STUDY PROTOCOL (Version 1, 1/17/2018)

Title: Retinal displacement after scleral buckling (SB) versus scleral buckle combined with vitrectomy (PPV+SB) for the management of primary retinal detachment: ALIGN SB vs. PPV-SB. An extension of the study of "Retinal displacement after pneumatic retinopexy (PnR) versus vitrectomy (PPV) for the management of primary retinal detachment (ALIGN) NCT04089033."

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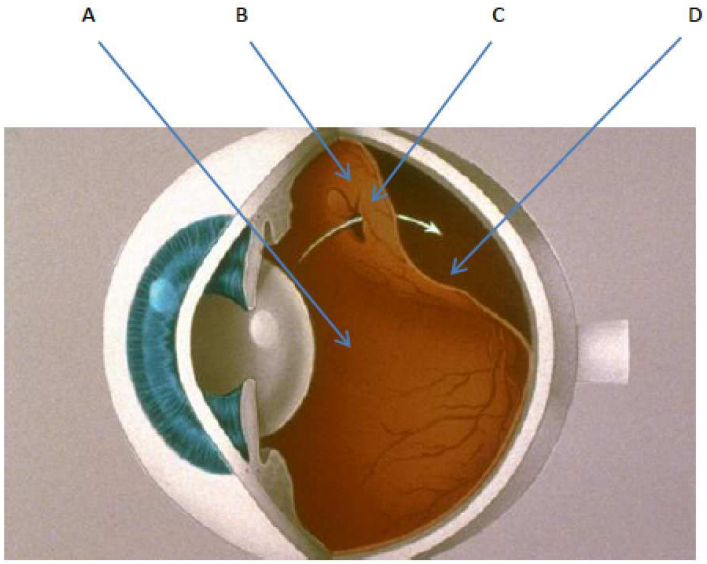
I. Background

Retinal detachment

Rhegmatogenous retinal detachment (RRD) is an acute, sight threatening condition,

with an incidence of approximately 10 per 100,000 people.[1] During normal ageing, the transparent vitreous gel (see figure 1:A), which fills the eye, liquefies and shrinks, and eventually detaches in 80% of the eyes. When detachment of the gel occurs, a tear in the retina may form (see figure 1:B). Liquified gel may now enter under the retina via the retinal tear (see figure 1:C), resulting in detachment of the retina (see figure 1:D). Once retinal detachment occurs, sight loss usually develops within several hours to days.

Figure 1: Retinal detachment



Factors that predispose an individual to developing retinal detachment are myopia (near sightedness), advancing age, trauma, and certain hereditary conditions.[2] Without any surgical intervention by a vitreoretinal surgeon, retinal detachment almost invariably results in permanent sight loss in the affected eye. There is an increased risk of delayed visual rehabilitation the longer the wait for surgery is.[3] Interventions for rhegmatogenous retinal detachment may include Scleral Buckling (SB), Pneumatic retinopexy (PnR), Pars Plana Vitrectomy (PPV), and PPV+SB in which the primary objectives are to close and seal the retinal break and reattach the neurosensory retina to the RPE.[4-10] The choice of which procedure to perform depends on the clinical examination and the surgeon's discretion as to which will be best for the patient in that specific scenario.

Interventions for retinal detachment[SEP]Pneumatic retinopexy (PnR) has been employed to repair retinal detachments since the late 1980s and is a minor surgical intervention, carried out in a treatment room. The initial success rate (i.e. the proportion of patients in whom the retina becomes attached after one treatment) is quoted as approximately 70%.[5-7] PnR is carried out under topical or local anaesthetic (a freezing injection under the conjunctiva, the superficial skin on the eye). The procedure involves injection of a

small gas bubble into the eyeball via a fine needle. This step takes a maximum of 15 minutes. Two gases can be injected into the eye: perfluoropropane (C3F8), which lasts 6 weeks, and sulfahexafluoride (SF6), which lasts about 2 weeks. Both are non-toxic, equally effective, have been validated for this use, and are widely used amongst retina surgeons in the world. After injection of the gas bubble, the patient is required to maintain a strict 'head posture' (for example, head tilt to left) for up to 10 days. The purpose of this 'head posture' is to align the gas bubble (which floats within the eye) to the retinal tear. The buoyant force of the gas bubble, as well as its surface tension, act to reattach the detached retina over several days. The gas bubble spontaneously dissipates after 2-6 weeks, depending on the gas selected. Additionally, laser treatment or cryotherapy is carried out either before or 1-2 days after injection of the gas bubble, to secure the retinal tear. Without this second step, the retina would re-detach once the gas bubble dissipates. Both laser and cryotherapy are widely accepted methods of securing the tears in the retina and both are considered equally safe and effective. In patients where the retina does not reattach with PnR alone, vitrectomy surgery (PPV) or repeat PnR is needed (see below).[8] However, the minority of patients who go on to need repeat treatment encounter similar final anatomical success rates and will experience the same gain in vision as those patients who underwent PPV in the first place.[9,11]

