Clinical Investigation Title:

EVA Nexus Field Observation Study

A monocentric, academic field observation study of a prototype of a new CE-labeled vitrectomy device developed by DORC BV (The Netherlands).

Clinical Investigation Acronym: EVA Nexus

Sponsor	*UZ Leuven*
Principal Investigator	*Prof. dr. Peter Stalmans*
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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

Principal Investigator Name: Peter Stalmans Title: Prof. dr. Signature: Date: Site: UZ Leuven
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This CIP describes the EVA Nexus clinical investigation and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary.

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	List of intra-operative complications
Appendix B	List of device issues not leading to (S)AE
Appendix C	Case Report Form (S)AEs reporting
Appendix D	Device deficiency Form
Appendix E	Informed Consent Form

3. ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BCVA	best-corrected visual acuity
CA	Competent Authorities
CIP	Clinical Investigation Plan
CRA	Clinical Research Associate
CRF	Case Report Form
EC	Ethics Committee (see REC)
EMR	Electronical Medical Record
GCP	Good Clinical Practice
GP	General Practitioner
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IRB	Independent Review Board
Log MAR	logarithm of the minimal angle of resolution
PI	Principle Investigator
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reactions

4. CLINICAL INVESTIGATION SUMMARY

Title	EVA Nexus Field Observation Study
Reference Number (Acronym)	EVA Nexus
Clinical Phase	Non applicable
Objectives	To perform a field observation study using the newly developed EVA Nexus vitrectomy device.
Endpoints	Primary endpoint: determine the safety and effectiveness of the device.
Design	Investigator-initiated, mono-center, academic, prospective, observational case study
Data Collection	*Total duration of study for each patient will be 2 days (from surgery date to last follow-up day)* *See Study Flow Chart 7.3*
Planned Clinical investigation Period	Q2-Q3 2021
Clinical investigation population	Patients that are scheduled for intra-ocular surgery regardless of the indication: • Vitrectomy surgery • Cataract surgery • Vitrectomy combined with cataract surgery
Number of Participants	Up to 250, inclusion period of three months.

Inclusion/Exclusion Criteria	<u>Inclusion criteria</u>
	• Patients that are scheduled for intra-ocular surgery regardless of the indication:
	  • Vitrectomy surgery
	  • Cataract surgery
	  • Vitrectomy combined with cataract surgery
	• In case of (combined) vitrectomy: primary or repeat vitrectomy
	• General or retrobulbar anesthesia, the latter can be combined with sedation
	• Patients aged ≥ 18 years
	<u>Exclusion criteria</u>
	• Patients aged < 18 years

Device Name	EVA Nexus (CE-labeled device)
Principle Intended Use	The device is intended to be used during ophthalmic surgery.

Manufacturer Name	DORC B.V.

5. INTRODUCTION

5.1 Vitrectomy device

In certain disorders of the retina and the vitreous a vitrectomy study can be performed.
For vitrectomy surgery, a surgical device is used, called "vitrectomy device". Such device integrates many functions:

1. **Vitrectome driver.**
   A vitrectome is a small device which is inserted in the eye to remove the vitreous gel. The vitrectome has a hollow blunt-ended hollow shaft with a side opening at the distal tip. An inner hollow metal tube is moved back-and-forth over this opening, creating a guillotine-like cutting effect on the vitreous gel. At slower speeds, the vitrectome will take larger bites out the vitreous gel, hence inducing a quicker removal of the vitreous. At higher speeds, the vitrectome takes smaller bites, which is a safer approach when working close to the retina. The cutting speed is controlled by the vitrectomy machine using a foot pedal. Most of the vitrectomes are driven pneumatically, although some electrically driven versions have existed in the past.
   Till about 15 years ago, the diameter of the vitrectome was 20G (1 mm), after that a switch happened to mostly 23G (0,6) and 25G (0,5) diameter instruments. Since a few years, vitrectomy instruments in 27G (0,35 mm) are available. However, this very small size has its limitations, hence is only used in less complicated surgeries.
   The DORC EVA drives a pneumatic vitrectome with a maximum of 8.000 cycles per minute.

2. **Aspiration system.**
   This is required to remove liquid from the eye. Several pump systems exist, with different ways to displace fluid:
   -Vacuum pumps generate a vacuum, which is controlled by the surgeon using the foot switch of the device. The amount of fluid displacement is dependent on the amount of vacuum, and on the amount of resistance in the tubing system and instrument inside the eye. Vacuum pumps can respond quickly and can generate a large flow, but lack control to keep the fluid displacement steady when the surgeon is operating in conditions with variable resistance. An example is when working close to the vitreous base at the retinal periphery: the tip of the vitrectome will move in and out of the vitreous, resulting in high variability of the flow and risk of aspiration the retinal tissue. A typical example of a vacuum system is a venturi-pump, which is used in most of the vitrectomy devices presently available.
   -Flow pumps displace a required amount of fluid, and only build up vacuum secondary to this fluid displacement. In conditions with low resistance, there is little or no vacuum-buildup. Most flow pumps are less powerful than vacuum pumps, but can provide a better control of the flow. This increases safety when working close to the retina.
   A typical example of a flow pump system is a peristaltic pump. Although such pump is popular in cataract surgery, it is only used for vitrectomy surgery in conjunction with a vacuum pump.
   Our present vitrectomy machine in the UZLeuven (DORC EVA) has a piston-pump which can be steered to perform as a vacuum system or as a flow system. This unique feature allows the surgeon to choose the best suitable mode for each individual step of the surgery.

3. **Infusion system.**
   Since vitreous is removed from the eye, an infusion system must be present to maintain the eye pressure. There are two infusion systems used for vitrectomy surgery:

   -Gravity system: the infusion bottle (or bag) is suspended on a telescopic infusion pole.

The pole can be extended using the vitrectomy machine to a higher or lower height, which increases the pressure at which the infusion liquid is driven towards the eye. The disadvantage of such system is that the infusion pole movement has its speed limits, which can be a problem when a fast pressure change is required in the eye (such as in case of hemorrhage).

-Air system: using a spike, air is blown into the infusion bottle. A higher air pressure will increase the force at which liquid is driving towards the eye. Such system can respond more quickly to required pressure changes. Our present vitrectomy machine in the UZLeuven (DORC EVA) has this type of infusion system.
A logistical side-effect of such air-driven system is that the infusion liquid connected to the eye must be packaged in glass bottles, since plastic bags or plastic bottles have an inherent flexibility which would cause unwanted hysteresis.
-In case of combined phaco-vitrectomy, both infusion in the anterior and in the posterior eye segment is required. Since our present vitrectomy device (DORC EVA) only has a single infusion line, the tubing needs to be reconnected from the phaco handpiece on the posterior segment infusion canula halfway the surgery.

4. **Light.**
A powerful light source is required to illuminate the inside of the globe during surgery. For this purpose, a PMMA fiber is connected to the light source of the vitrectomy machine and guided into the eye.
Historically, a halogen light source was used. About 15 years ago, more powerful Xenon light sources became available and are still present in many vitrectomy devices. More recently, LED light sources became more popular. Also our present vitrectomy device (DORC EVA) is equipped with an LED light source.
Increasing light output is required when using ultra-small gauge surgery (27G), since the diameter of the light fiber is extremely thin. However, care must be taken by the surgeon to avoid light toxicity when the light source is held too close to the same area of the retina for too long. Retinal damage due to light toxicity after vitrectomy can have a major effect on the visual acuity of the patient.
In most light sources for vitrectomy surgery, the light is filtered, eliminating more bluish wavelengths to increase its safety.

5. **Phaco ultrasound**.
To remove an opacified lens from the eye (cataract), the lens needs to be emulsified in the eye. For this purpose, a small needle is used that is oscillating on an ultrasonic frequency. These oscillations emulsify the lens material, after which can be aspirated (using the aspiration system of the device). The DORC EVA has an analog driver board and operates at a frequency of 40 kHz.

6. **Laser module**.
To reattach the retina in case of retinal detachment, laser coagulates need to be placed around the breaks in the retina. For this purpose, a vitrectomy machine has a built-in laser module. A glass fiber is used to guide the laser light into the eye on the retina. Using the foot switch of the device, laser coagulates can be directed towards the desired location on the retina. The DORC EVA uses a 532 nm endo laser which has been the standard for ophthalmic use.

7. **Silicone oil injection.**
Not infrequently, the eye needs to be filled with silicone oil during surgery for retinal detachment. For this purpose, a system is present that drives the silicone oil from a (glass) syringe into the eye. The DORC EVA can drive (pre) filled syringes of silicon oil with a pressure up to 6 bars.

