Gas for Vitreomacular Traction RCT (Protocol AG)
Gas for Macular Hole Single-Arm Study (Protocol AH)

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute

NIH National Eye Institute

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Protocol AG

Randomized Clinical Trial Assessing the Effects of Pneumatic Vitreolysis on Vitreomacular Traction

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Background

- Treatment options for VMT include **observation**, intraocular injection of **ocriplasmin,** and **vitrectomy.**
  - **Observation:** VMT may spontaneously resolve
    - Multiple reports (**30-40%** given sufficient waiting period, but unpredictable, prolonged)
  - **Ocriplasmin:** reports of ocular complications
    - **26 to 48%** success; high cost; anecdotal reports of complications (vision loss, ERG changes, photoreceptor/zonule dehiscence, dyschromatopsia)
  - **Vitrectomy:** costly and includes usual risks of surgery
    - **>90%** success, invasive, high cost

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Background

- 1.5% of the population is estimated to have eye diseases caused by or associated with vitreomacular adhesion[1]
- Pneumatic vitreolysis (PVL) may serve as an alternative
  - Lower cost
  - In-office setting (no scheduling or coordinating issues associated with surgery)
  - Case series (1995 to 2017) have reported:
    - 56-85% success rate of VMT release
    - Low rate of adverse events

1. Karth, PA, Shah SA. Vitreomacular traction syndrome. http://eyewiki.aao.org/Vitreomacular_Traction_Syndrome. Oct 17, 2015

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Public Health Impact

- Retrospective data alone (with all the confounding variables) are unable to provide sufficient information to guide management options
- If level-one evidence is achieved in favor of PVL, it can lead to a change in practice pattern on management of VMT not only in the US, but also on the global stage
- Such a paradigm shift in management of VMT could have major implications on medical economics and cost savings

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Study Objective

- Primary
  - To compare the proportion of eyes with foveal VMT (symptomatic VMA) release on OCT after PVL with gas injection vs. observation (sham injection) in eyes with VMT without an associated macular hole
- Secondary
  - To evaluate visual function outcomes at 24 weeks after gas injection is performed compared with observation.

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Study Design

Multi-Center Randomized Clinical Trial
(124 Eyes)

At least 1 eye that meets all of the following criteria:

- Vitreomacular adhesion on OCT ≤3,000 µm
  - Reading center confirmation required for eligibility
- Best corrected ETDRS visual acuity equivalent of 20/32 to 20/400
- Decreased visual function attributed to VMT
- No macular or lamellar hole
- Prompt Vitrectomy not required

PVL
(Injection of C3F8 gas)

Observation (Sham injection)

Primary Outcome: Proportion of eyes with VMT release on OCT without rescue vitrectomy at 24 weeks

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Major Patient Eligibility Criteria

- Able and willing to avoid high altitude travel, including airline travel, until gas resolution (~6-8 weeks)
- Able and willing to avoid supine position until gas resolution for phakic patients
- Able and willing to wear a wristband that informs any medical personnel that the patient has a gas bubble in the eye

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Major Ocular Eligibility Criteria

- Investigator and participant willing to wait 6 months before surgical intervention if visual acuity remains stable (unless complications; e.g. macular hole development, retinal tears or detachment)
- Exclusions:
  - History of prior gas injection, ocriplasmin injection, or intraocular injection for any reason
  - Prior vitrectomy
  - High level of myopia
  - History of uncontrolled glaucoma
  - IOP ≥ 30 mmHg

