, light fiber, vitrectome and laser fiber either in 27G or larger gauge sizes. In case of a combined surgery also a phaco hand piece and phaco needle are used.
Principle Intended Use	All devices are used within their claimed intended use. In general, all devices are intended to be used during ophthalmic surgery.
Manufacturer Name	D.O.R.C. Dutch Ophthalmic Research Center (International) B.V.

5. INTRODUCTION

Vitrectomy surgery was first described by Machemer in 1971 and became more common in the early 1980's [1]. At that time, vitrectomy was performed transscleral after peritomy of the conjunctiva and exposing the sclera to make the vitrectomy incisions. These incisions need suturing at the end of the surgery. The size of the commercially available instruments was 0.91 mm, commonly referred to as "20 gauge".

Wire Gauge Chart

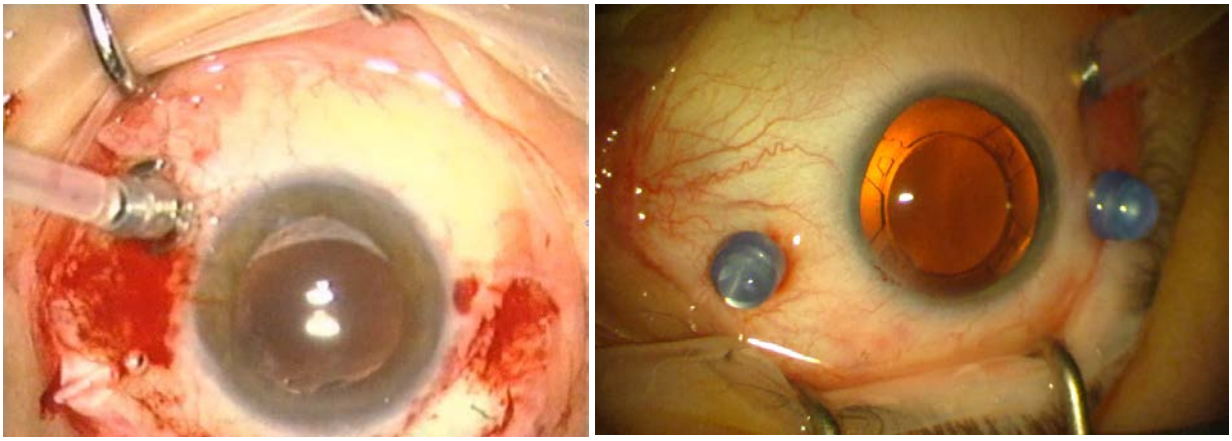
Gauge	Inches	Equivalent in mm	Gauge	Inches	Equivalent in mm
8	0.16	4.06	27	0.0164	0.417
9	0.144	3.66	28	0.0148	0.376
10	0.128	3.25	29	0.0136	0.345
11	0.116	2.95	30	0.0124	0.315
12	0.104	2.64	31	0.0116	0.295
13	0.092	2.34	32	0.0108	0.274
14	0.08	2.03	33	0.01	0.254
15	0.072	1.83	34	0.0092	0.234
16	0.064	1.63	35	0.0084	0.213
17	0.056	1.42	36	0.0076	0.193
18	0.048	1.22	37	0.0068	0.173
19	0.04	1.02	38	0.006	0.152
20	0.036	0.91	39	0.0052	0.132
21	0.032	0.81	40	0.0048	0.122
22	0.028	0.71	41	0.0044	0.112
23	0.024	0.61	42	0.004	0.102
24	0.022	0.60	43	0.0036	0.091
25	0.02	0.51	44	0.0032	0.081
26	0.018	0.46	45	0.0028	0.071

The size of vitrectomy instruments is named to the sizing used for steel wire, namely gauge. Left: comparative table of different sizes, Right: measurement tool for steel wire.

In 2002, the first 25 gauge vitrectomy instruments became available: the TSV-25 system from Bausch & Lomb, introduced into the market by De Juan [2]. With these instruments, a new surgical approach was introduced: transconjunctival surgery. In this technique, the conjunctival is left untouched, and the vitrectomy surgery is performed through funnel-shaped instrument cannulas, which are retracted from the eye at the end of the surgery. In ideal conditions, these incisions did not require suturing at the end of the surgery. Both the smaller size of the incisions, the transconjunctival approach and omitting the need for sutures at the end reduced markedly the postoperative morbidity for the patient and accelerated recovery after vitrectomy surgery.

However, the TSV-25 system had many disadvantages. Firstly, the inserters of the instrument cannulas lacked sharpness, hence required a huge force on the eye to be inserted. Also, the smaller diameter of the instruments made them very flexible, making the surgery much more difficult. Furthermore, the smaller inner lumen of the vitrectome reduced the flow of vitreous aspiration which increased significantly the duration of the surgery. Finally, the smaller diameter of the endo-illumination instrument reduced extensively the amount of intra-ocular light coming from a (halogen) light source. Personally, I started using the TSV-25 system in 2002 and used it till 2005. Even at the

end of this 3-year period, I was not able to perform more than 5% of my vitrectomy cases with the TSV-25 system, falling back to 20G surgery in all other cases.



Intra-operative view of 20 gauge transscleral surgery (left) and 27 gauge transconjunctival surgery (right).

In 2005, the use of 23 gauge instruments was introduced by Eckardt [3]. These instruments allowed the surgeon to perform transconjunctival vitrectomy surgery, but the instruments were a little larger in size and were also technically enhanced to have less flex and improved inner lumen allowing better flow and light throughput. I started using the 23 gauge system in 2005, and after 6 weeks I already performed 50% of my cases using this system. A few years later, we completely abandoned the 20G approach, and performed all cases 23 gauge. In 2009, we published a comparative report between the 20G and 23G approach, clearly indicating better postoperative morbidity in favor of the 23G system[4]. Nevertheless, in spite of improved shape and sharpness of incision blades, suturing of the incisions still remains required in a significant percentage of patients.

More recently, 27 gauge instruments became available [5]. Although these are even smaller than the TSV-25 instruments introduced 15 years ago, we found that the improved design of these instruments (e.g. twin duty cycle cutters), in combination with improved vitrectomy devices allowing good vacuum and flow rate, and markedly improved light sources (xenon and LED) do allow the surgeon to perform more than half of the cases using this technique. Because of the extremely small size of the incision, suturing is almost never required, the incisions are closed upon the moment when the instruments are retracted from the eye. We also found that the postoperative recovery is spectacular: the day after the surgery, it is often difficult to see which eye was operated.