Vitrectomy surgery (PPV) involves 'keyhole' surgery to the eyeball, via three tiny (23/25 gauge) incisions to the sclera. This procedure is carried out in the operating room, under regional anaesthetic (a freezing injection to the retro-bulbar space, the space behind the eyeball, where nerves which sense pain and control eye movement are situated) plus sedation (medication to reduce patient anxiety). During PPV, the vitreous gel is removed from the eye using a fine metal instrument called a 'vitrector'. The vitreous gel is removed to allow space for a larger gas bubble than is possible in PnR, and also to relieve any vitreous traction which may otherwise impair reattachment of the retina. A large gas bubble (same gases as mentioned for PnR) is injected (to reattach the retina, as in PnR), and laser or cryotherapy is applied around the retinal tear to secure it (as in PnR). After treatment, a patient may be required to maintain a 'head posture' (for example, head tilt to left) for up to one week. The purpose of this 'head posture' is to support the area of the retinal tear optimally, by 'floating' the gas bubble up against it. As the gas bubble is larger in PPV, the head posturing requirements are less strict. The gas bubble reabsorbs after 2-6 weeks, depending on the gas selected. The surgery takes 1-1.5 hours. The success rate (i.e. the proportion of patients in whom the retina becomes attached after one treatment) is reported as being as high as 90% in the scientific literature.[7,12,13]

Scleral buckling (SB) is another method used for repair of RD that involves encircling the eye with a silicone band, and may or may not involve the use of a gas bubble. This

has been reported to have better visual results than PPV in phakic patients.[15]

Another surgical technique for repair of RD is PPV combined with SB (PPV/SB), and this is used commonly in treatment of larger or more complex detachments. The surgery combines the two techniques, and involves the use of a large and often long-acting gas bubble similar to what is done in PPV surgeries.

All the treatment options may be associated with complications such as bleeding, infection, increased intraocular pressure or cataract. The risk of a sight threatening complication such as a severe intraocular infection or hemorrhage is less than 1:1000. The risk of cataract development (clouding of the lens, requiring cataract extraction surgery) is less in PnR[11,14] and SB compared to PPV.[15]

Distortion and retinal displacement after retinal detachment repair

Image distortions such as metamorphopsia and micropsia are common complaints after surgery for retinal detachment. In 2010 Shiragami et al were the first to demonstrate hyper-fluorescent lines, adjacent to the retinal blood vessels in Fundus auto-fluorescence imaging (FAF) of the retina after retinal detachment (RD) repair surgery.[26] They proposed a theory in which these lines which are called also Retinal Vessel Printing (RVP) correspond to the area where the retinal blood vessels were located before the retinal detachment. According to this theory the RVP in FAF imaging is due to increased metabolic activity of RPE cells. Prior to surgery these RPE cells were obscured to light rays by retinal blood vessels while after surgery, due to displacement of the retina, these RPE cells became exposed to the light which leads to increase in the cells metabolic activity. This increase in metabolism is thought to be the cause for the hyper fluorescence seen in FAF imaging. Displacement of the retina after RD repair surgery can serve as anatomy basis of vision distortion. Moreover, these reference lines allow us to quantify the displacement of the retina after retinal detachment surgeries. By doing this, we can compare retinal displacement of different retinal detachment repair surgeries and may reduce post operation visual distortion.

Since Shiragami's first report, several other studies looked into retinal displacement after RD repair[26-32], epiretinal membrane[33] and macular hole[34]. Codenotti et al have shown that retinal displacement ratio is higher in patients with intravitreal gas compare to patients with silicon oil (71.4% vs. 22.2%).[27] Lee et al proposed a way of quantifying the rotational displacement of the retina.[28] They showed that there is more than a simple rotation and probably also a temporal stretch of the retina. Recently Dell'omo published the biggest study so far of 125 patients after pars plana vitrectomy (PPV) with 35.2% of patient showed signs of retinal displacement.[30]

Recently we showed in PIVOT trial that patients after pneumatic retinopexy has less vertical distortion than patients after PPV. To the best of our knowledge, no study so far looked into retinal displacement after Pneumatic Retinopexy. Moreover, wide field FAF was not used in previous studies. We think there is a reason to believe that Pneumatic Retinopexy will cause less retinal displacement than PPV. Thus, we propose a prospective cohort study which will compare retinal displacement of patients after RD repair by PPV versus Pneumatic Retinopexy.