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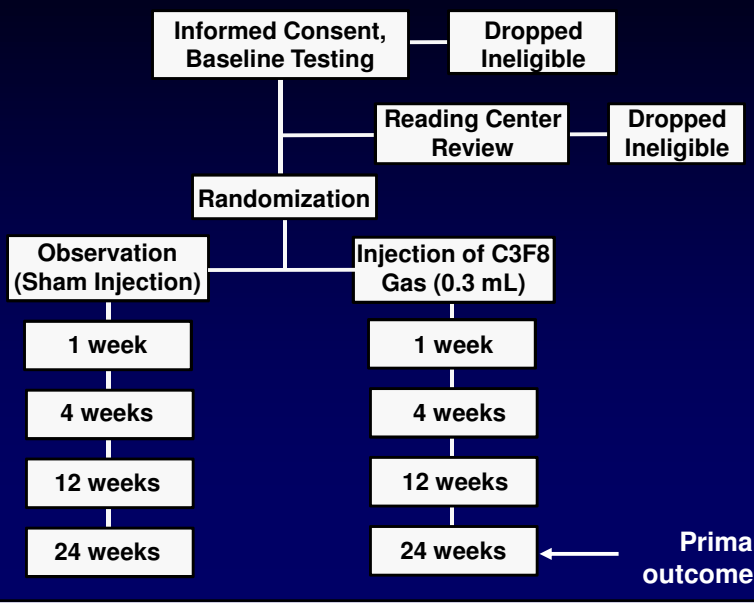
Study Design



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Baseline Testing Procedures

1. The following will be performed on both eyes
   - E-ETDRS visual acuity
   - Visual function testing (myVisionTrack)
   - OCT
   - Eye exam
2. Reading Center will review OCT scans to confirm eligibility
   - Same day RC review will be available if required but should be limited to cases when scheduling a separate randomization day is difficult
3. Eligible eyes may then be randomized (must be within 8 days of baseline testing)

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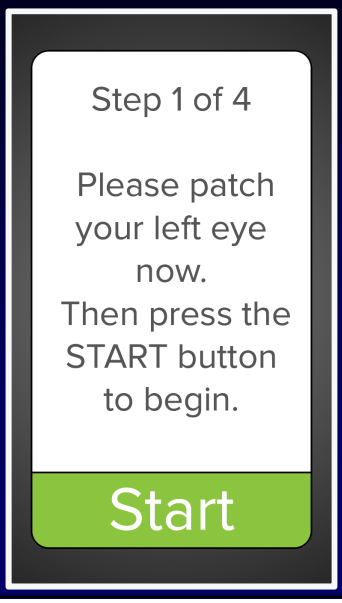
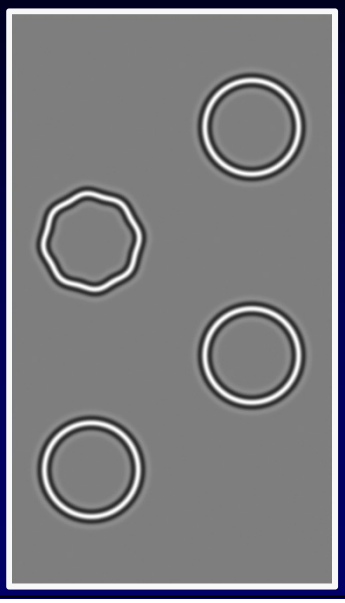
myVisionTrack





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Process of Reading Center Confirmation

- The Reading Center must confirm study eye eligibility on OCT
- For same day grading, OCT scans must be uploaded by 2 pm Eastern
- Otherwise, the participant will need to return on a separate day for randomization (RCT only) and the injection

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Follow-Up Testing Procedures

- E-ETDRS visual acuity
- Visual function testing (myVisionTrack)
  - 12 and 24 weeks only
- OCT
  - study eye only
- Eye exam
  - study eye only

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Criteria for Rescue Vitrectomy

- For study eyes in both treatment groups, vitrectomy may be performed if one of the following occurs:
  1. Visual acuity decreases at least 10 letters at a single visit (not including the 1-week visit) or at least 5 letters at two consecutive visits (not including the 1-week visit) compared with baseline that is thought to be related to VMT
  2. Complication requires prompt surgical intervention (e.g., macular hole, retinal detachment, non-clearing vitreous hemorrhage).
- Otherwise, protocol chair approval must be obtained for alternative treatment.

