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**Ophthalmology Network**

**South Australian Institute of Ophthalmology**

# PROTOCOL

## The Effect of Near-infrared Laser on Contrast Sensitivity in Human Glaucoma: a prospective, randomized, double-masked pilot study (NIRG TRIAL)

### INVESTIGATOR DETAILS AND QUALIFICATIONS

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## 3. PURPOSE OF STUDY

To conduct a prospective, randomized, double-masked pilot study testing the hypothesis that near-infrared (NIR) laser acts as a neurorecoverant and improves contrast sensitivity in glaucoma patients.

This is a pilot study designed to provide motivation (or not) to proceed to further research. It would be inappropriate to proceed without a pilot study of this nature.

Our particular research focus is on neuroprotection for glaucoma. Glaucoma is a chronic intraocular pressure (IOP)-sensitive optic neuropathy[1] and the most common cause of irreversible blindness worldwide. Clinically, it is characterized by typical degeneration of the optic nerve as it exits the eye and associated visual field defects, routinely measured using computerized automated perimetry. More subtle aspects of vision, including contrast sensitivity are also affected.

In the broadest sense, *neuroprotection refers to the capacity to prevent or limit neuronal injury*, and in the context of glaucoma, refers to the preservation and protection of threatened retinal ganglion cells (RGCs; Fig. 1). Currently, the only treatment strategy for glaucoma is to lower the intraocular pressure (IOP), a form of indirect neuroprotection. Although this strategy is moderately successful, some patients continue to progress despite best efforts at IOP control, either because IOP reduction is an incomplete strategy in these patients or the "true" target IOP is not reached; hence, an alternative neuroprotective strategy is highly clinically desirable.

Fig.1

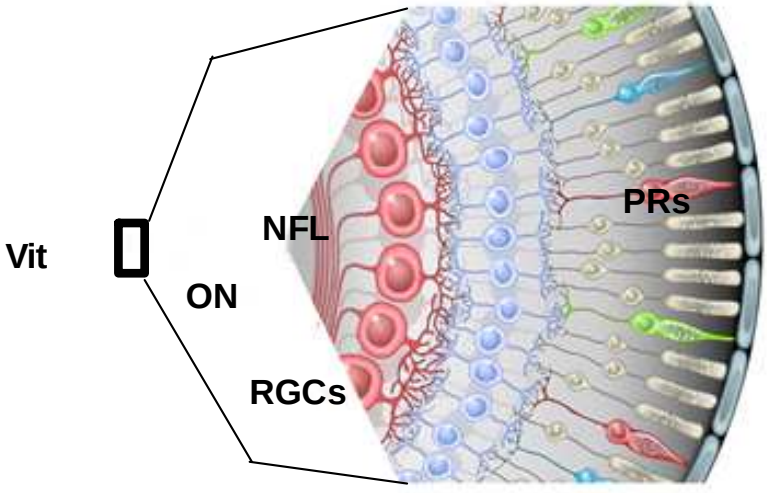



***Fig. 1*** *In glaucoma, the retinal ganglion cells (RGCs) degenerate. Their axons in the retina comprise the nerve fibre layer (NFL) and become the optic nerve (ON). Loss of RGCs eventually results in loss of vision. Currently, the only treatment strategy is reduction of the intraocular pressure by medication, laser, or surgery. PR = photoreceptor; Vit = vitreous*

## 4. BACKGROUND AND PRELIMINARY STUDIES

Although there is a plethora of laboratory evidence demonstrating pharmacological neuroprotection in experimental glaucoma, this has not been translated to the clinic. There are several reasons for this: (1) demonstrating progression of chronic glaucoma is expensive and time consuming; (2) laboratory outcome measurements e.g. RGC counts, do not have clinical correlates; (3) the efficacy of the neuroprotectant may be modest, making signal to noise ratios in the analyses small (4) animal models may not reflect the human condition; (5) a neuroprotectant may be effective in one subtype of glaucoma but not another. In my opinion, further long-term randomized controlled trials (RCTs), without initial supportive human data, would be ill-considered.