Size comparison between vitrectomes (left picture) and intra-ocular forceps (right picture).
Left to right: 20 gauge – 23 gauge – 25 gauge – 27 gauge

The aim of this study is to objectively measure a possible difference in postoperative outcome after vitrectomy surgery for either floater removal or macular surgery, with or without combined cataract (phaco) surgery either in 27G and a larger gauge size.

At present, in most centers 27G instruments are used besides larger gauge instruments of 23G of 25G. In this clinical trial, in each individual center the use of 27G instruments will be compared to the other instrument size being used in the standard of care. Also, the pre- and postoperative eye care (including medication) that is currently used in each site will be used for all patients included in that center. For statistical analysis, a comparison will be made between both study arms included *in each center*. Using this approach, it will be possible to evaluate the possible benefit of the use of ultra-small instruments compared to the larger gauge being used in different surgical settings.

6. OBJECTIVES

6.1 Primary objective

The primary objective and primary endpoint are shown in the table below:

Primary objective	**Primary endpoint**
The aim of this study is to perform a prospective randomized comparison of postoperative recovery between the 27G and larger gauge surgical approach. Patients will be randomized to be operated using 27 gauge or a larger gauge size.	The outcome of the trial is to prospectively determine whether ultra-small gauge surgery (27G) improves postoperative outcome and patient morbidity. For this purpose, the following postoperative parameters will be used: - Post-operative redness (Eye Photo) - Ophthalmic examination including biomicroscopy to evaluate the amount of intra-ocular inflammation.

The secondary objective and secondary parameters are shown in the table below:

Secondary objective	**Secondary endpoint**
To obtain additional outcome parameters for both the 27 gauge and larger gauge surgery	Postoperative parameters: - Visual Acuity (LogMAR BCVA) - Intra-ocular pressure (mmHg) - Pain assessment (Questionnaire with visual analogue scale)

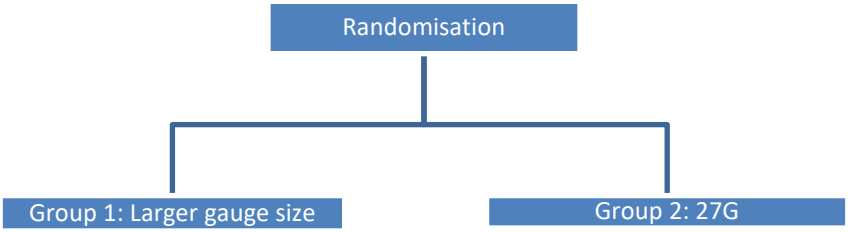
7. CLINICAL INVESTIGATION DESIGN

7.1 Trial Design

Investigator-initiated, comparative double-arm, mono-center, prospective, interventional case study

50 patients as a target will be enrolled for each site. The study will consist of 3 patient visits. Study follow-up is one week after the vitrectomy surgery.

7.2 Study diagram



7.3 Study Flowchart

	Day 0: Surgery	Day 1 Postoperative (+/- 0 days)	Week 1 Postoperative (+/- 2 days)
Surgery	X	0	0
Visual Acuity	0	X	0
Pain assessment	0	X	0
Intra-Ocular Pressure	0	X	0
Slit lamp	0	X	0
Eye photo	0	X	0
Questionnaire	0	0	X

8. CLINICAL INVESTIGATION POPULATION

8.1. Number of participants

A total of 500 patients will be included (up to 50 per site).

Enrolment time is 12 months.

8.2. Inclusion criteria

- Patients aged over 18
- No prior vitrectomy surgery in the study eye (for the same eye)
- No prior inclusion in this trial
- Scheduled for vitrectomy for floater removal or macular surgery (including macular holes) without endotamponades such as PFCL, Gas, Silicone oil). (Air tamponade is allowed)

8.3. Exclusion criteria

The participant may not enter the clinical investigation if ANY of the following apply:

- Patients with serious heart, lung, liver, or kidney dysfunction
- Patients with proliferative diabetic retinopathy, endophthalmitis, uveitis, eyes with refraction >+5D or exceeding -8D , or other eye disease that impacts the outcome of vitrectomy surgery
- Patients with HIV
- Patients with history of drug abuse or alcoholism
- Patients participating in other drug or medical device clinical trials before screening for this trial

- Pregnancy, preparation for pregnancy during clinical trial, or breast-feeding
- Belief by the investigator that a patient's condition would hinder the clinical trial, such as a patient prone to mental stress, loss of control of mood, or depression

It should be noted that smoking or vaping is not considered an exclusion criteria.

9. PARTICIPANT SELECTION AND ENROLMENT

9.1. Identifying participants

Patients that are scheduled for vitrectomy surgery that is commonly performed either using 27G or larger gauge instruments will be included.

Similar to the normal clinical path, patients that are referred to the surgical center for either vitreous floaters or macular surgery will be suggested to undergo surgery. After obtaining consent from the patient to be enrolled for surgery, an explanation will be given by the investigator about this clinical trial, and the patient will be invited to participate in the trial. The informed consent will be handed over to the patient at that time to allow to read this through at home. After 1-2 weeks the patient will be called by the study nurse to ask for final approval or disapproval to be enrolled in the trial, and to answer any questions on the trial.

Alternatively, patients that are already waitlisted for vitrectomy for vitreous floaters or macular surgery will be called by the investigator or study nurse to inform them about the ongoing clinical trial. After this informative call, the informed consent form will be mailed to the patient. After 1-2 weeks, the patient will be called again to ask for final approval or disapproval to be enrolled in the trial and to answer any questions, if required.

9.2. Consenting participants

Patients that are scheduled for vitrectomy surgery for either floater removal or macular surgery will be given the informed consent and will be asked to participate in the clinical trial. Per patient, only one eye will be eligible for inclusion in the study.

Following Ethics Committee (EC) approval and before any investigation related procedure, potential participant must personally sign and date the latest approved version of the informed consent form before any clinical investigation specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the clinical investigation; the implications and constraints of the clinical investigation plan; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the clinical investigation at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the clinical investigation. Written Informed Consent will then be obtained by means of participant dated signature and dated

signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Coordinating/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the clinical investigation site. See also document "recruitment".

In case of updates of the participant information and Informed consent the participant must personally sign and date the latest approved version of the informed consent form before any further clinical investigation specific procedures are performed.

For this clinical trial, signature for approval from the patient will be obtained at the moment of admittance in the hospital on the day of the surgery.