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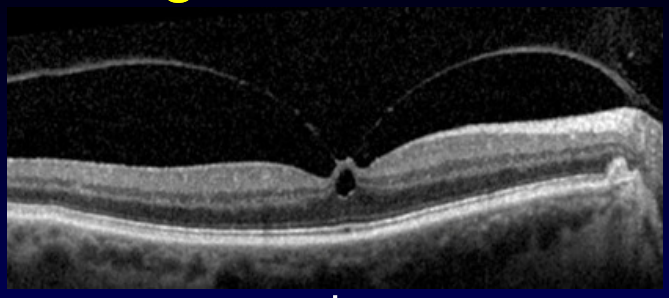
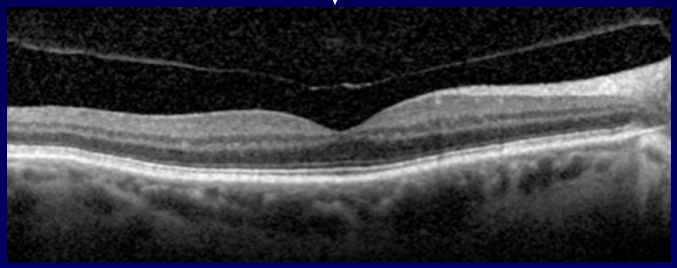
Example of a good candidate for AG (RCT)



PVL



- "Eagle sign"

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Protocol AH

Single-Arm Study Assessing the Effects of Pneumatic Vitreolysis on Macular Hole

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Background

- PVL for Macular Hole (MH) offers a lower cost, low risk alternative to Vitrectomy
- Understanding the rates of MH closure and VMT release in eyes with full-thickness macular holes treated with PVL is of interest given the low cost and convenience of gas injection in the office setting as well as a low rate of adverse events reported in prior retrospective studies

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Prior case series of PVL for Macular Hole

- Chan (1995)
  - Closure of stage-2 MH: 50% (N = 6)
- Jorge et al
  - Closure of stage-2 MH: 83% (N = 6)
- Steinle et al
  - Closure of full-thickness MH: 67% (N = 3)
- Chan and Mein (Retina, 2017)
  - Closure stage-2 MH: 67% with single injection (N = 15)

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Rationale for Single-Arm Study

- Eyes with MH need treatment, therefore randomization to a sham arm would be inappropriate
- Vitrectomy results in nearly 100% hole closure making it an unnecessary (and expensive) control group choice
- Even if this proposed study finds that PVL is only moderately successful, physicians and patients may decide to attempt PVL in the office first, before proceeding with more costly, invasive surgery
- Thus, even without a control group, the results from this study will provide data of value for physicians and patients to make informed decisions about treatment course

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Public Health Impact

- If a large percentage of eyes can achieve MH closure with a simple in-office, low-cost procedure, while averting the invasiveness and expense of a vitrectomy for this condition, this would provide a viable first-line treatment option

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Study Objective

- To obtain estimates for the proportion of eyes with macular hole closure of the inner retinal layers for eyes with VMT and full-thickness macular holes treated with PVL

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Study Design

Multi-Center Single-Arm Study
(50 Eyes)

At least 1 eye that meets all of the following criteria:

- Full-thickness macular hole ≤250 microns at the narrowest point, confirmed by central reading center
- Vitreomacular adhesion on OCT ≤3,000 microns, confirmed by central reading center
- Best corrected ETDRS visual acuity equivalent of 20/25 to 20/400

↓

PVL (Injection of C3F8 gas)

↓

Primary Outcome: Proportion of eyes with macular hole closure of the inner retinal layers at 8 weeks without rescue treatment

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Major Patient Eligibility Criteria

- Able and willing to avoid high altitude travel, including airline travel, until gas resolution (~6-8 weeks)
- Able and willing to avoid supine position until gas resolution for phakic patients
- Able and willing to wear a wristband that informs any medical personnel that the patient has a gas bubble in the eye
- Able and willing to position face down for at least 50% of the time for at least 4 days post-injection to facilitate macular hole closure

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Major Ocular Eligibility Criteria

- **Exclusions:**
  - History of prior gas injection, ocriplasmin injection, or intraocular injection for any reason
  - Prior vitrectomy
  - High level of myopia
  - History of uncontrolled glaucoma
  - IOP ≥ 30 mmHg