A recent Cochrane review on neuroprotection in glaucoma reported: "Further clinical research is needed to determine whether neuroprotective agents may be beneficial for individuals with OAG". [2] Although no large scale RCT data on glaucoma neuroprotection has been published, several small RCTs have actually reported non-IOP related, pharmacologically-induced improvement in visual function in glaucoma patients.[3] [4] One of these studies, by Bose et al.,[3] measured an improvement in contrast sensitivity (CS) in glaucoma patients over a short time frame.

CS is well known to be affected by glaucoma,[5] and is one of the strongest correlates of vision-related quality of life.[6] Although not routinely tested, it can be measured with a simple, rapid, non-invasive, inexpensive clinical test.

We have recently demonstrated the success of this strategy by showing that topical glucose can temporarily improve contrast sensitivity in individuals affected by glaucoma.[7] This result was exciting and demonstrates a proof of principle of this methodology. In this study, we will trial a novel light therapy on the retina in an attempt to recover vision in a more sustainable fashion. The light therapy that we will administer is a form of NIR laser delivered by a slit lamp. It is the same laser that is currently being trialed in individuals with diabetic eye disease (NCT02181400)

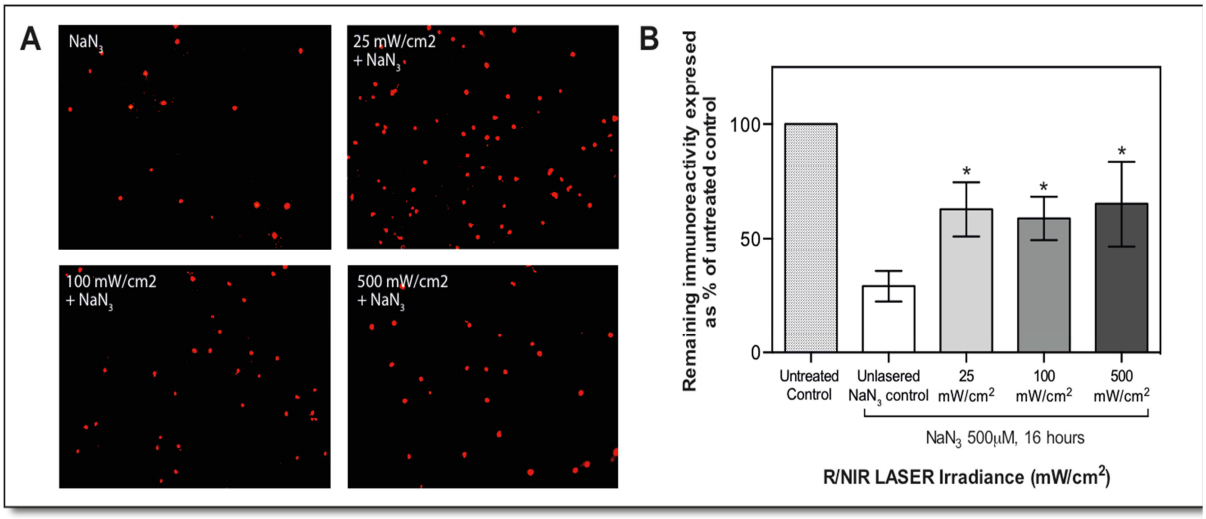
### Near Infrared Light Therapy

Near-infrared (NIR) light at power densities a hundred times lower than conventional thermal treatments have been shown in animal models to promote the healing of injured cells, including blood vessels and neurons in the retina. Studies indicate that NIR treatment augments cellular energy metabolism, enhances mitochondrial function, increases cytochrome C oxidase activity, stimulates antioxidant protective pathways and promotes cell survival.

We have laboratory based data to indicate that the laser can also improve the function of retinal nerve cells with the potential to improve vision in humans.

Preliminary Laboratory Data

We have demonstrated that the NIR laser can protect retinal nerve cells against an oxygen-impairment type injury. Figure 2 shows the significant improvement in nerve cell survival following a metabolic insult (sodium azide; NaN) at laser energy settings of 25, 100 and 500 mW/cm2 versus the unlasered group.