9.3. Randomisation

A 25:25 patient randomization list will be generated in the eCRF (RedCap) to determine whether the surgery will be performed using 27G or larger gauge instruments.
This randomization list will be masked for the surgeon: only prior to the next patient scheduled for surgery, the study arm will be visible for the surgeon since the difference in size will be visible during surgery.

9.4. Withdrawal of participants

Subjects are free to discontinue participation in the investigation at any time, and without prejudice to further treatment. Subjects who discontinue the investigation should always be asked about the reason(s) for their discontinuation and about the presence of any Adverse Event/Adverse Device Effect or Device Deficiency and, if possible, be assessed by an investigator. Adverse Event/Adverse Device Effect should be followed up.

Subjects may be withdrawn from investigation treatment and assessments at any time, at the discretion of the investigator.

Incorrectly enrolled subjects will be withdrawn from further investigation treatment and assessments. A subject may, however, continue the investigation under special circumstances (i.e. if continuation of investigation treatment or follow-up actions are necessary for the subject's safety and well-being, or if only a follow-up period remains, and the continuation of the investigation is not expected to be associated with any risk or discomfort for the subject)

10. INVESTIGATIONAL DEVICE

10.1. Investigational device details

The following devices are used within the clinical investigation:

Product	Product name	Reference number	Disposable/ reusable	CE-marked/ registered
EVA cassette	EVA Cartridge with 0.5 L Collection Bag	8100.CAR01	Disposable	Yes
Dual Air Fluid Tubing	Disposable EVA Air Fluid Dual Tubing	8110.AFD01	Disposable	Yes
VGPC Input Set	Disposable EVA VGPC Input Set	8110.VGP01	Disposable	Yes
23G Vitrectome	Disposable High Speed TDC Cutter 23 G / 8000 CPM DORC Continuum range	8268.VIT23	Disposable	Yes
23G Light fiber shielded wide	Shielded TotalView Endoillumination Probe, including illuminated scleral depressor.(23 gauge / 0.6 mm)	3269.SBS06	Disposable	Yes
23G Trocar set	Disposable One step Cannula System.(23 gauge / 0.6 mm)	1272.ED206	Disposable	Yes
23G Laser fiber	Directional Laser Probe with DORC connector.(23 gauge / 0.6 mm)	7223.DORC	Disposable	Yes
25G Vitrectome	Disposable High Speed TDC Cutter 25 G / 8000 CPM DORC Continuum range	8268.VIT25	Disposable	Yes
25G Light fiber shielded wide	Shielded TotalView Endoillumination Probe, including illuminated scleral depressor.(25 gauge / 0.5 mm)	3269.SBS05	Disposable	Yes
25G Trocar set	Disposable One Step Cannula System (25 gauge/0.5 mm)	1272.ED205	Disposable	Yes
25G Laser fiber	Directional Laser Probe with DORC connector.(25 gauge / 0.5 mm)	7225.DORC	Disposable	Yes
27G Vitrectome	Disposable High Speed TDC Cutter 27 G / 8000 CPM DORC Continuum range	8268.VIT27	Disposable	Yes
27 Light fiber shielded wide	Shielded TotalView Endoillumination Probe, including illuminated scleral depressor.(27 gauge / 0.4 mm)	3269.SBS04	Disposable	Yes
27G Trocar set	Disposable One step Cannula System.(27 gauge / 0.4 mm)	1272.ED204	Disposable	Yes
27G Laser fiber	Laser Probe, Stepped, Curved with DORC® Connector 27 gauge / 0.4 mm	7527.DORC	Disposable	Yes
Phaco handpiece*	Phaco Sure Touch Handpiece	3002.P	Reusable (steam sterilized)	Yes
Phaco needle*	EVA Custom Phaco Pack VGPC 2.2 mm Triple step angled flared phaco needle with 45 degrees tip	8510.22AF2	Disposable	Yes
Membrane Blue Dual liquid	MembraneBlue Dual	MBD-05-S	Disposable	Yes
ILM Blue Liquid	ILM-Blue	ILMB-05-S	Disposable	Yes

*Other phaco handpiece or needles (i.e. larger or different angle) are allowed

All of the above device are presently in use in the UZLeuven for daily vitrectomy surgery. Hence, there is no need for any dedicated device or instrument in this clinical trial.

10.2. Device manufacturer

Manufacturer of devices included in section 10.1 is D.O.R.C. Dutch Ophthalmic Research Center (International) B.V., Scheijdelveweg 2, 3214 VN Zuidland, The Netherlands.

10.3. Device accountability

Devices used for each surgery will be documented. In the hospital, there is a standard procedure for returning faulty products. This procedure will be followed, similar to the standard clinical path.

10.4. Storage conditions

All disposable devices come pre-sterilized and will be used before expiration date. The reusable instruments will be steam-sterilized according to the guidelines provided by the manufacturer.

10.5. Concomitant Treatments

Before, during and after the surgery, the same medication and antiseptic treatment will be applied as in patients following the standard clinical path. This includes:

- Preoperative application of mydriasert to dilate the pupil
- Preoperative antiseptic treatment with betadine
- BSS plus infusion liquid during the surgery
- Injection of parabulbar triamcinolone and clindamycin at the end of the surgery
- Postoperative dexamethasone anti-inflammatory eyedrops

At the discretion of the investigator, additional medication may be prescribed.

11. CLINICAL INVESTIGATION ASSESSMENTS

11.1. Subject Characteristics

The following parameters will be collected:

1. History: prior eye surgery (excluding previous vitrectomy)
2. Surgical parameters:
    - Indication of the surgery
    - Anesthesia type: local / general / local with sedation / general with parabulbar
    - Technique: 23G, 25G or 27G
    - Combined phacovitrectomy: yes / no
      If yes: Phaco power used: Total phaco time, effective phaco time and average phaco power
    - Surgery time:
        - total time of surgery
        - phaco time
        - vitrectomy time
        - peeling time
    - Tamponade(s) used (only air allowed)
    - Diathermy applied (Yes/No)
    - Phaco femto applied (Yes/No)
    - Cryo applied (Yes/No)
    - Laser applied (Yes/No)
    - Vital dyes used: yes/no
      If yes: type:
    - ILM peeling performed: yes/no

PVD created: yes/no

- Vitreous stain used: yes/no
  If yes: Type:

- Anticoagulants used by subject: recorded in the eCRF in list of concomitant medication(s):
  - Yes/No
  - Type
  - Stopped: Yes/No
  - Time stopped
- Medications used:
  - Preoperative disinfection:
  - Preoperative preparation (dilation drugs):
  - Infusion liquid use:
  - Additives in infusion liquid:
  - Intra-operative: intra-cameral or intravitreal medication
  - Postoperative:
    - Parabulbar:
    - Topical:
    - General:
- Actions required to close the eye at the end of the surgery
  - None
  - Sclerotomy massage
  - Sclerotomy squeezing
  - Injection of air bubble
  - Suturing of the sclerotomy
    If yes: number of sutures placed
- Adverse events during surgery[6,7,8,9]:
  - Phaco:
    - Zip in capsulorhexis
    - Posterior capsule tear
    - Vitreous prolapse
    - Iris prolapse
    - Dropped nucleus
  - Vitrectomy:
    - Iatrogenic retinal tear
    - Lens touch
    - Choroidal hematoma
    - Infuse subchoroidal
    - Iatrogenic retinal damage
    - Subretinal haemorrhage
    - Iris trauma
    - Retinal incarceration
    - PFCL subretinal
    - Oil subretinal
    - Hemorrhage from retinal vessel
    - Hemorrhage from choroid

3. Postoperative parameters:
   - Amount of pain during the first 24 postoperative hours (using pain scale)
   - Visual acuity day 1 postoperative

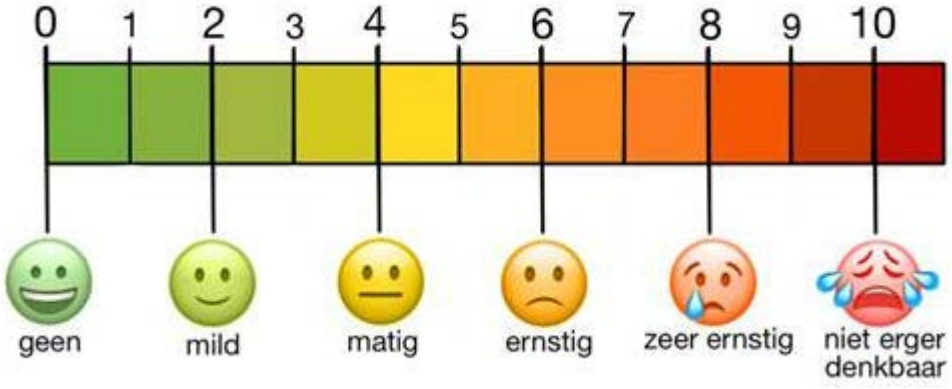
- Intra-ocular pressure day 1 postoperative
- Slit-lamp examination day 1 postoperative: flare and cells in the anterior chamber
- Photograph of the external eye to assess reddishness and swelling of eyelids

4. Questionnaire
   To be completed by the patient about postoperative morbidity during the first postoperative week

11.2. Clinical investigation assessments

Patients that are scheduled for vitrectomy surgery that is commonly performed either 23G or 27G instruments will be included. The preoperative preparation of the patient and the surgery itself will not be different from the standard of care. In the postoperative period, some additional examinations will be performed on the first postoperative day:

- The patient will be asked to grade the amount of postoperative pain experienced (using a pain scale as below)



- A photograph will be taken from the outside eye, and the amount of reddishness will be graded by and independent observer. See annex A. Photos to be made without flash, with eyes looking in all directions (e.g. 4 directions with lid up and down) and distance chosen such to have the eyes on photo with subjects not recognizable.

- A questionnaire will be given to the patient upon discharge from the hospital with questions to assess the postoperative recovery. The patient will be asked to mail us these questions back after one week.

1. Are you self-employed / employed/ retired / disabled / other:
2. Did you sleep less well during the first night after surgery due to eye pain? Yes / No
3. Did you sleep less well during the first week after surgery due to eye pain? Yes / No
4. Did you wake up during the first night due to eye pain? Yes / No
5. Did you wake up during the first week due to eye pain? Yes / No
6. Did you take pain medication during the first night after surgery due to eye pain? Yes / No
7. Did you take pain medication during the first week after surgery due to eye pain? Yes / No
8. Did you use an eye cream after the surgery during pain or abrasive feeling? Yes / No

11.3. Surgical procedure

The patient will be operated under local anesthesia, local anesthesia with sedation or general anesthesia, depending on the surgeon's and patient's preferences and general status of health. In the patients is phakic, the surgery may be combined with a cataract surgery (phaco-emulsification). As in the standard of care in each surgical center, the patients may stay overnight in the hospital after the surgery or can be treated on an outpatient basis.

11.4. Safety assessments

Medical device incidents will be routinely collected and reported under the national rules at the discretion of the Investigator.

11.4.1 Adverse events that do not require reporting

After vitrectomy, the following transient adverse events are commonly present during the first week after surgery, hence will not require reporting:

- Decreased visual acuity compared to preoperative measurement
- Reddish eye
- Increased ocular pressure
- Mild to moderate intra-ocular inflammation
- Mild corneal edema

12. DATA QUALITY ASSURANCE

12.1. Monitoring, Audit and Inspections

Investigator and the institution(s) will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents.

12.2. Training of staff

The Principal Investigator will ensure that appropriate training relevant to the investigation is given to the medical, nursing and other staff at the site involved and that new information of relevance to the performance of this investigation is forwarded to the staff involved.

The staff at the investigational site will sign a confirmation document that they are trained.

12.3. Data Management

In this study, an electronic case report form (eCRF) within the RedCap platform will be used for data capture. For each surgical center, a different RedCap database will we created, allowing only access to the corresponding investigator and CRO (in case assigned by the CTC). Hence, there will be no sharing of data between the different surgical centers. Also, the data of the different centers will not be pooled for comparison between the centers, only comparison within each center will be performed (see section statistical analysis). Hence, during the whole trial there will be a strict separation of study data between each center.

All documents will be stored safely in confidential conditions. On all clinical investigation-specific documents, other than the signed consent, the participant will be referred to by the clinical investigation participant number/code, not by name.

All clinical investigation documentation will be kept for 10 years from the clinical investigation plan defined end of clinical investigation point. When the minimum retention period has elapsed, clinical investigation documentation will not be destroyed without permission from the sponsor.

13. STATISTICS

General comment: for the statistical analysis, a comparison will be made between both study arms included *in each center*. Hence, there will only be a comparison between both study arms in each site. No pooling of the data from the different sites will be performed nor will there be a comparison between the different study sites.