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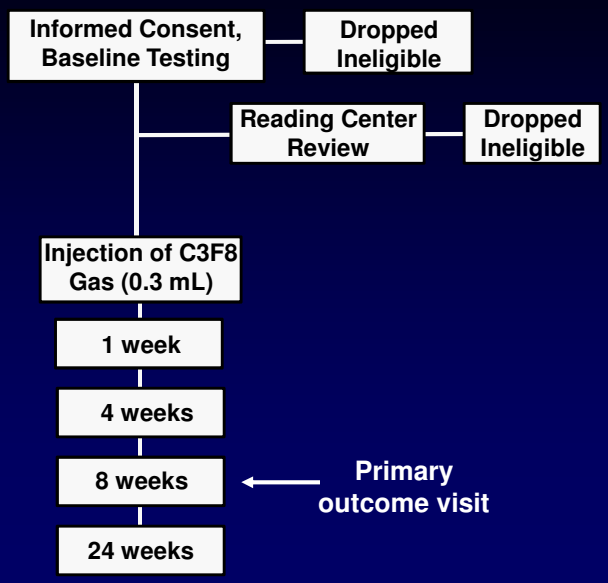
Study Design



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Baseline Testing Procedures

1. The following will be performed on both eyes
   - E-ETDRS visual acuity
   - OCT
   - Eye exam
2. Reading Center will review OCT scans to confirm eligibility
   - Same process as Protocol AG regarding Reading Center confirmation of study eye eligibility
3. Eligible eyes may then receive gas injection (must be within 8 days of baseline testing)

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Follow-Up Testing Procedures

- E-ETDRS visual acuity
- OCT
  - study eye only
- Eye exam
  - study eye only

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Criteria for Rescue Vitrectomy

- Vitrectomy should not be performed due to failure of macular hole closure prior to 4 weeks without protocol chair approval
- Between 4 and 8 weeks, vitrectomy may only be performed (but is not required) if the macular hole size is not improving from baseline
- After 8 weeks, vitrectomy can be performed at investigator discretion.

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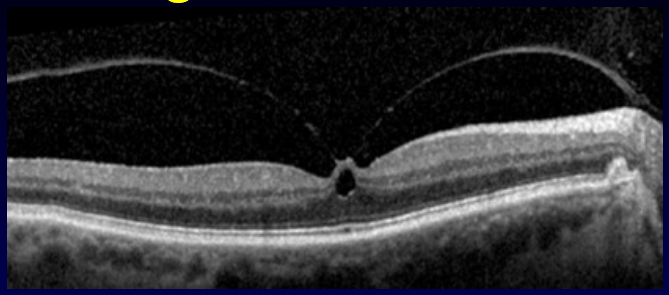
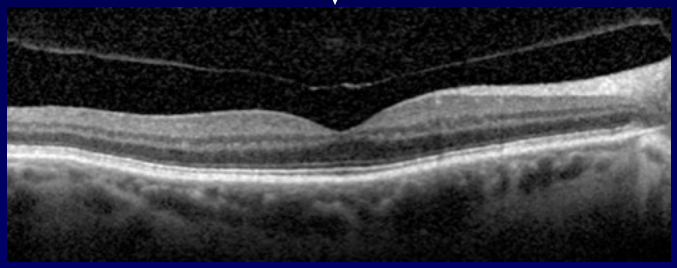
Example of a good candidate for AG (RCT)



PVL



- "Eagle sign"

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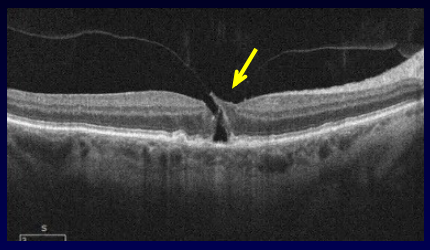
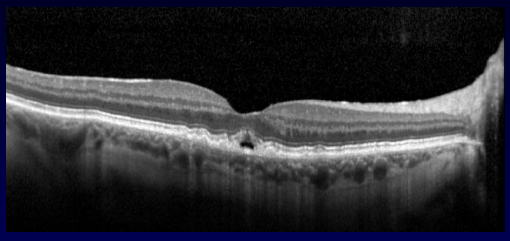
Example of good candidate for AH (single-arm)