## Preliminary Clinical Data

We have safety data from the application of this laser to living rats indicating that at the clinically relevant energy settings, there is no discernible injury to the retina. **Furthermore, in collaboration with colleagues at Sydney Eye Hospital, we have already treated 14 individuals with diabetic eye disease, with no safety concerns** (**NCT02181400**)**.**

## Outcome Measurement

## Hypothesis

*NIR laser improves contrast sensitivity in glaucoma patients*

Recent evidence indicates that certain drugs can improve contrast sensitivity in glaucoma patients after relatively short periods. This effect is a strong indicator that the particular drug has neuroprotective properties and may delay blindness. In addition, the improvement in contrast sensitivity is a highly desirable clinically meaningful endpoint in itself: a drug that can improve contrast sensitivity in glaucoma patients (without significant adverse effects) would have a beneficial impact on quality of life.

## 5. PARTICIPANTS

A total of 32 eyes are required from patients with open-angle glaucoma recruited from Prof. Casson's Glaucoma Clinic. If both eyes are eligible in a patient then both eyes will be included and randomly allocated.

### Statistical Analysis

The design is a randomized double-masked study using a mixed linear model for analysis to account for correlation between the two eyes in patients were both eyes are eligible. The eye is the unit of analysis.
The sample size calculation was based on results from our previous study[7]. Assuming a treatment effect of a 0.26 log unit improvement in contrast sensitivity with a standard deviation of 0.34 log units, a correlation of 0.7 between eyes in the same patient, a power of 0.8 and alpha at 0.05, then 14 eyes are required in each group. Allowing for possible loss to follow-up, we will recruit a total of 32 eyes.

## 6. STUDY PLAN AND DESIGN

**Study type**: a pilot, prospective randomized, double-masked study

**Subjects**: Patients with open-angle glaucoma will be recruited from the Principal Investigator's (PI's) Glaucoma Clinic at the Royal Adelaide Hospital.

### Patient Consent

The study requires that written informed consent is obtained from each participant prior to their enrolment in the study. The participant will be asked to sign the consent form only after an investigator has explained the purpose of the study and the participant has had time to read and understand the information sheet.
With the consent of the participant, it is the Investigator's responsibility to notify the primary care physician of the participant's participation in the study, provided that such a physician can be identified for the participant. A letter will be sent to the physician stating the nature of the study. A copy shall be retained by the study site.

### Inclusion Criteria:

- Age 50 years or older
- moderate to severe glaucoma (MD < -6)
- Visual acuity logMAR < 1.0

**Exclusion Criteria:**

- Significant retinal disease
- Severe media opacity
- Patient has a condition or is in a situation that in the investigator's opinion may put the patient at significant risk, may confound the study results, or may interfere significantly with the patient's participation in the study

**Withdrawal Criteria:**

- Development of adverse reactions, including reduction in visual acuity.
- Patient request.

**Screening visit**: the PI will ensure the inclusion criteria are met.

**Randomization and masking**: after informed consent at the screening visit, the eye will be randomized to receive either treatment (T) or sham (S). If both eyes are eligible then both eyes will be randomized.
The randomization process will use a predetermined code in an envelope which will be opened at the time of treatment/sham procedure. In addition, t**he investigators performing the baseline and outcome measurements will be masked as to whether the patient has received treatment or sham procedure.**

**Baseline measurements**:

(1) Auto refraction

(2) best-corrected logMAR visual acuity,

(3) best-corrected CS (CSV-1000 system; Vector Vision, Arcanum, OH) Three measurements over a 15-minute period will be taken. The third measurement will be used as baseline to allow for any learning effect, as previously described

(4) Humphrey Visual Field Test 24-2 (within 3 months)

(5) slit-lamp anterior segment assessment

(6) Intraocular pressure (eye care equipment)

(7) OCT (Optical Coherence Tomography) optic discs and macula.

These tests will take approximately 1 hour.