13.1. Description of statistical methods

Missing data handling

The missing processes was described by Rubin (1987) who made a distinction between (a) Missing Completely At Random (MCAR), (b) Missing At Random (MAR), and (c) Missing Not At Random (MNAR)[1]. We will test with the statistical test of Jamshidian and Jalal (2010), implemented in the MissMech R Package (Jamshidian et al., 2014), whether missing data were MCAR. If they are not MCAR, we will investigate whether or not the missing mechanism could be explained by baseline characteristics (eg, sociodemographic, medical features) of patients using logistic regression, which would suggest an MAR mechanism. If missing data are not MCAR or MAR, they will considered as MNAR. As indicated by Molenberghs et al. (2008) one can never totally exclude a MNAR process, but every MNAR model has an MAR counterpart with equal fit. Therefore, in case of MCAR, MAR, or MNAR missing processes, maximum likelihood (ML) and multiple imputation (MI) were used, using the mice R package for the last one (Raghunathan et al. (2001) ; van Buuren & Oudshoorn (2016)) with a predefined seed. Indeed, ML and MI use all available data in the study and produce unbiased estimates of the treatment effect and correct *P* values. MI is also a method of choice because it allows not only to impute missing values on the outcome but also on the covariate (Dziura, 2013) and is valid for MCAR, MAR, and MNAR. (Molenberghs et al. (2008)) Molenberghs and Kenward (2007) recommended ML estimation without imposing a structure on the covariances among the repeated measures.

Analysis of primary outcomes

The primary outcomes will be analysed by a set of Wilcoxon-Mann-Whitney tests, but complementary tests will be done using mixed models for ordinal data (Hedeker & Gibbons, 2006) to take the multicenter nature of this trial into account. It is likely that patients in the same centre will tend to have correlated outcomes, meaning that they are more similar to other patients recruited within the same centre that to patients: same clinical care paths within centres will be observed, medical centre having their own medical practice preferences, and, therefore, the independence assumption underlying classical statistical tests is likely to be violated. We will therefore take this correlation between the patients of a same centre into account by using mixed models with the centre included as random effect for continuous outcomes (Chu et al., 2001; Kahan &

[1] (a) Missing Completely At Random (MCAR): the missingness pattern is independent from observed and unobserved data; (b) Missing At Random (MAR): conditional on the observed data, the dropout is independent of the unobserved measurement; and (c) Missing Not At Random (MNAR): when neither MCAR nor MAR hold, the missingness depends on the observed, as well as on the unobserved data.

Morris, 2013) and mixed models for discrete data will be used to model binary outcomes (Kahan & Harhay, 2015).

For demographic and baseline data, continuous data will be compared by means of T-test when homogeneity of variances, tested with the Bartlett's test, and normality of the residuals, tested with the Shapiro-Wilks test, will be reached and means and standard deviations (means ± StDev) will be reported. When homogeneity of the variance or normality of the residuals won't be proved, Wilcoxon signed rank test will be performed on rank data and medians and inter-quartile ranges (median [Q_{25} – Q_{75}]) will reported. For count data, the Pearson Chi-Squared test will be performed to compare proportions. We will use the software R, version 3.6.2 or above (R Core Team, 2017) to perform the statistical analyses.

Chu, R., Thabane, L., Ma, J., & al. (2011). Comparing methods to estimate treatment effects on a continuous outcome in multicentre randomized controlled trials: A simulation study. BMC Medical Research Methodology, 11:21.

Hedeker D, Gibbons RD (2006). Longitudinal Data Analysis. Wiley-Interscience, Hoboken, NJ.

Kahan, B.C. & Haray, M.O. (2015). Many multicentre trials had few events per centre, requiring analysis via random-effects models or GEEs. Journal of Clinical Epidemiology, 68(12), 1504-1511.

Kahan, B.C. & Morris, T.P. (2013). Analysis of multicentre trials with continuous outcomes: when and how should we account for centre effects? Statistics in Medicine, 32(7), 1136-1149.

Verbeke G, Molenberghs G. *Linear Mixed Models for Longitudinal Data. Springer Series in Statistics*. New-York: Springer-Verlag; 2000.

Rubin DB. Inference and missing data. *Biometrika*.1976;63:581–592.

Jamshidian M, Jalal S. Tests of homoscedasticity, normality, and missing completely at random for incomplete multivariate data. *Psychometrika*. 2010;75:649–674.

Jamshidian M, Jalal S, Jansen C. MissMech: an R package for testing homoscedasticity, multivariate normality, and missing completely at random (MCAR). *J Stat Software*. 2014;56:1–31.

Molenberghs G, Beunckens C, Sotto C, Kenward MG. Every missing not at random model has got a missing at random counterpart with equal fit. *J R Stat Soc*. 2008;70:371–388.

Raghunathan TE, Lepkowski JM, Van Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol*. 2001;27:85–95.

van Buuren S, Oudshoorn CGM. Multivariate Imputation by Chained Equations: MICE V1.0 User's Manual." *TNO Report PG/VGZ/00.038, TNO Preventie en Gezond-heid, Leiden*. 2000. Available at: http://www.stefvanbuuren.nl/publications/mice%20v1.0%20manual%20tno00038%202000.pdf. Accessed June 15, 2016.

Dziura JD, Post LA, Zhao Q, Fu Z, Peduzzi P. Strategies for dealing with missing data in clinical trials: from design to analysis. *Yale J Biol Med*. 2013;86:343–358.

Molenberghs G, Kenward MG. *Missing Data in Clinical Studies*. Chichester, UK: John Wiley and Sons Ltd; 2007.

13.2. The number of participants

We estimated the number of participants by calculating the number of participants needed for the three chosen outcomes (bio cellen, bio tyndall and redness of the eye), based on the pilot data. The target p-value was 0.5/3 (=0.0167) in order to correct for multiple testing, and the power was set to 80%. Because we want to see a difference on the three outcomes, we choose the highest sample size estimation, based on the work of Zaho, Rahardja & Yongming (2008), who proposed sample size estimators ordinal data using the Wilcoxon-Mann-Whitney test and available in the R package *sample size*. The percentages for each categories of the ordinal variables by group are used as input for the sample size estimations. The next table presents the results obtained.

	Total by group	Total individuals
Bio cellen	428	858
Bio tyndall	430	860
Redness eye	27	54

Based on this table, a total of 860 patients would be required by group in order to show a difference between 23G and 27G on the three parameters of the outcome: bio tyndall, bio cellen and redness eye.

Zhao YD, Rahardja D, Qu Yongming. Sample size calculation for the Wilcoxon-Mann-Whitney test adjusting for ties. Statistics in Medicine 2008; 27:462-468

For each surgical site 25 patients will be recruited by group (i.e. 50 patients will be included at each site).