In addition, we wish to include VitreoRetinal Surgery, PA in Minnesota and Bhagwan Mahavir VitreoRetinal Services, Sankara Nethralaya in India as the site to study retinal displacement following RD repair using either SB or PPV with SB, since this practice has a much higher volume of those surgical methods.

II. Aim (SB and PPV+SB arm)

To compare retinal displacement and visual distortion of primary retinal detachment repair following scleral buckling (SB) versus scleral buckle combined with pars plana vitrectomy (PPV+SB).

III. Study design

(i) Hypothesis The primary study hypothesis is that scleral buckling alone may cause less retinal displacement and less visual distortion at the first 12 months for patients with primary retinal detachment than other methods.

(ii) Experimental design A prospective, cohort trial, evaluating scleral buckling alone and scleral buckling combined with vitrectomy outcomes for patients with primary retinal detachment.

(iii) Participants Patients presenting to vitreo-retinal service with rhegmatogenous retinal detachment. Eligibility for study participation will be ascertained by the examining physician at the time of presentation:

Inclusion criteria:

- Age ≥ 18
- Diagnosis of macula off primary rhegmatogenous retinal detachment

Exclusion criteria:

- Previous retinal detachment and/or retinal detachment repair surgery in the study eye
- Retinal detachment with macula on.
- Patients with other retinal pathologies causing structural changes to the retina in the study eye, such as diabetic retinopathy, previous vascular occlusion (artery or vein occlusion), macular dystrophy, among others.
- Previous vitreoretinal surgery in the study eye
- Inability to come for follow ups up to 12 months.
- Inability to take FAF imaging due to neck stiffness or other medical issue.
- Inability to maintain post operation head positioning
- Mental incapacity
- Inability to sign on informed consent.
- Patient is unwilling or unable to follow or comply with all study related procedures or to sign informed consent form

Criteria for participant withdrawal from study: - Patient withdraws consent

(v) Interventions

The only interventions in the study are performed at the 3 and 12 month postoperative visit, and include fundus imaging (FAF and OCT), and sensory testing with the M chart and the Aniseikonia test, as detailed below.

Participants will be chosen from those undergoing either scleral buckling alone or scleral buckling combined with vitrectomy for repair of a macula-off retinal detachment. Patients are not randomized to the procedure, rather the procedure is chosen by the surgeon in the best interests of the patient.

In the event of primary intervention failure (i.e. failure of retinal re-attachment following primary intervention), the decision to proceed with secondary intervention, and the nature of such intervention, will rest with the treating physician in conjunction with the patient. Secondary intervention may involve any surgical procedure, as deemed clinically appropriate.

Note: Additional laser retinopexy, cryotherapy, gas injection or head positioning are not considered a failure.

(vi) Timing of observations See flow diagram (Appendix 1)

Imaging

Fundus AutoFluorescence (FAF)
Fundus autofluorescence (FAF) imaging is a noninvasive imaging method and requires relatively little time. It highlights the fluorophores accumulating in lipofuscin (LF) within retinal pigment epithelium cells (RPE). No radiation is involved therefore this imaging method is safe without any clear contraindications.

M Chart

Recently, several tools have been developed for quantification of metamorphopsia severity including M-CHARTS (Inami Co., Tokyo, Japan). In the patients with metamorphopsia, a straight line appeared curved or irregular. On M-CHARTS, straight lines are replaced with dotted lines, and the dot intervals (range: 0.2° - 2.0°) are changed from fine to coarse. With increasing dot interval, the line distortion decreases until the dotted line becomes straight. The visual angle that denoted the dot interval of the line seen as straight was considered as the patient's M-CHARTS score. When a

patient was tested with vertical dotted lines, the result was defined as the vertical M-CHARTS score. After the M-CHARTS were rotated 90°, the horizontal M-CHARTS score also was measured according to horizontal dotted lines[35].

Aniseikonia test

Aniseikonia is a phenomenon in which the size or shape of perceived images differs between eyes. The anomaly is reported to be associated with interocular differences in refractive error and some retinal diseases. Following successful repair for rhegmatogenous retinal detachment, some patients have complained that objects appeared distorted in size or shape. The Aniseikonia Test measures the ratio of image size difference between the 2 eyes[36].

(vii) Outcome measures

Primary outcome:

- retinal displacement by the presence of retinal vessels printing on FAF imaging.