**NIR Light Treatment**

**The patient will be treated on 3 occasions in one week, ideally on a Monday, Wednesday and Friday.**

The procedure will be performed whilst the participant is seated at a slit lamp according to the set protocol:
The patient will be seated at the slit lamp laser delivery system and after the eye has been dilated with a drop of tropicamide 0.5% and anesthetized with topical amethocaine eye drops a standard fundus contact lens (area centralis) will be placed on the eye through which the posterior pole will be visualized while the treatment is delivered.

Each NIR light treatment will consist of a 90 second exposure of the macular region of the study eye to the ELLEX Integre NIR laser with the patient fixating on the central aiming beam. The laser light beam is 4.5mm in diameter with a central masked area of 1.0 mm diameter containing the central fixation target. The laser energy delivery is set at $25mW/cm^2$. In this way, the central macula will be spared in the event of an adverse effect of the laser, which we do not anticipate.

**Outcome**: 7 days after the final treatment/sham (the following Friday) the baseline measurements will be repeated in the same order. The primary outcome will be the change in the CS measurement at 12 cycles per degree compared to baseline. This single outcome was chosen based on our previous study showing an improvement in this parameter after glucose-induced neurorecovery,[7] and to avoid reductions in the alpha value due to multiple hypothesis testing.

**Sham control:** patients will receive the same set up at the slit-lamp laser except that the infra-red laser will not be fired when the laser application foot pedal is activated. This foot pedal makes a sound indistinguishable from actual laser delivery and the aiming beam is also rendered indistinguishable from actual laser therapy. Hence, the patient is genuinely masked to the nature of the treatment.

## 7. OUTCOMES

Baseline contrast sensitivity will be measured using the routine CSV-1000 apparatus. The contrast sensitivity will be measured again 7 days after treatment/sham procedure and the difference between measurements will be the primary outcome variable.

Secondary outcomes:
LogMAR VA
Change in AVF (Automated Visual Field)

Safety outcomes will be:
Any loss of BCVA/VA
Any changes in OCT

## 8. ETHICAL CONSIDERATIONS

### Potential criticisms

*Is the procedure safe?*
This procedure using the laser dosing of 90 secs at 25mW//25cm2 has already been performed on 7 diabetic patients in current clinical trial (**NCT02181400**).

This is at the lower end of the dose range. Patients have also received 100 mW/cm2 with no ill effects to the retina or patient vision. We have preliminary data to indicate an improvement in macular thickness in these diabetic patients at the 25 mW/cm2 setting. This was designed as a phase I safety study. Hence it does not seem necessary to reproduce multiple dosing regime.

*How do we know that the interval between last treatment and re-measurement (7 days) is suitable?*
This is an estimate based on treatment effects described in the literature and our own lab results. 7 days is a reasonable period to expect a change.

*If there is a treatment effect and evidence of neurorecovery, where to from here?*
The hopeful outcome is obviously that we will see a treatment effect. However, it seems likely that this improvement in vision would not be permanent. This is an important point that will be made clear to the patient during the consent process. If there was a successful outcome, potentially even in individual patients then patients could potentially be offered further treatment pending TGA approval.

### Adverse Events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed as appropriate. An adverse event is any undesirable sign, symptom or medical condition occurring after starting study treatment, even if the event is not considered to be treatment-related.

Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment. Clinical events occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Case Report Form only if the patient receives study treatment.

### Ethics and Good Clinical Practice.

This study will be performed according to the principles of Good Clinical Practice [Chapter 2 of the ICH Harmonized Tripartite Guideline for Good Clinical Practice

(GCP)], the declaration of Helsinki, and national laws and regulations about clinical studies. The study may not start without written Institutional Review Board/Independent Ethics Committee/Research Ethics Board approval and the written informed consent of the patient.

Notification of serious adverse events will be reported to REC Chairman

***within 72 hours***.

## 9. SPECIFIC SAFETY CONSIDERATIONS

Not applicable

## 10. DRUGS

Minims tropicamide (eye drops) to dilate the pupil

## 11. ANALYSIS AND REPORTING OF RESULTS

Data will be collected and accessible only by the below investigators and clinical trials coordinator Kylie Dansie, on a password protected excel spreadsheet on laptop computer and backed up regularly to external hard drive. The data and results will be owned by the South Australian Institute of Ophthalmology. At the completion of the study the data will be de-identified and paper source documents kept locked in the SA Institute of Ophthalmology.