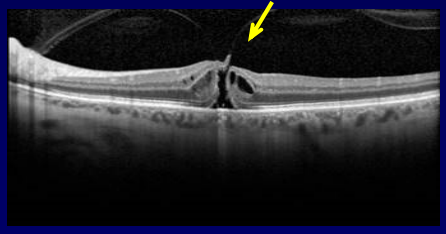
- Case 1



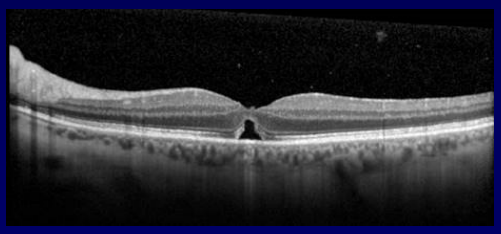
PVL



- Case 2



PVL



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Procedures for Both Studies

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C3F8 Perfluoropropane

- Commercially available C3F8 (Alcon or Sonomed Escalon) delivered from a pressurized canister and passed through a Millipore filter for injection into the vitreous cavity
- FDA approved as a surgical aid for use in the treatment of retinal detachment by pneumatic retinopexy
- Diffuses from the eye in ~6-8 weeks
- Nitrous Oxide should not be administered when a gas bubble is present in the eye
- Increase in elevation may cause elevated IOP
- Proper head positioning is required for phakic patients and patients with a macular hole

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Injection Procedure

- For the RCT, the injection must be given on the day of randomization
- ***Two individuals*** must confirm the study eye and treatment assignment against the printout or website
- Injection preparation
  - Apply topical anesthetic (solution or gel)
  - Place a lid speculum
  - Apply povidone iodine
  - Pre- and post-injection topical antibiotics should NOT be used without prior approval from the Protocol Chair or Coordinating Center designee

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Injection Procedure: PVL

- Confirm the C3F8 supply has not expired
- Prepare the C3F8 in agreement with manufacturer requirements (detailed in Gas Injection Procedures)
- The injection may be performed supratemporal, infratemporal, or infranasal at the discretion of the investigator
  - The position of the needle tip should be monitored by an assistant during the process
- Inject 0.3 mL C_3F_8 into the vitreous
- Immediately block the injection site with a sterile cotton tipped applicator, and rotate the study participant's head away from the injection site to avoid bubble leakage

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Injection Procedure: Observation
(RCT Only)

- Use a syringe <u>without</u> a needle
- Apply syringe hub to the conjunctival surface, pressing gently to stimulate the force of an actual injection

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Post-Injection

- Assess for any complications via either an indirect ophthalmoscopy or a vision check to confirm perception of vision
- Review and provide the post-injection subject instruction sheet
- Participants in Protocol AH (single-arm study) are automatically unmasked
- PVL participants in Protocol AG (RCT) may be unmasked to their treatment group since the gas bubble will be visible
- For the RCT, sham injection participants must remain masked and should be given the same post-injection instructions as the PVL group

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Post-Injection Subject Instructions

INSTRUCTIONS FOR CARE AFTER AN EYE INJECTION

1. Do not rub your eye or swim for one day after the injection.
2. If you have discomfort or headache after the injection, you may take any over the counter medication you normally take in such situations, such as acetaminophen (Tylenol), ibuprofen (Advil), or naproxen (Aleve).
3. Many patients experience some blurring of vision following an eye injection. Sometimes the blurring is described as seeing spots floating in the eye ("floaters"). The gas bubble will be visible for several weeks and may at times block vision. You may also have a temporary loss of depth perception. The gas bubble typically goes away after 6 to 8 weeks, but some floaters may persist.
4. You may have mild discomfort or itching in the eye for a few days after the injection. You may have a red spot at the site of the injection, which will go away over time.
5. **If you experience increased eye discomfort or pain (compared to right after the injection), significant decreased vision, flashes of light, numerous new black floaters beyond those seen immediately after the injection, a "curtain" or shadow of darkness moving from the side to the center of the vision, increased eye redness, discharge from the eye, increased sensitivity to light, fever, or other unexpected symptoms, contact us immediately.**