13.3. The level of statistical significance

For all analyses, the level of significance will be 5% two-sided significant level. P-values will be adjusted for any multiple comparisons in order to maintain an overall type I error rate of 5%.

13.4. Criteria for the termination of the clinical investigation

Clinical investigation will be terminated 1 week post-op.

13.5. Procedure for accounting for missing, unused and spurious data

Missing data will be reported with reasons given where available, and the missing data pattern will be examined. We will explore the mechanism of missing data by means of logistic regression models which will explore if missingness (i.e. whether the primary outcome is missing or not) is related to measured baseline variables. Covariates found to be predictive of missingness will, where appropriate, be included as a covariate in the analysis model.

13.6. Procedures for reporting any deviations from the original statistical plan

The final statistical plan will be agreed prior to final data lock and prior to any analyses taking place. Any deviation thereafter will be reported in the final trial report.

13.7. Inclusion in analysis

All randomised patients will be included in the trial.

14. CLINICAL INVESTIGATION MANAGEMENT

14.1. Clinical investigation management group and parties involved

The clinical investigation management group consists of the following participants:

Coordinating Investigator Name: Peter Stalmans Title: Vitreoretinal surgeon Address: UZ Leuven, Herestraat 49 3000 Leuven Email: peter.stalmans@uzleuven.be
Statistician Name: Mr. Jean-François Fils, Ars Statisica Title: Bio-Statistician Address: Boulevard des Archers 40, 1400 Nivelles
Clinical investigation Management Name: Ingeborg Vriens Title: Clinical Trial Assistant (CTA) Address: UZ Leuven, Herestraat 49, 3000 Leuven Telephone: + 32 16 34 22 29 Email: ingeborg.vriens@uzleuven.be

Clinical investigation Coordination Centre

For general queries, supply of clinical investigation documentation, and collection of data, please contact the Clinical Investigation Coordinator:

Name: Ingeborg Vriens
Title: Clinical Trial Assistant (CTA)
Address: UZ Leuven, Herestraat 49, 3000 Leuven
Telephone: + 32 16 34 22 29
Email: ingeborg.vriens@uzleuven.be

Clinical Queries

Clinical queries should be directed to oogziekten@uzleuven.be who will direct the query to the appropriate person.

Investigation sites

Name: UZ Leuven
Address: Herestraat 49, 3000 Leuven

Email: oogziekten@uzleuven.be

Additional investigational sites:

Name: Christiane Falkner-Radler
Title: Dr.
Signature:
Date:
Site: Rudolf Foundation Hospital (Austria)

Name: Chérif Mazit , Mounir Benzerroug
Title: Dr.
Site: Anjou Clinic – Centre Retine Anjou (France)

Name: Mitrofanis Pavlidis
Title: Prof. Dr.
Signature:
Date:
Site: Augencentrum Köln (Germany)

Name: Luigi Caretti
Title: Dr.
Signature:
Date:
Site: Caretti Rovigo (Italy)

Name: Virgilio Morales Canton
Title: Dr.
Signature:
Date:
Site: Mexico

Name: Luis Arias
Title: Dr.
Signature:
Date:
Site: Bellvitge University Hospital (Spain)

Name: Renardel de Lavalette
Title: Prof. Dr.
Signature:
Date:
Site: UMC Groningen (The Netherlands)

Name: Aysegul Mavi
Title: Dr.
Signature:
Date:
Site: Retina Göz Hastanesi (Turkey)

Name: Zac Koshy
Title: Dr.
Signature:
Date:
Site: University Hospital Ayr (United Kingdom)

Sponsor

Name: UZ Leuven
Address: Herestraat 49, 3000 Leuven
Email: oogziekten@uzleuven.be

14.2. Clinical investigation steering committee

Patients included in this clinical trial follow the standard clinical path, using the standard vitrectomy device and using the currently used instruments. Hence, there is no increased safety risk for patients enrolled in this investigation. For this this reason, no steering committee or DMC will be constituted.

14.3. Data monitoring committee

N/A, see section 14.2.

14.4. Monitoring plan

The study protocol will be reviewed by the CTC prior to study approval. If the CTC evaluates that the study should be monitored, a monitor will be appointed by the CTC. In this case, the monitor will visit the Investigator site prior to the start of the clinical investigation and during the course of the clinical investigation if required, in accordance with the monitoring plan. Monitoring will be performed according to ISO 14155:2011. Data will be evaluated for compliance with the clinical investigation plan and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical investigation is conducted and data are generated, documented and reported in compliance with the clinical investigation plan, GCP and the applicable regulatory requirements.

15. GOOD CLINICAL PRACTICE

15.1. Declaration of Helsinki

The Investigator will ensure that this clinical investigation is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

15.2. Guidelines for GCP

The Investigator will ensure that this clinical investigation is conducted in full conformity with relevant regulations and with the International standard for Good Clinical Practice for clinical investigations of medical devices for human subjects (ISO 14155:2011).

15.3. Ethics review

The clinical investigation plan, Investigator's Brochure, Case Report Forms (CRFs), informed consent form, participant information sheet and any other documents needed

for review by an appropriate Ethics Committee (EC) or regulatory authority will be submitted to obtain written approval. Any additional requirements imposed by the EC or regulatory authority will be followed, if appropriate.

The Investigator will submit and, where necessary, obtain approval for all amendments to the original approved documents. Furthermore, the clinical investigation will not begin until the required approval/favourable opinion of the EC or regulatory authority has been obtained.

15.4. Patient Information and Consent Form

The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the investigation. Subjects must also be notified that they are free to discontinue participation in the investigation at any time. The subject should be given the opportunity to ask questions and time for consideration.

The subject's signed informed consent has to be obtained before conducting any investigation related procedures. The original must be filed by the Principal Investigator. A copy of the Patient Information including the signed Consent Form should be given to the subject. If modifications are made according to local requirements, the new version must be approved by the EC.

15.5. Subject data protection

The clinical investigation staff will ensure that the participants' anonymity is maintained. The participants will be identified only by initials and a participants ID number on the CRF and any electronic database. All documents will be stored securely and only accessible by clinical investigation staff and authorised personnel. The clinical investigation will comply with the Data Protection Act which requires data to be pseudonymized as soon as it is practical to do so.

15.6. Procedures in case of medical emergency

The Principal Investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the investigation.