## 13. OTHER RELEVANT INFORMATION

Results to be published in peer reviewed journals.

## 14. OTHER ETHICS COMMITTEES TO WHICH THE PROTOCOL HAS BEEN SUBMITTED.

No other submissions.

## 15. DATE OF PROPOSED COMMENCEMENT

1st November 2017

## 16. RESOURCE CONSIDERATIONS

Additional staffing and resources beyond what would be expected in normal clinical practice to be funded by the Department of Ophthalmology.

The study will not cause any stress to the current department sessions, staff or consumables.

The subject selection, reviews, follow ups and clinical visits will only be organised and staffed by the Investigators and the Clinical trial coordinator.

### Medical records required

The subject being been treated will be required to have their case notes available as they will be utilized as a source document in conjunction with a check list.

## 17. INVESTIGATIONAL EQUIPMENT

### 17.1 Description

The Ellex Integre NIR Laser is a slit lamp microscope mounted 670nm light source that can be varied in brightness by the operator to set the required power density from 50 to 500 mw per square centimetre. This level is between 1x and 10x the brightness of the NIR LED device used in the Wisconsin Study but even at the highest level of intensity is only just comparable to the energy density of the aiming laser used in a standard thermal laser photocoagulator. At its highest brightness this is 50X lower in energy density than a photocoagulator. As an additional safety measure the Ellex Integre NIR laser beam is 4.5mm in diameter with a central masked area of 1.0 mm diameter in order to avoid illuminating the central macula with light.

The Ellex Integre NIR Laser system has a user selectable exposure duration control permitting the user to preset the treatment time duration.

### 17.2 Maintenance of Machine/Equipment

The Ellex Integre NIR laser equipment will be installed and calibrated at the start of the trial and inspected and tested for accurate calibration at least annually for the duration of the trial.

## 18 CONTRAST SENSITIVITY ASSESSMENT (CS)

**18. Description** CSV-1000 system; Vector Vision, Acranum, OH.

The CSV-1000 instrument is the recognized world-wide leader for standardized contrast sensitivity. The patented auto-calibration circuitry provides for standard and consistent test conditions. The instrument automatically controls the test lighting to a level of 85 cd/m2, which is the light level recommended for vision testing by the National Academy of Sciences and adopted by the FDA as the required testing light level for clinical trials.

Three measurements

## 19. OPTICAL COHERENCE TOMOGRAPHY

### 19.1 OCT Exam Procedure

The eyes should be maximally dilated to help ensure optimal quality scans.
Zeiss Cirrus SD OCT machine used to scan the disc and macular.

## 20. SCHEDULE OF VISITS

| | Screen | treatment 1 | treatment 2 | treatment 3 | follow up visit (7 days later) | Early exit |
|---|---|---|---|---|---|---|
| Informed consent | X | | | | | |
| treatment allocation/randomisation | X | | | | | |
| Con Meds | X | | | | X | X |
| Adverse Events and con procedures | | X | X | X | X | X |
| Blood Pressure | X | | | | X | X |
| LogMar BCVA | X | X | X | X | X | X |
| Best Correct CST | X | | | | X | X |
| AVF Automated Visual Field | X | | | | X | X |
| IOP | X | | | | X | X |
| Slit lamp anterior segment assess | X | | | | X | X |
| OCT | X | | | | X | X |
| NIR laser treatment | | X | X | X | | |

## 20. REFERENCES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4. EVANS, DW, HOSKING, SL, GHERGHEL, D*, et al.* 2003. Contrast sensitivity improves after brimonidine therapy in primary open angle glaucoma: a case for neuroprotection. *The British journal of ophthalmology,* 87**,** 1463.

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**Signature Page.**

Professor Robert Casson

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Date