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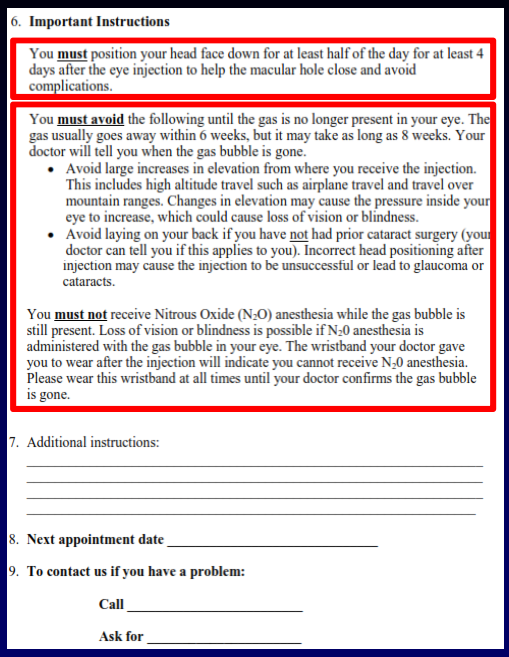
Single-arm study only →

Both studies →



6. **Important Instructions**

You **must** position your head face down for at least half of the day for at least 4 days after the eye injection to help the macular hole close and avoid complications.

You **must avoid** the following until the gas is no longer present in your eye. The gas usually goes away within 6 weeks, but it may take as long as 8 weeks. Your doctor will tell you when the gas bubble is gone.

- Avoid large increases in elevation from where you receive the injection. This includes high altitude travel such as airplane travel and travel over mountain ranges. Changes in elevation may cause the pressure inside your eye to increase, which could cause loss of vision or blindness.
- Avoid laying on your back if you have not had prior cataract surgery (your doctor can tell you if this applies to you). Incorrect head positioning after injection may cause the injection to be unsuccessful or lead to glaucoma or cataracts.

You **must not** receive Nitrous Oxide (N_2O) anesthesia while the gas bubble is still present. Loss of vision or blindness is possible if N_20 anesthesia is administered with the gas bubble in your eye. The wristband your doctor gave you to wear after the injection will indicate you cannot receive N_20 anesthesia. Please wear this wristband at all times until your doctor confirms the gas bubble is gone.

7. Additional instructions:

_____
_____
_____
_____

8. **Next appointment date** _____

9. **To contact us if you have a problem:**

Call _____

Ask for _____

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Optional Paracentesis for PVL Eyes

- Pre-injection paracentesis should be considered due to the 4x expansion of C_3F_8 gas and the associated risk of shallowing of the anterior chamber
- However, the choice of when or whether or not to do a paracentesis is ultimately at the investigator's discretion

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Aqueous Sample Collection

- It is expected that sites with the capability to ship intraocular fluids will participate, though not a requirement
- Participants will consent to the optional sample collection separately from the main study consent
- If paracentesis is performed and participant consent is obtained, aqueous fluid already being drawn as part of paracentesis may be collected and shipped on dry ice to a central laboratory for storage for future analyses

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Reporting of Adverse Events

- Unlike prior DRCR.net studies, not all adverse events will be collected
- Reportable Adverse Events include:
  - An ocular adverse event in the study eye
  - A serious adverse event
  - An adverse device effect (AE that may have been caused by the gas)
  - An adverse event occurring in association with a study procedure

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DRCR.net Website

- Like all DRCR.net trials, the website will help guide you though each visit, including:
  - Assessing eligibility
  - Rescue vitrectomy criteria
  - Visit schedule

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Certification

- Both studies are expected to start in October 2018
- C3F8 is considered a device, thus both studies are considered IDE studies
  - The FDA has approved the use of C3F8 in both studies
- Any U.S. site that believes they can enroll at least 3 participants (2 for RCT, 1 for Single-Arm study) are invited to indicate interest on the DRCR website.
  - 51 sites have indicated interest so far
  - It is expected sites will participate in the single-arm study as well
- Be on the lookout for certification materials following expressing interest
- <u>All sites must use the Jaeb IRB</u>
  - Please contact Jaeb IRB to begin reliance agreement if needed

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Certification Requirements

- Protocol acknowledgement form
- Delegation log
- C3F8 Form
- Injection experience form
- IDE investigator agreement
  - Required by the FDA for IDE studies
  - All coordinators must be included on the form
  - Needs to be signed ASAP so FDA can approve site participation in study
- Masked OCT technician, VA tester, and refractionist for (RCT only)
- Aqueous sampling certification form
- Ipad or Tablet for myVisionTrack (RCT only)

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Thank You

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