8. **Silicone oil extraction**.
   For removal of the silicone oil, a system is present that generates a high vacuum to remove the viscous oil from the eye through a small opening. The DORC EVA generates a vacuum up to 660 mmHg to remove the silicon oil.

9. Endodiathermy.
   In case a hemorrhage occurs inside or outside of the eye, a diathermy probe can be connected to the vitrectomy device to coagulate the bleeding vessel
   The DORC EVA operates at frequency of 1 Mhz to create the coagulation.

5.2 DORC EVA Nexus device

For the safety of the patient, the need for a performant vitrectomy device is essential.

In our center, we have been using the DORC EVA vitrectomy machine since 2012. DORC will release a novel version of this surgical platform, named the EVA Nexus.

This new device has several improved features compared to the present DORC EVA.

1. Vitrectome

Both EVA and EVA NEXUS provide vitrectomy. The cut speed range of EVA NEXUS, 10.000 cycles per minute, is broader than that of EVA. A higher cut speed is generally accepted as a clinical benefit, without addition of new risk.

2. Aspiration system

The aspiration system of the EVA NEXUS is the same with one additional feature.

EVA NEXUS has an additional proportional controlled backflush.

The aspiration system in the DORC EVA was designed to be used with 23G/25G vitrectomy instruments. However, 27G vitrectomy is become more mainstream each year [1-5]. This feature should increase the safety during surgery when performing vitreous removal very close to the retina, also known as "vitreous base shaving".

3. Vitrectome

The maximum cut-speed of the EVA Nexus vitrectome is 20 000 cycles per minute, which is almost twice the current speed of the DORC EVA device. As explained above, this increased cut rate will also contribute to a safer removal of the vitreous close to the retina.

To maximize surgical ergonomy, the hand piece of the vitrectomy is now covered with a dampening sleeve, which reduces the amount of vibration for the surgeon holding the vitrectome during the surgery.

4. Infusion system

Our present vitrectomy device generates a desired amount of pressure in the infusion bottle (by changing the bottle height of by injection of air in the bottle), but there is no control over the actual amount of liquid that is infused in the eye. This can cause danger in two directions:

-In some circumstances, the infusion flow will be too high, which impedes normal arterial perfusion of the eye, which can create ischemic damage in the eye. Such vitrectomy-related vascular damage is not infrequently described in the literature [6].

-In other circumstances, the aspiration of liquid can be higher than the infusion flow, hence the eye pressure can become too low, which can cause hemorrhage or even collapse of the eye.

The EVA Nexus system has an active infusion system, which constantly provides a stable infusion to the eye and a stable intra-ocular pressure during surgery. Hence, it features automated control of the intra-ocular pressure during anterior and posterior segment surgery.

The fixed and gravity modes are both pressure controlled and can be regarded similar technology with the same functional result. The eIOP mode in EVA NEXUS supports the surgeon to maintain the IOP by maintaining the Irrigation/Aspiration balance (regulated by the pump system to get precise Intra Ocular Pressure control), where in EVA Intra Ocular Pressure is a result of the surgeon controlled settings of the system.

The EVA Nexus has twin irrigation lines, which omits the need to switch the infusion halfway the surgery in case of combined phaco-vitrectomy

Another, logistical implication is that the infusion liquid used during cataract surgery or vitrectomy surgery must not be packaged anymore in a glass bottle, since the DORC EVA Nexus actively aspirates the infusion liquid from the container. Therefore, less expensive packages of infusion liquid can be used (fluid bags or plastic bottles).

5. Light

The system had a LED-powered light source, with filtered output to eliminate the shorter light wavelengths that induce light toxicity during prolonged exposure to the retina. This is the same light source as in the present DORC EVA device.

6. Phaco ultrasound

The phaco handpiece that fits to EVA Nexus is the same CE-labeled commercial handpiece already used on our present surgical device.

Although the design is somewhat different, both EVA and EVA NEXUS use similar principles of operation to drive the phaco handpiece for emulsification or fragmentation of the lens. All performance requirements are the same.

7. Laser module

The EVA Nexus has a built-in 532 nm diode-laser. This is the same laser module as used in our present vitrectomy device.

8. Silicone oil injection (VFI).

There are no differences between the EVA and EVA NEXUS for silicone oil injection.

9. Silicone oil extraction.

There are no differences between the EVA and EVA NEXUS for silicone oil extraction.

10. Micro Injection

In addition to the EVA the EVA NEXUS has a Micro Injection functionality, which is basically the same functionality as VFI, in a smaller and more precise volume dosing. The VFI function can be set in the range 0-6 bar, with step size 0,5 bar. The MI function can be set in the range 0-2 bar, with step size of 0,1 bar.

10. Endodiathermy.

Although the design is somewhat different, both EVA and EVA NEXUS use similar principles of operations to drive the diathermy handpiece to coagulate tissue

5.3 Patient safety with the EVA Nexus device

This field observation study will be performed to obtain more information on the safety and daily use of the EVA Nexus device in routine phaco/vitrectomy surgery. This information can lead to small adjustments to the device to further fine tune a safe device which can be used by other surgeons.

During a vitrectomy surgery, the surgeon removes the vitreous gel. This is done using a mini-guillotine of half millimeter diameter (or even less in 27G surgery) that is inserted in the eye. Meanwhile, an infusion fluid is injected in the eye. Sufficient fluid irrigation is mandatory to avoid a drop in the eye pressure which can lead to retinal or choroidal hemorrhage. On the other hand, it must be avoided to have the eye pressure elevate too high, since this can block the arterial blood supply which can lead to permanent damage of the eyesight of the patient.

The EVA Nexus device has an automated system, which allows better control of the eye pressure during the surgery compared to existing vitrectomy technology.

Another novel feature on this device is the improvement of the guillotine itself. The faster the guillotine can go backwards and forwards, the safer the surgery can be performed. The EVA Nexus device can keep up to a speed of 20000 cuts per minute, whereas in even the most performant devices the speed is limited to 16000 cuts per minute.

Often vitrectomy is combined with lens surgery. The removal of the lens is nowadays done using a device that emulsifies the lens with ultrasonic waves. This technique is called "phaco-emulsification", which has been the golden standard in cataract surgery for more than 20 years. The hand-held phaco-emulsification probe connected to the EVA Nexus is the same probe as used on our present DORC EVA device, but the internal steering is redesigned to allow better fine-tuning of the surgical settings according to the preferences of the surgeon.

Besides the EVA Nexus itself, several of the disposable supplies of this surgical platform were optimized:

- Newly designed phaco needles improve anterior chamber stability during cataract surgery.
- The instrument cannulas used during vitrectomy were redesigned. The smaller outside part occupies less space hence will allow more movement of the eye during the surgery.
- The infusion line can connect to the infusion canula without the need to remove its sealing cap. This reduces the amount of surgical movements and allows better surgical flexibility when the infusion needs to be switched to another instrument cannula during surgery.
- The infusion line locks onto the infusion canula, reducing the incidence of a commonly occurring issue that the infusion line disconnects from the cannula during the surgery.

After brought under anesthesia, the patients is draped while the vitrectomy device is being prepared. This involves connecting of all the surgical supplies (see above) and priming of the device. This whole procedure takes 10-20 minutes, depending on the complexity of

the case.The packaging of the surgical supplies was reworked (reduction in the amount of packaging materials) and the infusion giving set has been simplified significantly for the EVA Nexus platform. This should shorten the total surgical time.

Surgical issues and/or (S)AE's that are related to the surgical device will always be observed either during the surgery or during the postoperative visit on day one. Late-onset complications such as proliferative vitreoretinopathy, retinal detachment etc. are considered non-related to the surgical device. Hence, in this study, data acquisition is terminated after the postoperative visit on day one, although the patient will have further postoperative follow-up according the standard of care.

6. OBJECTIVES

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

The main purpose of this study is to evaluate the intra-operative safety of a new surgical device.	Therefore, having no idea of the percentage of patients having complications, we make the hypothesis that minimum 5% of the patients will have complications. In order to make sure that we have at least 10 patients with complications, we plan recruit 250 patients in total in order to get at least 10 complications with EVA Nexus. For this purpose, typical surgical parameters will be recorded during vitrectomy surgery: • Surgical indication • If combined phaco-surgery is performed: amount of phaco power used • Staining dyes (if used) • Amount of laser coagulates (if used) • Type of tamponade left in the eye: BSS+ liquid, air bubble, air, gas (type + concentration) or silicone oil (type) Specific adverse events that may occur during (phaco)vitrectomy will be recorded to assess the surgical safety [15-18]: see list in Appendix A. This AE reporting is already present in the surgical report (KWS-Formasa) used for daily vitrectomy surgery using the DORC EVA device. The occurrence of these AE's during surgeries using the EVA Nexus will be compared to historical data retrieved from surgeries using the DORC EVA platform. Device issues that caused some hindering during the surgery but that do not lead to an (S)AE, such as error messages/warnings that did occur, malfunctioning of supplies that required replacement etc. will be recorded. See Appendix B for a full list, which is already part of our present surgical report (KWS-Formasa). The occurrence of these issues during surgeries using the EVA Nexus will be compared to historical data retrieved from surgeries using the DORC EVA platform.