16. CLINICAL INVESTIGATION CONDUCT RESPONSIBILITITES

16.1. Clinical investigation plan amendments

Amendments to the clinical investigation plan must be submitted to the Sponsor for review before submitting to the appropriate EC and Regulatory Authority for approval.

16.2. Clinical investigation plan violations, deviations and serious breaches

The Clinical investigator will not implement any deviation from the clinical investigation plan without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to clinical investigation participants.

In the event that the Clinical investigator needs to deviate from the clinical investigation plan, the nature of and reasons for the deviation will be recorded in the CRF and notified to the Sponsor. If this necessitates a subsequent clinical investigation plan amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and

Regulatory Authority for review and approvals as appropriate. It is Sponsor policy that waivers to the clinical investigation plan will not be approved.

In the event that a serious breach of GCP is suspected, this will be reported to the Sponsor immediately.

16.3. End of clinical investigation

The end of clinical investigation is defined as the last participant's last visit.
The investigator and/or the clinical investigation steering committee have the right at any time to terminate the clinical investigation for clinical or administrative reasons.

The end of the clinical investigation will be reported to the EC and Regulatory Authority within 90 days, or 15 days if the clinical investigation is terminated prematurely. The Investigators will inform participants of the premature clinical investigation closure and ensure that the appropriate follow up is arranged for all participants involved.
A summary report of the clinical investigation will be provided to the EC and Regulatory Authority within 1 year of the end of the clinical investigation.

16.4. Insurance and indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

16.5. Funding

Study grant from D.O.R.C. Dutch Ophthalmic Research Center (International) B.V. (DORC), Zuidland, The Netherlands.

17. REPORTING, PUBLICATIONS AND NOTIFICATIONS OF RESULTS

17.1. Authorship policy

Ownership of the data arising from this clinical investigation resides with the clinical investigation team. On completion of the clinical investigation, the clinical investigation data will be analysed and tabulated, and a clinical investigation report will be prepared in accordance with ISO14155:2011.

17.2. Publication

The Principal Investigator may decide to publish the obtained study data. The statistician will provide a study report, which will be used as source data to write the results section of the manuscript. The publication will also cover authorship, acknowledgements (mentioning the grant provider of the trial), and an overview of relevant scientific publications.
Before submitting for publication, the manuscript will be send to the grant provider, allowing the grant provider give feedback on the manuscript within 2 weeks. It is up to the Principal Investigator to decide to make any changes to the manuscript based on this feedback.

18. REFERENCES

1. Vitrectomy: a pars plana approach. Machemer R, Buettner H, Norton EW, Parel JM. Trans Am Acad Ophthalmol Otolaryngol. 1971 Jul-Aug;75(4):813-20.
2. A new 25-gauge instrument system for transconjunctival sutureless vitrectomy surgery. Fujii GY, De Juan E Jr, Humayun MS, Pieramici DJ, Chang TS, Awh C, Ng E, Barnes A, Wu SL, Sommerville DN. Ophthalmology. 2002 Oct;109(10):1807-12; discussion 1813. Erratum in: Ophthalmology. 2003 Jan;110(1):9.
3. Transconjunctival sutureless 23-gauge vitrectomy. Eckardt C. Retina. 2005 Feb-Mar;25(2):208-11
4. Comparison of postoperative comfort in 20 gauge versus 23 gauge pars plana vitrectomy. Mentens R, Stalmans P. Bull Soc Belge Ophtalmol. 2009;(311):5-10.
5. A 27-gauge instrument system for transconjunctival sutureless microincision vitrectomy surgery. Oshima Y, Wakabayashi T, Sato T, Ohji M, Tano Y. Ophthalmology. 2010 Jan;117(1):93-102.
6. Pars plana vitrectomy for vitreomacular traction syndrome: a systematic review and metaanalysis of safety and efficacy. Jackson TL, Nicod E, Angelis A, Grimaccia F, Prevost AT, Simpson AR, Kanavos P. Retina. 2013 Nov-Dec;33(10):2012-7
7. United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery Report 3, Retinal Detachment. Timothy L. Jackson, PhD, FRCOphth, Paul H.J. Donachie, MSc, Ahmed Sallam, PhD, FRCOphth, John M. Sparrow, DPhil, FRCOphth, Robert L. Johnston, FRCOphth. Ophthalmology 2014;121:643-648
8. The Royal College of Ophthalmologists' National Ophthalmology Database Study of Vitreoretinal Surgery Report 6, Diabetic Vitrectomy. Timothy L. Jackson, PhD, FRCOphth; Robert L. Johnston, FRCOphth; Paul H. J. Donachie, MSc; TomH. Williamson, MD, FRCOphth; John M. Sparrow, DPhil, FRCOphth; David H.W. Steel, FRCOphth. JAMA Ophthalmol. 2016;134(1):79-85. doi:10.100United Kingdom National Ophthalmology Database Study of Vitreoretinal Surgery: Report 2, Macular Hole. Timothy L. Jackson, PhD, FRCOphth, Paul H. J. Donachie, MSc, John M. Sparrow, DPhil, FRCOphth, Robert L. Johnston, FRCOphth. Ophthalmology 2013;120:629–634
9. THE ROYAL COLLEGE OF OPHTHALMOLOGISTS' NATIONAL OPHTHALMOLOGY DATABASE STUDY OF VITREORETINAL SURGERY Report 4, Epiretinal Membrane. TIMOTHY L. JACKSON, PHD, FRCOPHTH, PAUL H.J. DONACHIE, MSC, TOM H. WILLIAMSON, MD, FRCOPHTH, JOHN M. SPARROW, DPHIL, FRCOPHTH, ROBERT L. JOHNSTON, FRCOPHTH. RETINA 35:1615–1621, 2015
10. R Core Team (2017). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/.

This list is open to changes.

19. SAFETY REPORTING

19.1. Definitions

Device Deficiency (DD)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note:

- Device Deficiencies include malfunctions, use errors, and inadequate labelling.

All Device Deficiencies that might have led to a Serious Adverse Device Effect shall be reported in accordance with Serious Adverse Event reporting procedures, as specified below.

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device.

Note:
- This definition includes events related to the investigational device or the comparator.
- This definition includes events related to the procedures involved.
- For users or other persons, this definition is restricted to events related to investigational devices.

Adverse Device Effect (ADE)
Adverse Event related to the use of an investigational device.

Note:
- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, or operation, or any malfunction of the investigational device.
- This definition includes any event resulting from use error or from intentional misuse of the investigational device.