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

Secondary objective	**Secondary parameters**
To evaluate the possible reduction of total surgical time.	The time that was required to prepare the EVA Nexus will be recorded (connecting of supplies + priming). During the study period, this time will also be recorded during surgeries performed with the DORC EVA device for comparison.
To evaluate possible (S)AE that may be related to the use of the surgical platform.	Rarely, adverse events that are related to the surgery may only become visible the day after the surgery. A typical example is a choroidal hemorrhage, which is related to variations in intra-ocular pressure during the surgery. Hence, standard as in the standard-of care, a postoperative check of the eye at the day after the surgery will be performed to determine the presence of such AE's.
To evaluate the impact of usage of the EVA NEXUS on the surgical parameters used during the procedure	The surgical parameters include a range of data collected on the following: Aspiration Irrigation / Infusion BSS Usage Vitrectomy Ultrasound Illumination Diathermy Micro-injection Silicone oil injection / extraction Laser

7. CLINICAL INVESTIGATION DESIGN

7.1 Trial Design

Investigator-initiated, academic, mono-center, prospective, field observation study using a novel CE-labeled surgical platform.

The study will be terminated after a time period of three months. A maximum of 250 patients will be enrolled. The study will consist of 3 patient visits. Study follow-up is 1 day after the date of the vitrectomy surgery.

During surgery, intra-operative complications and issues will be recorded for safety assessment: see list in previous paragraph.

Typical postoperative follow-up after vitrectomy includes the clinical tests to assess that normal postoperative outcome is present, without the presence of adverse events.
Hence, the same clinical data will be collected in the study patients as in patients undergoing the standard-of-care.

This field observation study is conducted to obtain information about the complication rate of the EVA Nexus system which will be compared with the incidence of these complications occurring is surgeries performed using our present DORC EVA platform. [15-18]

7.2 Study Flowchart

	Preop (inclusion)	Surgery	Postop day 1
Vitrectomy		X	
Visual acuity	X		X
Eye pressure	X		X
Biomicroscopy	X		X
Ophthalmoscopy	X		X
OCT	X[1]		
Ultrasound	X[2]		X[2]
Adverse events	X[3]		X
Surgical summary		X	

X[1] if required, depending on indication for surgery, e.g.: macular pucker, macular hole, vitreomacular traction, …

X[2] if required, depending on indication for surgery, e.g.: vitreous hemorrhage

X[3] any pre-operative clinical condition that is known to affect the incidence of (S)AE's during surgery (e.g. zonular dehiscence, tamsulosine medication, axial length, …)

8. CLINICAL INVESTIGATION POPULATION

8.1. Number of participants – sample size analysis

With a complication rate ranging from 5% up to 30% in previous studies, we have no a priori about the complication rate of the EVA Nexus system. We therefore consider a rather conservative hypothesis and expect to have around 5% of complications with the EVA Nexus system. We plan recruit 250 patients in total in order to get at least 10 complications with EVA Nexus. The estimated enrolment time is 6 months.

8.2. Inclusion criteria

- Patients that are scheduled for vitrectomy surgery, cataract surgery or combined surgery, regardless of the indication
- Primary or repeat vitrectomy
- General or local anesthesia, or combination
- Patients Aged ≥ 18 years

8.3. Exclusion criteria

- Patients aged < 18 years old

9. PARTICIPANT SELECTION AND ENROLMENT

9.1. Identifying participants

The trial will be initiated only after the device manufacturer (DORC B.V.) has received a CE-label for both the surgical device (EVA Nexus) and its surgical supplies. Hence, no FAGG application will be necessary for this study.
Since no experimental device is used in this field observation study, the patient is not asked for permission to have the surgery done using this device, but approval is needed from the patient to use his/hers EMR data for a clinical trial. Patients that are not asked for study participation could also undergo surgery with the EVA Nexus device, since it will be fully approved for clinical used at the time of the study.
Hence, it is important to emphasize that whether the patient is included in trial has in no way any influence on the clinical care: the surgery might be performed with the same device, and the same clinical data will be recorded before, during and after the surgery. There are no supplementary study visits, nor is any specific study-related clinical or technical examination performed.

Patients will be asked for permission for inclusion in the study on the evening of the day of the surgery. After finishing all surgeries, the surgeon always does a round in the one-night-stay department to see the patients that were operated that day. During that post-operative patient briefing, the surgeon will ask the patient for inclusion in the trial and to sign the informed consent.
This 'approval after surgery' instead of asking before the surgery had several advantages:

- Although the patients follow exactly the same clinical path as in the standard-of-care (including the device used for the surgery), it is very disturbing for a patient to hear pre-operatively that he/she will be included in a clinical study. Patients usually do not understand that only the use of their EMR for a study also requires their informed consent and signature. Rather, patients that are asked for such approval before the surgery will experience more stress because they may (incorrectly) believe some experimental therapy is being done.
- The surgeon will not know in advance whether a patient will be included in the study. Indeed, when asked after the surgery, a patient may or may not give their consent for participation.
  Hence, neither the decision to perform the surgery nor the scheduling of the surgery will be influenced by participation in the trial, further eliminating any possibility that participation in the trial may influence the clinical care of the patient.

However, in theory, a surgeon may decide not to ask permission for study participation in patients that have more surgical risk. For example: high myopia, very small eye size, previous ocular trauma etc. all make the surgery more prone for adverse events. Therefore, in this study, the investigator will ask ALL patients that were operated that day for their approval to participate in the trial and keep an (pseudonymized) list of how many patients refused participation This way, this theoretical bias in patient selection is also omitted.
In case a patient prefers not to have their EMR used for this field observation study, the further clinical tract remains unaltered.

9.2. Consenting participants

Patients that are underwent phaco and/or vitrectomy surgery will be given the informed consent and will be asked to participate in the clinical trial.

Following Ethic 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 the EMR is used for this study.

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 (if present). 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 authorized 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.

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 evening of the day of the surgery (see above).

9.3. 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.

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 device used for this clinical trial and its supplies will have a CE-label. Hence, no FAGG approval will be requested to use the device for this trial.

10.2. Device manufacturer

Manufacturer of devices included in section 10.1 is DORC BV, Scheijdelveweg 2, 3214 VN Zuidland, The Netherlands.

10.3. Device accountability

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 supplies used with the device come pre-sterilized and will be used before expiration date. The reusable instruments (mainly: phaco handpiece) 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
- Intra-operative injection of Mydrane if pupillary dilation is required
- Intra-operative injection of Miostat if pupillary miosis is required
- 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.

10.6. FAGG Approval

Not applicable, see 10.1

11. CLINICAL INVESTIGATION ASSESSMENTS

11.1. Subject Characteristics

During vitrectomy surgery, typical surgical parameters will be recorded:

- Surgical indication
- If combined phaco-surgery is performed: amount of phaco power used
- Staining dyes (if used)
- Amount of laser coagulates (if used)
- Type of tamponade left in the eye: BSS+ liquid, air bubble, air, gas (type + concentration) or silicone oil (type)

11.2. Clinical investigation assessments

Patients that are scheduled for vitrectomy and/or cataract surgery that is commonly performed will be included. The preoperative preparation of the patient and the surgery itself will not be different from the standard of care.

Typical postoperative follow-up after vitrectomy includes the clinical tests to assess that normal postoperative outcome is present, without the presence of adverse events.
Hence, the same clinical data will be collected in the study patients as in patients undergoing the standard-of-care.

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 case of vitrectomy surgery, in case the patient is phakic and over 50 years old, the surgery will be combined with a cataract surgery (phaco-emulsification) in most cases. As in the standard of care, the patients will stay overnight in the hospital after the surgery (one-night stay).

11.4. Safety assessments

The EVA Nexus device and it supplies are CE certified per Medical Device Directive (93/42/EEC) and comply therefore with the safety and performance requirements as stated in the Essential Requirements of this directive. Compliance with applicable safety and performance standards has been confirmed during extensive testing as part of the development process and the associated records are part of the design history file. These records are subject to periodic surveillance audits by Notified Body DEKRA.

11.4.1 Adverse events that do not require reporting

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

- Decreased visual acuity compared to preoperative measurement
- Reddish eye
- Moderately and temporarily increased ocular pressure (<35 mmHg)
- Mild to moderate intra-ocular inflammation
- Mild corneal edema In addition see section 18.2.