Serious Adverse Event (SAE)
Adverse Event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
    1) a life-threatening illness or injury,
    2) permanent impairment of a body structure or a body function,
    3) hospitalization or prolongation of patient hospitalization,
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
    5) chronic disease
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note:
Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE)
Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

19.2. Procedures for reporting SAE /SADE or DD that could have led to a SADE

All SAEs/SADEs that occurs during the Clinical Investigation shall be reported, whether or not they are considered causally related to the investigational device.

Device Deficiencies that might have led to SADE must be reported as a SADE if either
a) suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate

The investigator is responsible for informing the EC/IRB and/or the Competent Authority of the SAE/SADE as per local requirements. For this reason, medical device incidents will be routinely collected and reported under the national materiovigilance rules at the discretion of the Investigator.

19.3. Procedures for Device Deficiency reporting

Device Deficiencies will be routinely collected and reported to the corresponding manufacturer(s) as soon as possible, without unjustified delay (i.e. on the same working day). If the Device Deficiency might have led to a SADE the reporting requirements for SADE described above must be followed.

19.4. Causality Assessment

The relationship between the use of the investigational device and the occurrence of each AE/SAE shall be assessed by the investigator and the manufacturer and classified as investigational device related or not related to investigational device.

19.5. Recording of safety information

All safety issues occurring during the clinical investigation observed by the investigator or reported by the participant, whether or not attributed to the device under investigation will be recorded on the CRF as specified in the clinical investigation plan.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship to the device will be assessed by a medically qualified investigator or the sponsor and will be followed up until resolution or the event is considered stable.

All ADE that result in a participant's withdrawal from the clinical investigation or are present at the end of the clinical investigation, should be followed up until a satisfactory resolution occurs.

Where relevant, any pregnancy occurring during the clinical investigation and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect.

19.6. Reporting procedure for all SAEs/SADEs

Reporting to the local national competent authority and the manufacturer will be done by the Principal Investigator.

- The principal investigator has a legal obligation to report all events that need to be reported to the Nominated Competent Authority immediately (without any unjustifiable delay) after a link is established between the event and the device, but no more than:2 days following the awareness of the event for Serious Public Health Threat.
- 10 days following awareness of the event for Death or unanticipated serious deterioration in health.
- 30 days following the awareness of the event for all other event meeting the SAE criteria.

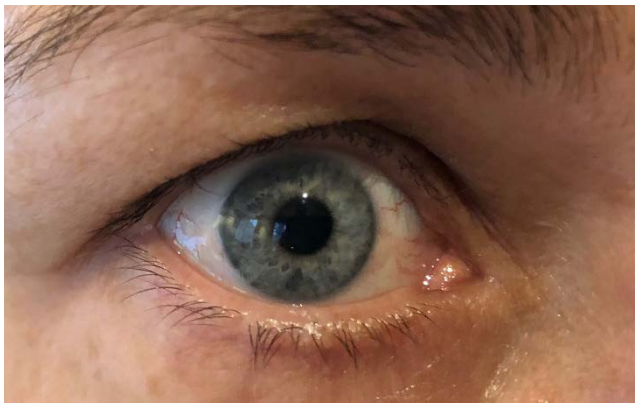
Device Deficiencies, including SAEs/SADEs will be reported to the corresponding manufacturer(s) as soon as possible, without unjustified delay (i.e. on the same working day).

19.7. Annual reports

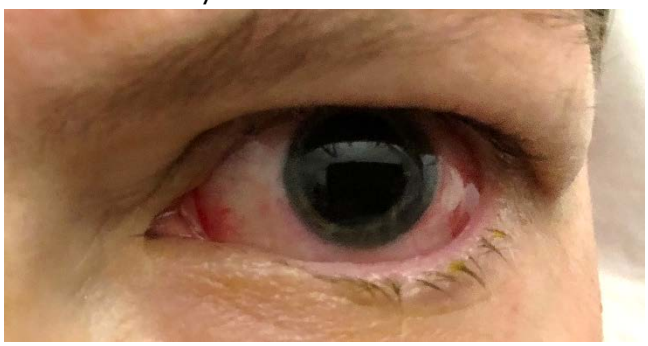
In addition to the expedited reporting above, the Principal Investigator shall submit once a year throughout the clinical investigation or on request a Safety Report to the Competent Authority and Ethics Committee.

Appendix A: Assessment of eye reddishness – Reference photographs

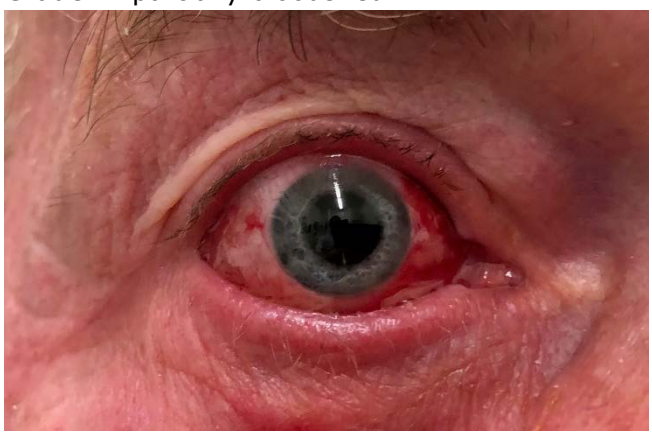
Grade 0: no reddishness



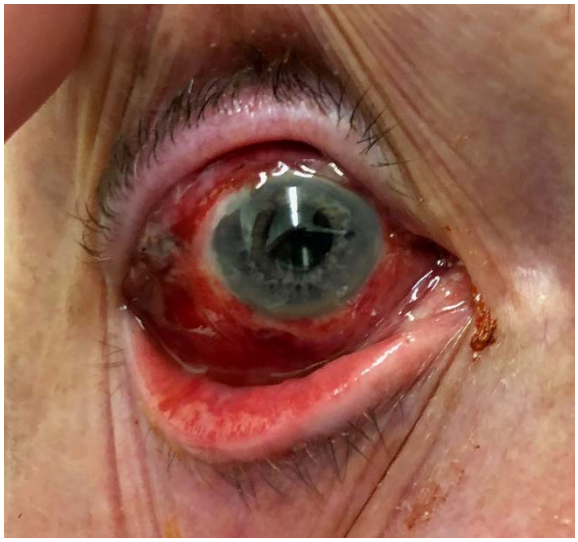
Grade 1: barely visible



Grade 2: partially bloodshed



Grade 3: diffuse bloodshed, globe only



Grade 4: diffuse bloodshed, including eyelids / orbit