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

An eCRF will be created on the RedCap platform. This platform provides all required functionality, security and traceability to be compliant with a CRF. To pseudonymize the patient data in the eCRF, a separate file containing the list of patients linked to the study number will be kept behind the hospital firewall, only accessible by the study personnel involved in this trial.

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 25 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

13.1. Description of statistical methods

Will be outsourced to a licensed medical statistician (Ars Statistica).
An pseudonymizedExcel-export will be generated from the eCRF for statistical analysis.

For the primary endpoint (complication rate of the EVA Nexus), a one-sample proportion test will be performed to test whether the obtained rate is different from rates found in the literature (30%, 15% and 5%).
For the remaining data (demographics and secondary objectives), group comparisons (no complications vs complications) of categorical variables will be analyzed using a Fisher's exact test and group comparisons (no complications vs complications) of continuous variables will be performed using the T-test or the Wilcoxon signed rank test, as appropriate (=when the normality of the residuals and the equality of the variances are met, the T-test will be used, and when the normality of the residuals or the homoskedasticity of the variances will not be met, the Wilcoxon signed rank test will be used). Last, in order to test a first predictive model, a logistic or Poisson regression, as appropriate, with backward selection method will be performed, starting with all variables associated with the target with a p-value lower than 0.1. The final model will contain variables associated with the outcome with a p-value lower than 0.05.

13.2. The number of participants

Maximum 250, inclusion time 4 months.

13.3. The level of statistical significance

For all analyses, the level of significance will be 5% two-sided significant level.

13.4. Criteria for the termination of the clinical investigation

Clinical investigation will be terminated after the postoperative visit on the day after the surgery.

13.5. suspension or premature termination of the trial

In case of suspension or premature termination of the trial a notification will be sent in writing to the CA and EC explaining the reason behind this decision.

13.6. 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 (MCAR, MAR) by means of the Jamshidian & Jalal's (2010)'s test for MCAR or logistic regression models for MAR which will explore if missingness (i.e. whether the primary outcome is missing or not) is related to measured baseline variables. As indicated by Molenberghs et al. (2008), one can never totally exclude a MNAR process, but every MNAR model has a MAR counterpart with equal fit. Therefore, in case of MCAR, MAR or MNAR missing processes, Maximum Likelihood (ML) and Multiple Imputation (MI) can be used, using the mice R package for the last one (Raghunathan et al., 2001; van Buuren & Oudshoorn, 2000), with a predefined seed. Indeed, ML and MI uses all available data in the study, produces 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 et al., 2013) and is valid for MCAR, MAR and MNAR (Molenberghs et al., 2008).

13.7. 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.

13.8. Inclusion in analysis

All patients will be included in the trial.

14. Clinical investigation management group and parties involved

14.1 The clinical investigation management group consists of the following participants:

Principal Investigator

Name: Peter Stalmans
Title: Vitreoretinal surgeon

Address:
UZLeuven
Herestraat 49
3000 Leuven
Telephone: 016/ 33 26 60
Email: oogziekten@uzleuven.be

Statistician

Name: Mr. Jean-François Fils, Ars Statistica
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Clinical investigation Management

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3000 Leuven
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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
Address: UZ Leuven campus Gasthuisberg – E107 - 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 site Name: UZ Leuven E107 Address: Herestraat 49, 3000 Leuven Telephone: +32 16 33 26 60 Email: oogziekten@uzleuven.be
Sponsor Name: UZ Leuven Address: Herestraat 49, 3000 Leuven Telephone: Email: oogziekten@uzleuven.be
Funder Name: DORC B.V. Address: Scheijdelveweg 2, 3214 VN Zuidland, The Netherlands Telephone: +31 6 55 23 91 00 and +31 1 81 74 50 90 Email: j.burckhardt@dorcglobal.com

14.2 Clinical investigation steering committee

N/A

14.3 Data monitoring committee

N/A

14.4 Monitoring plan

The study protocol was reviewed by the CTC prior to study approval. In case the CTC decides to appoint a monitor for this trial, the monitor will be able to 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. In such case, monitoring can 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.

14.5 Statistical Analysis plan

13.13.1. Descriptive statistics

Summary statistics (Nb observations, minimum, Q_{25}, median, Q_{75}, maximum, standard deviation) of the whole studied group will be provided.

13.13.2. Primary outcome

For the primary endpoint (complication rate of the EVA Nexus), a one-sample proportion test will be performed to test whether the obtained rate is different from rates found in the literature (30%, 15% and 5%).

13.13.3. Inferential statistics

For the primary endpoint (complication rate of the EVA Nexus), a one-sample proportion test will be performed to test whether the obtained rate is different from rates found in the literature (30%, 15% and 5%).
For the remaining data (demographics and secondary objectives), group comparisons (no complications vs complications) of count variables will be analyzed using a Fisher's exact test and group comparisons (no complications vs complications) of continuous variables will be performed using the T-test or the Wilcoxon signed rank test, as appropriate (=when the normality of the residuals and the equality of the variances are met, the T-test will be used, and when the normality of the residuals or the homoskedasticity of the variances will not be met, the Wilcoxon signed rank test will be used). Last, in order to test a first predictive model, a logistic or Poisson regression, as appropriate, with backward selection method will be performed, starting with all variables associated with the target with a p-value lower than 0.1. The final model will contain variables associated with the outcome with a p-value lower than 0.05.

15. GOOD CLINICAL PRACTICE

14.1. 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).

14.2. 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).

14.3. 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 trial will be conducted in compliance of the Belgian Law of 7 May 2004 on experiments on the human person.

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/favorable opinion of the EC or regulatory authority has been obtained.

14.4. 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 collecting 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.

14.5. Subject data protection

The clinical investigation staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a sequential ID number on the eCRF. All documents will be stored securely and only accessible by clinical investigation staff and authorized 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.

14.6. 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

15.1. 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.

15.2. 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.

15.3. 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.

15.4. 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."

15.5. Funding

This is a monocentric, academic field observation study. A study grant will also be provided by DORC BV to cover the administrative and personnel expenses for this study.

17. REPORTING, PUBLICATIONS AND NOTIFICATIONS OF RESULTS

16.1. 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 analyzed and tabulated, and a clinical investigation report will be prepared in accordance with ISO14155:2011.

16.2. Publication

The Principal Investigator intents to publish the obtained study data in a specialized journal for retinal surgery. 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 sent 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.

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This list is open to changes.

18. SAFETY REPORTING

18.1 Definitions

The definitions and reporting requirements adopted in this Clinical Investigation Plan (CIP) are based on the ISO 14155:2011 standard and the MEDDEV 2.7/3 – rev 3 guideline.

18.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational medical device.

Note 1: This definition includes events related to the investigational medical device or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

18.1.2. Serious Adverse Event (SAE)

A SAE is an adverse event that:

a) led to death,
b) led to serious deterioration in health of the subject, that either resulted in:
- a life-threatening illness or injury, or
- a permanent impairment of a body structure or a body function, or
- requires in-patient hospitalization or prolongation of existing hospitalization, or
- in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

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

18.1.3. Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device.

Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
Note 2: This includes any event that is a result of a use error or intentional misuse of the investigational medical device.

18.1.4. Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

18.1.5. Unanticipated Serious Adverse Device Effect (USADE)

An USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

18.1.6. Device Deficiency (DD)

A DD is an inadequacy of an investigational medical device with respect to its identity, quality, durability, reliability, safety or performance.

Note: This may include malfunctions, use errors, and inadequate labelling.

18.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the trial:

- Decreased visual acuity compared to preoperative measurement
- Reddish eye
- Moderately and temporarily increased ocular pressure (<35 mmHg)
- Mild to moderate intra-ocular inflammation
- Mild corneal edema

All these event will be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalizations unless the condition for which the hospitalization was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalization as part of a standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.

18.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms.

The following minimum information will be recorded for each AE:

- AE description

- start and stop date of the AE

- severity

- seriousness

- causality assessment to the Investigational Medical Device (IMD) and/or study procedures

- outcome

For more information see Appendix A, B and C.

18.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality**[1]**:**

Not related	Relationship to the device or procedures can be excluded when: - the adverse event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the investigational device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the adverse event can be attributed to another cause (e.g., an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment or other risk factors); - the adverse event does not depend on a false result given by the investigational device used for diagnosis, when applicable; - harms to the subject are not clearly due to use error; - in order to establish the non-relatedness, not all the criteria listed above
Unlikely	The relationship with the use of the device seems not relevant and/or the adverse event can be reasonably explained by another cause, but additional information may be obtained.

[1] Guidelines on Medical Devices. Clinical Investigations: Serious Adverse Event Reporting Under Directives 90/385/EEC/and 93/42/EEC; MEDDEV 2.7/3 revision 3; May 2015

Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the adverse event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal relationship	The adverse event is associated with the investigational device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedure; - the event involves a body-site or organ that - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; - the adverse event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); - other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; - in order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures.

18.3.2 Timelines for reporting

- After informed consent has been obtained but prior to first use of the IMD, only adverse events caused by a study specific procedure should be reported
- After first use of the IMD, adverse events will be reported as follows:
    - All AEs, SAEs, AESIs and Device Deficiencies will be reported until 7 days after last use of IMD or until last follow-up visit (whichever occurs first)

All SAEs and AESI as defined in the protocol must be reported to the principal investigator within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

SAE details will be reported by the (sub-)investigator:

- By completing the SAE form in the (e)CRF

If an authorized Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

18.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and until all related queries have been resolved.

SAEs after the end of the trial: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMD or experiment after the subject has ended the trial, the Investigator should report this SAE within the same timelines as for SAEs during the trial.

18.3.4 Death

All deaths (unless defined under section 'Adverse events that do not require reporting' that deaths should not be reported for the trial as SAE) will be reported without delay to the principal investigator (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). The principal investigator will notify all deaths as soon as possible after becoming aware to the Central EC and the EC of the concerned site and provide additional information if requested.

18.4 Recording and reporting of Device Deficiencies

Each Device Deficiency must be documented by the Investigator in the source documents and reported to the Sponsor on a Device Deficiency form (Appendix B).

If the Device Deficiency leads to the occurrence of a (S)ADE, the (S)ADE must also be reported by the Investigator to the Sponsor on the appropriate forms and within the specified timelines.

18.5 Reporting requirements to Ethics Committee's (EC's) and Competent Authorities (CA's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the principal investigator in accordance with instructions provided below.

The principal investigator will promptly evaluate all SAEs, AESIs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, ECs and applicable CA's based on applicable legislation.

18.5.1 Sponsor's reporting of Serious Adverse Events and Device Deficiencies

The sponsor (PI) is responsible to report to the EC's and CA's where the clinical investigation has commenced:

- Any SAE,
- Any Device Deficiency that might have led to a SAE if:
    a) Suitable action had not been taken or,
    b) Intervention had not been made or,
    c) If circumstances had been less fortunate
- New findings/update in relation to already reportable events.

These 'reportable events' must be reported within the following timelines:

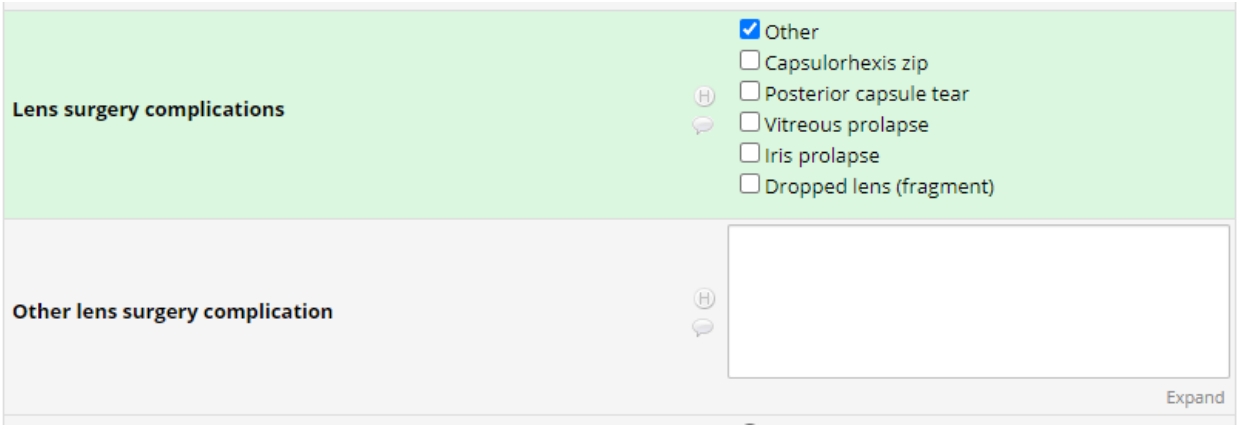
- an SAE which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other patients, users or other persons or a new finding to it must be reported immediately, but not later than **2** calendar days after awareness of a new reportable event or of new information in relation with an already reported event.
- another SAE or a new finding/update to it must be reported immediately, but not later than **7** calendar days following the date of awareness of the new reportable event or of new information in relation with an already reported event.

18.6 Annual reporting

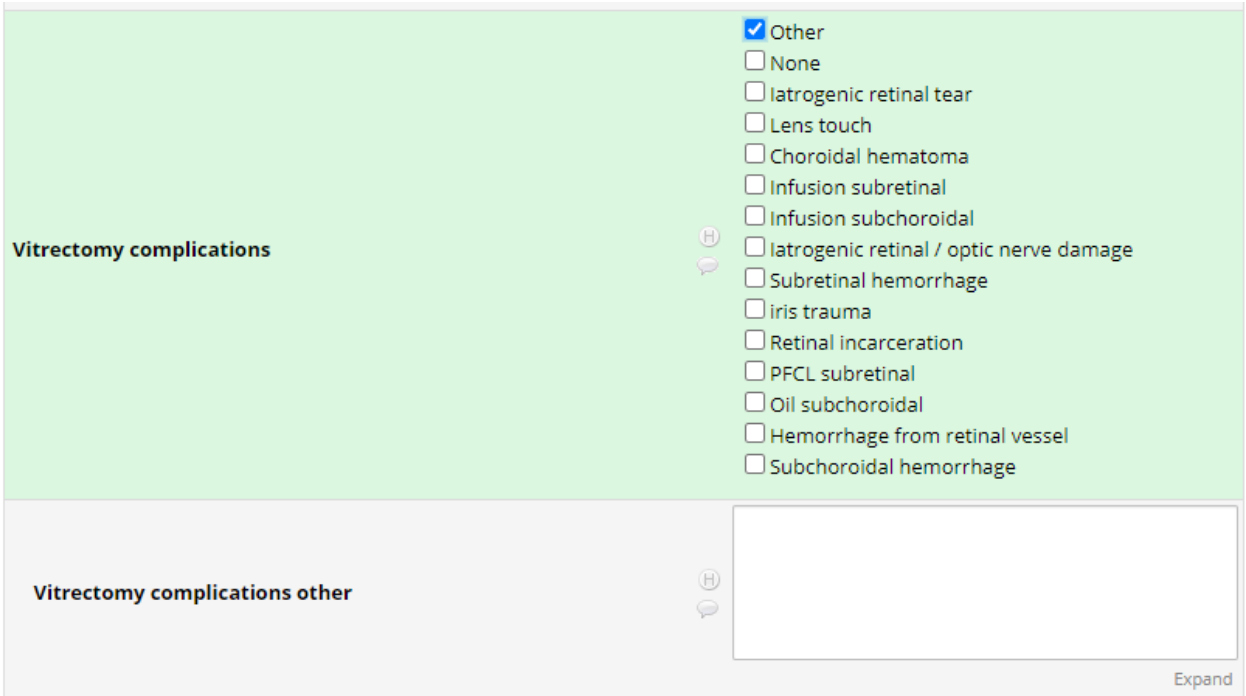
The sponsor (PI) has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's and CA's containing an overview of all SAEs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

Appendix A: List of adverse events in eCRF (source document in Formasa)

- **Anterior segment surgery**



- **Posterior segment surgery**

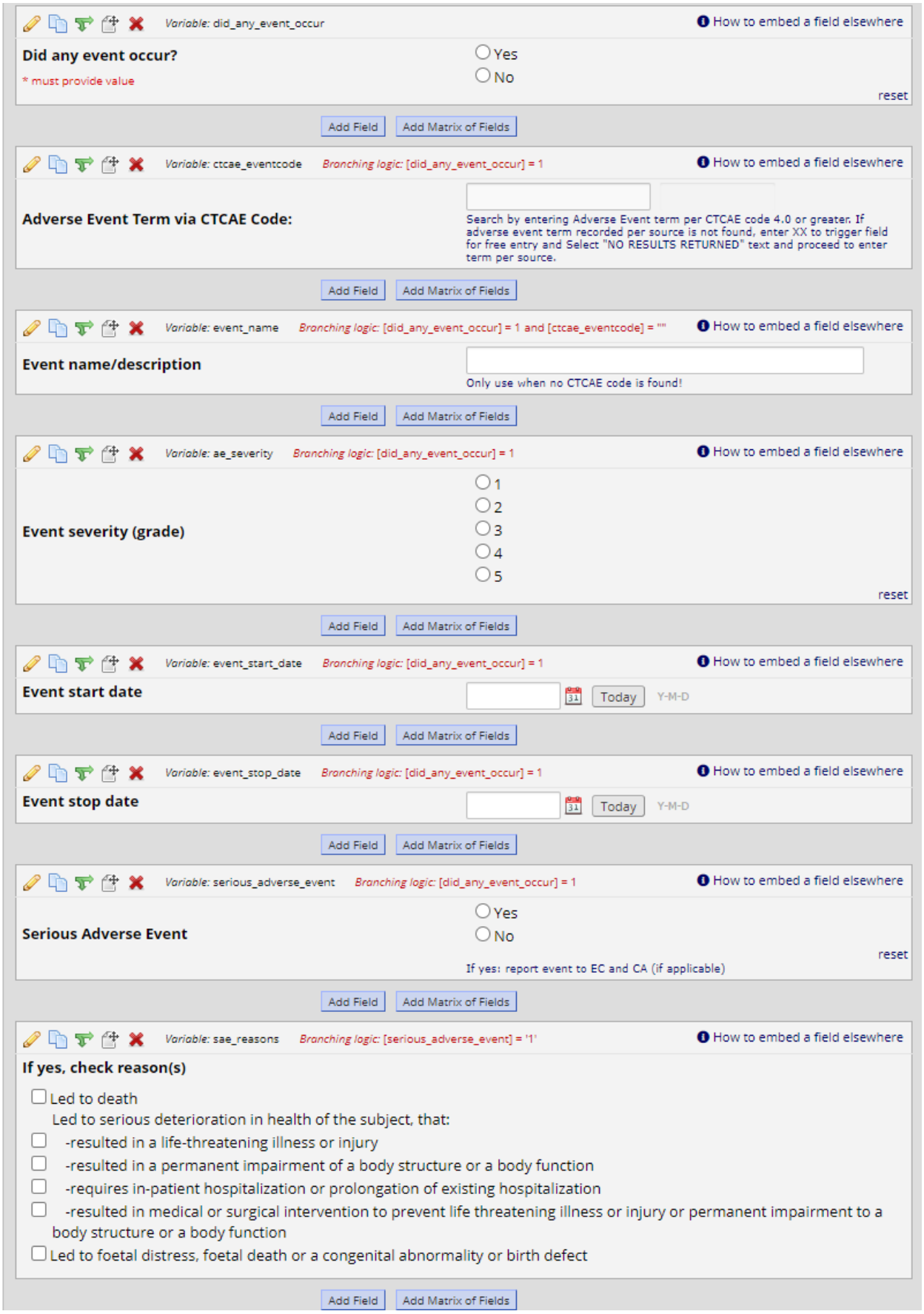


Appendix B: List of device issues not leading to (S)AE recorded in the Formasa surgical report (and in the eCRF)

Device name	DORC EVA Nexus
Device preparation time (HH:MM:SS)	00:04:15
Vitrectomy device problem	◉ Yes ○ No reset
Infusion bottle empty	◉ Yes ○ No reset
Infusion bottle empty detected	◉ Yes ○ No reset
Phaco problem	◉ Yes ○ No reset
Phaco problem description	☐ Phaco needle detached from hand piece ☐ Phaco handpiece delivered insufficient power ☐ Error message phaco during priming
Vitrectome problem	◉ Yes ○ No reset
Vitrectome problem description	☐ Vitrectome did not function / blocked - required replacement ☐ Vitrectome pulled 'wires' on the vitreous ☐ Vitrectome obstructed ☐ Inner mechanism failed during surgery - required replacement
Vacuum problem	◉ Yes ○ No reset
Vacuum problem description	☐ Insufficient vacuum built-up - anterior ☐ Insufficient vacuum built-up - posterior ☐ Vacuum did not stop when needed - anterior ☐ Vacuum did not stop when needed - posterior ☐ Insufficient flow control - anterior ☐ Insufficient flow control - posterior ☐ Leak on aspiration line - air aspiration ☐ Device error message during vacuum built-up ☐ Cassette needed replacement during surgery
Infusion problem	◉ Yes ○ No reset
Infusion problem description	☐ Air bubbles in eye through infusion line ☐ Eye pressure too low - required increased infusion pressure ☐ Eye pressure too high - required lowering of infusion pressure ☐ Infusion stopped ☐ Infusion line detached from irrigation canula ☐ Infusion line detached from phaco handpiece ☐ Infusion hindered by nick in infusion line

Illumination problem	◉ Yes ○ No reset
Illumination problem description	☐ Insufficient amount of light in the eye ☐ Too much light in the eye ☐ Light fiber did not work - required replacement ☐ Inner mechanisme of light fiber failed / detached - required replacement ☐ Uneven output from light fiber ☐ FIber not recognized by device
Laser problem	◉ Yes ○ No reset
Laser problem description	☐ Laser fiber not recognized by device ☐ Insufficient laser output - required fiber replacement ☐ No laser output (no aiming beam) - required fiber replacement ☐ Air bubbles escaping from tip laser fiber ☐ Sliding mechanism of fiber failed ☐ Inner mechanism of fiber failed - rotated inside the shaft
Viscous fluid problem	◉ Yes ○ No reset
Viscous fluid problem description	☐ Insuffucient vacuum built-up ☐ Leak on the VFI line ☐ Injection canula detached from VFI syringe ☐ Aspiration canula detached from VFI syringe ☐ Oil syringe broken ☐ Attachment on oil syringe detached
Diathermy problem	◉ Yes ○ No reset
Diathermy problem description	☐ Diathermy failure - cable required replacement ☐ Diathermy failure - probe required replacement ☐ Insufficient power output from diathermy ☐ Fluctuations in power output from diathermy
General device issues	◉ Yes ○ No reset
General device issues description	☐ Device did not boot up correctly, required restarting ☐ Problem during priming cycle, required repeat priming

Appendix C: (S)AE Report form in eCRF (source document in Formasa)



Variable: date_of_death_sae Branching logic: [sae_reasons(1)] = 1 How to embed a field elsewhere

Date of Death (D-M-Y) Today D-M-Y

Add Field Add Matrix of Fields

Variable: event_date_of_hospitalization Branching logic: [sae_reasons(4)] = '1' How to embed a field elsewhere

Date of hospitalization Today Y-M-D

Add Field Add Matrix of Fields

Variable: event_date_of_discharge Branching logic: [sae_reasons(4)] = '1' How to embed a field elsewhere

Date of discharge Today Y-M-D

Add Field Add Matrix of Fields

Variable: name_of_device Branching logic: [did_any_event_occur] = 1 How to embed a field elsewhere

Name of study device

Add Field Add Matrix of Fields

Variable: event_device_related Branching logic: [did_any_event_occur] = 1 How to embed a field elsewhere

Was the event device related?

- ○ Not related
- ○ Unlikely
- ○ Possibly
- ○ Probably
- ○ Definitely

reset

Add Field Add Matrix of Fields

Variable: event_procedure_related Branching logic: [did_any_event_occur] = 1 How to embed a field elsewhere

Was the event study-procedure related?

- ○ Yes
- ○ No
- ○ Not applicable

reset

Add Field Add Matrix of Fields

Variable: name_of_procedure_ae Branching logic: [event_procedure_related] = 1 How to embed a field elsewhere

Name of study procedure

A study-specific procedure, performed outside the standard of care

Add Field Add Matrix of Fields

Variable: event_action_taken Branching logic: [did_any_event_occur] = 1 How to embed a field elsewhere

Was any action taken?

- ☐ None
- ☐ Medication
- ☐ Non-drug therapy
- ☐ Surgery/Procedure
- ☐ Hospitalization
- ☐ Stop study due to AE
- ☐ Further investigation / other

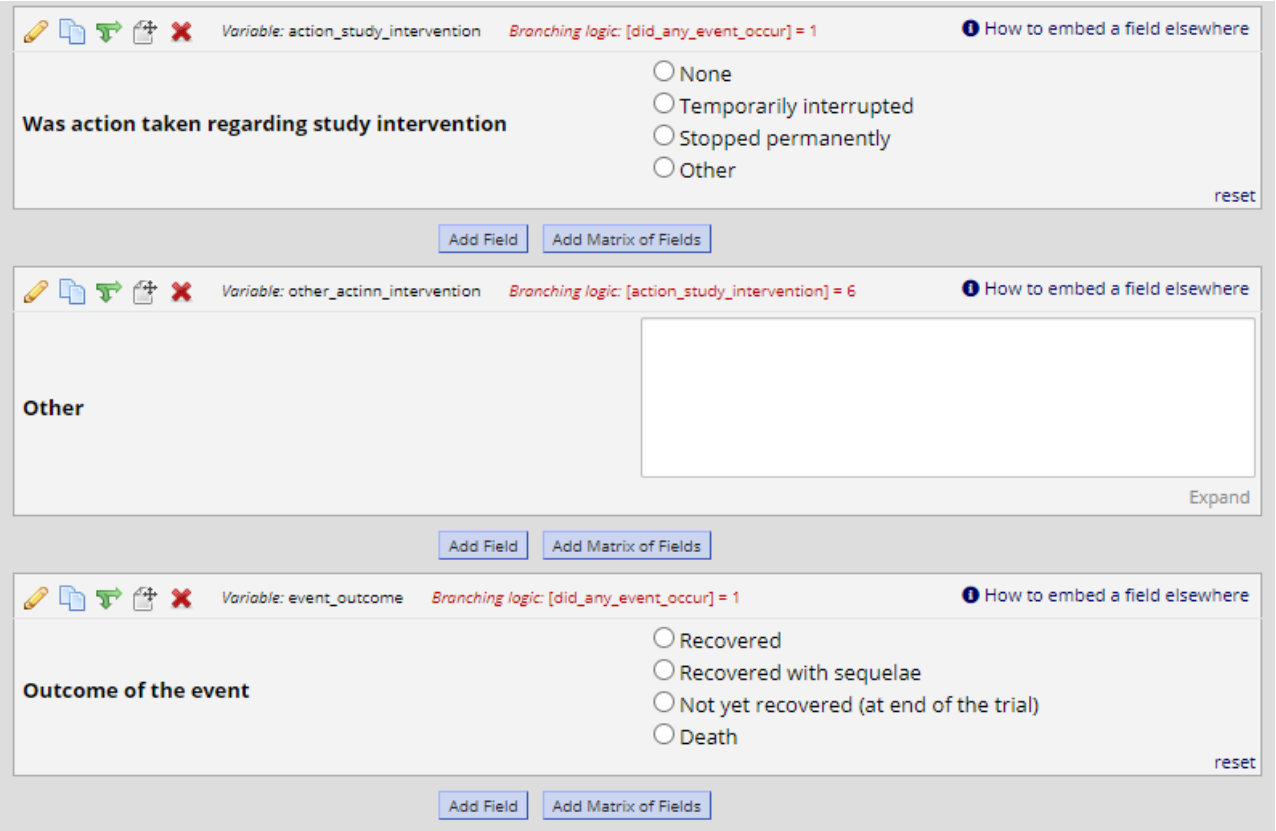
Check all that apply

Add Field Add Matrix of Fields

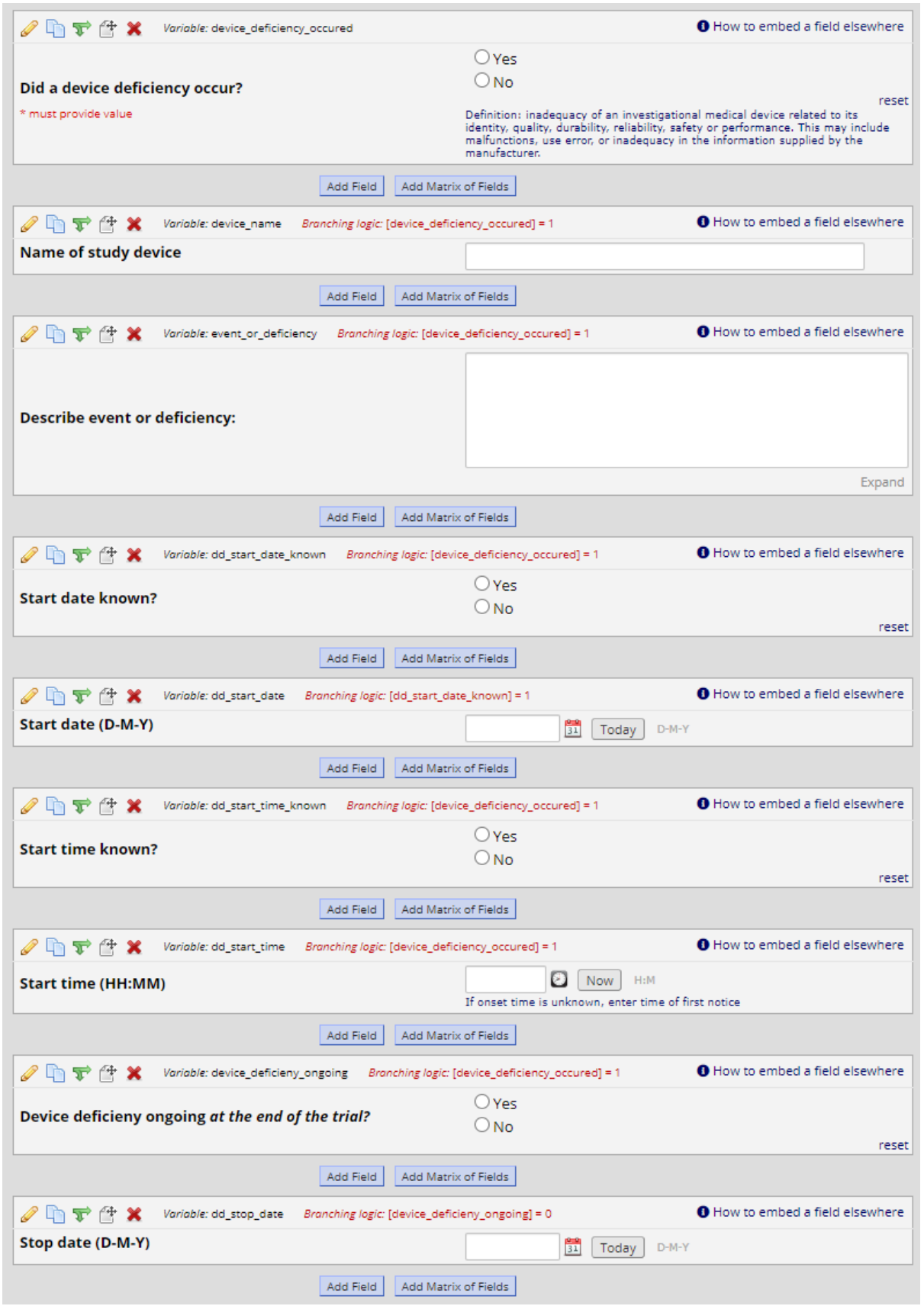
Variable: event_other_action Branching logic: [event_action_taken(7)] = '1' How to embed a field elsewhere

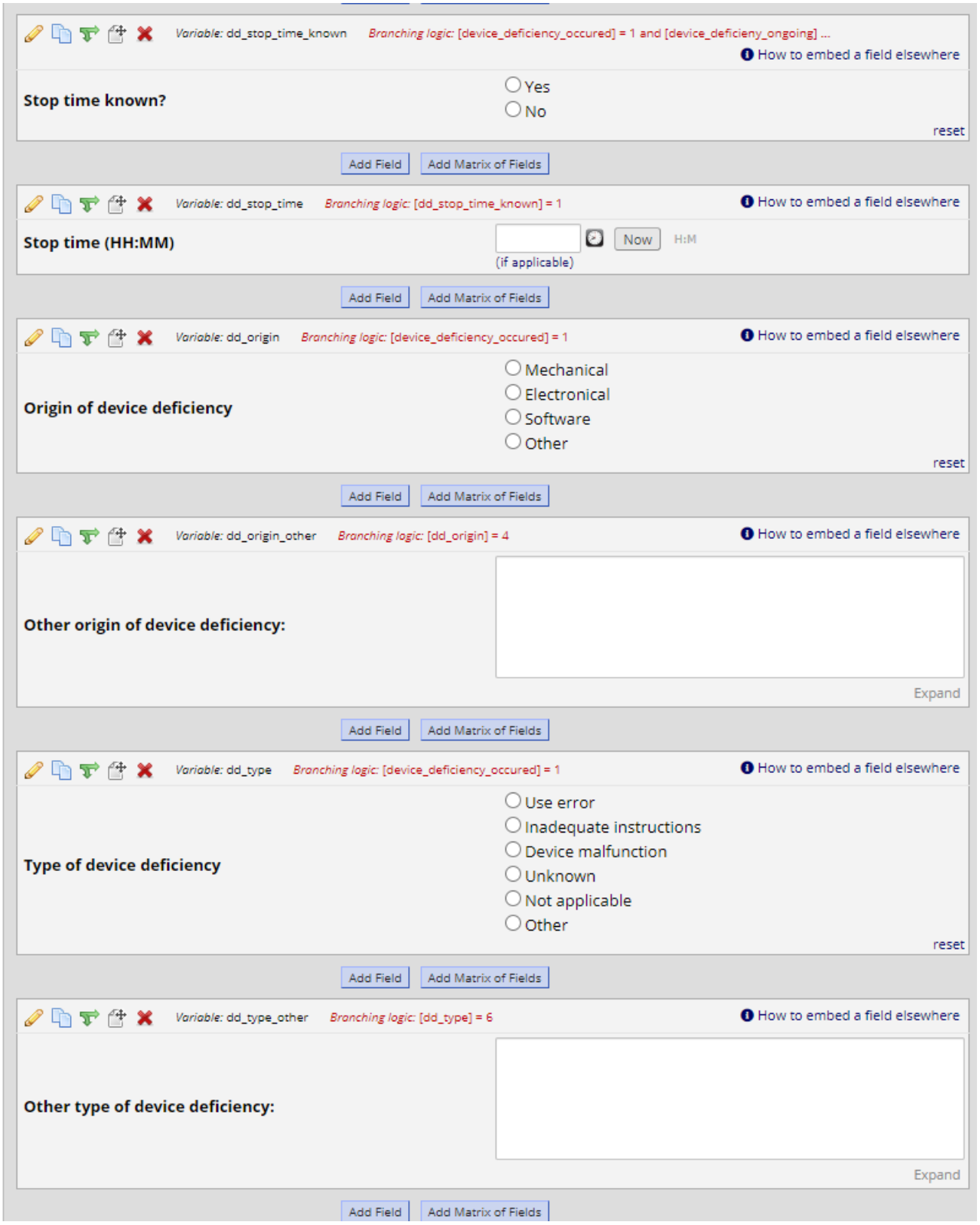
Specify further investigation or other:

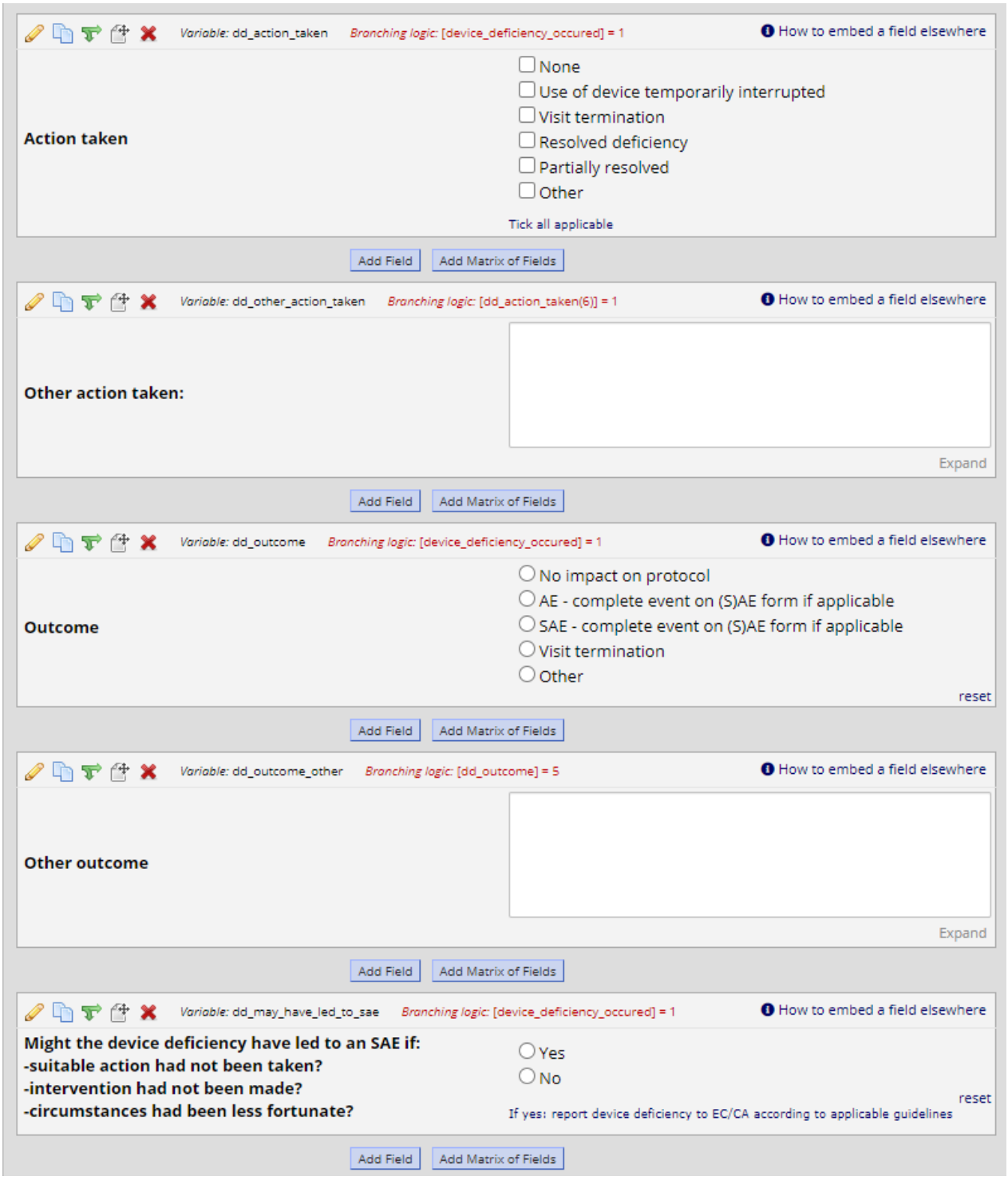
Add Field Add Matrix of Fields


Variable: action_study_intervention
Branching logic: [did_any_event_occur] = 1
How to embed a field elsewhere
Was action taken regarding study intervention
None
Temporarily interrupted
Stopped permanently
Other
reset
Add Field
Add Matrix of Fields
Variable: other_actinn_intervention
Branching logic: [action_study_intervention] = 6
How to embed a field elsewhere
Other
Expand
Add Field
Add Matrix of Fields
Variable: event_outcome
Branching logic: [did_any_event_occur] = 1
How to embed a field elsewhere
Outcome of the event
Recovered
Recovered with sequelae
Not yet recovered (at end of the trial)
Death
reset
Add Field
Add Matrix of Fields

Appendix D: Device deficiency report form in eCRF (source document in Formasa)




Variable: dd_stop_time_known
Branching logic: [device_deficiency_occured] = 1 and [device_deficieny_ongoing] ...
How to embed a field elsewhere
Stop time known?
Yes
No
reset
Add Field
Add Matrix of Fields
Variable: dd_stop_time
Branching logic: [dd_stop_time_known] = 1
How to embed a field elsewhere
Stop time (HH:MM)
Now
H:M
(if applicable)
Add Field
Add Matrix of Fields
Variable: dd_origin
Branching logic: [device_deficiency_occured] = 1
How to embed a field elsewhere
Origin of device deficiency
Mechanical
Electronical
Software
Other
reset
Add Field
Add Matrix of Fields
Variable: dd_origin_other
Branching logic: [dd_origin] = 4
How to embed a field elsewhere
Other origin of device deficiency:
Expand
Add Field
Add Matrix of Fields
Variable: dd_type
Branching logic: [device_deficiency_occured] = 1
How to embed a field elsewhere
Type of device deficiency
Use error
Inadequate instructions
Device malfunction
Unknown
Not applicable
Other
reset
Add Field
Add Matrix of Fields
Variable: dd_type_other
Branching logic: [dd_type] = 6
How to embed a field elsewhere
Other type of device deficiency:
Expand
Add Field
Add Matrix of Fields


Variable: dd_action_taken
Branching logic: [device_deficiency_occured] = 1
How to embed a field elsewhere
Action taken
None
Use of device temporarily interrupted
Visit termination
Resolved deficiency
Partially resolved
Other
Tick all applicable
Add Field
Add Matrix of Fields
Variable: dd_other_action_taken
Branching logic: [dd_action_taken(6)] = 1
How to embed a field elsewhere
Other action taken:
Expand
Add Field
Add Matrix of Fields
Variable: dd_outcome
Branching logic: [device_deficiency_occured] = 1
How to embed a field elsewhere
Outcome
No impact on protocol
AE - complete event on (S)AE form if applicable
SAE - complete event on (S)AE form if applicable
Visit termination
Other
reset
Add Field
Add Matrix of Fields
Variable: dd_outcome_other
Branching logic: [dd_outcome] = 5
How to embed a field elsewhere
Other outcome
Expand
Add Field
Add Matrix of Fields
Variable: dd_may_have_led_to_sae
Branching logic: [device_deficiency_occured] = 1
How to embed a field elsewhere
Might the device deficiency have led to an SAE if:
-suitable action had not been taken?
-intervention had not been made?
-circumstances had been less fortunate?
Yes
No
reset
If yes: report device deficiency to EC/CA according to applicable guidelines
Add Field
Add Matrix of Fields