Secondary outcome:

- Visual Distortion measured with M chart.

- Anisokenia testing.

- Optical Coherence Tomography (OCT) changes.

- Metamorphopsia according to the patient symptoms.

- Visual acuity (ETDRS 12 months post intervention)

- Metamorphopsia questionnaire

(viii) Recruitment plan

Recruitment will begin after Research Ethics Board approval has been granted and will continue until the required number of patients are enrolled and have completed the study. Patients visiting the retina clinic with primary RRD will be given the option to participate if they meet the criteria. Based on our clinic's routine volume, we anticipate recruiting approximately 4 patients per sub-study per week, with complete recruitment over a 12-month period. Each patient will be followed for 12 months.

(ix) Screening Procedures

Patients will be screened by the investigators in the same manner as standard patients. The tests to be performed are typically used for diagnosis and follow-up of retinal detachment: best-corrected Snellen visual acuity assessment, slit-lamp exam, tonometry, fundoscopy, and Optical Coherence Tomography (OCT) at every visit. ETDRS visual acuity (ETDRS - 'Early treatment of Diabetic Retinopathy Study' – this study defined a method of visual acuity assessment that has become the gold standard for use in eye research) will be assessed at 12 months after the treatment for RRD.

Assessment of Clinical Parameters:

The following clinical data will be obtained from each patient: age, gender, extent of the detachment (quadrants), duration of subjective symptoms (days), vitreous status (presence/absence of vitreous hemorrhage), macular status (attached/on or detached/off), the location of main retinal tears (fundus sketch), refractive power (emmetropic, hyperopic, myopic <6 or > 6 diopters, lens status (phakic or pseudophakic) and medications in use.

(x) Sample size

Sample sizes were calculated to appropriately power the study. A total sample size of 40 subjects with macula-off detachments undergoing scleral buckles will be recruited. A second group of 40 subjects with macula-off retinal detachments undergoing combined vitrectomy an scleral buckle placement will also be recruited. Anticipating a dropout rate of 20%, we calculated a total of 100 patients in the entire study.

IV. Data management

Initial data collection (clinical examination findings, visual acuity, and questionnaire data) will take place in a paper format. Subsequently, this data will be transferred to a digital database (Microsoft Excel). Paper data will be stored in a locked filing cabinet in the principal investigator's office and away from the study data, and will be destroyed once digital data entry has taken place. The digital spreadsheet will be held on a password protected computer in a locked room, and an encrypted memory stick. At recruitment, each patient's name and date of birth will be obtained to facilitate onward administration of follow-up appointments and safety monitoring and stored on a face sheet (master linking log). The face sheets will be stored in a locked filing cabinet, away from the study data. Each patient will be allocated a unique study identification number, which will be used to label all paper and digital data pertaining to that patient. The face sheets (master linking log) and all paper/electronic data will be destroyed once publication takes place. The de-identified study data will be destroyed five years after publication has taken place.

V. Consent:

Written, informed consent for imaging and sensory testing as part of the study will be obtained from each participant. Important: the clinical care of the patient will not be affected by the patient's participation or non-participation in this study of post-surgery imaging and sensory testing. Given that 12-month followup can be problematic for patients who live a great distance from the study sites, a 20% dropout rate is anticipated. There is no charge to the patient for the sensory testing, which is the only element that differs from standard care.

On no occasion should consent be obtained by the treating physician or study investigator. During working hours: The study will be introduced to the patient by the examining physician. Interested patients are directed to Research Technician who will obtain informed consent.

Late evenings / weekends: Informed consent may instead be obtained by the vitreoretinal surgery fellow (assuming that they are not the treating physician and will not be involved in the patient's surgery). The resident/fellow will be familiar with both interventions (SB and PPV+SB), the nature of the study and trained to the consent discussion and obtaining written informed consent. As retinal detachments are usually unilateral conditions, patients can still read the informed consent. If the patient has any bilateral visual impairment, a witness, usually being the accompanying relative of the patient or a staff member not involved in the study, will also be present.

VI. Data Analysis:

Continuous data: Data will be checked for normality. Normal data will be compared using a non-paired t-test. Non-normal data will be compared using non parametric tests. Categorical data: Chi squared test. Coefficients with 95% confidence intervals will be reported. A p-value of 0.05 will be considered for statistical significance. Data will be analyzed using SPSS (SPSS Inc., Chicago, IL). Per protocol analysis will be used.

VII. Safety Monitoring Plan

This study will be conducted in accordance to the Declaration of Helsinki. The local principal investigator will meet monthly with study team members to review the progress of the study. Furthermore, to ensure that all members are performing their roles in accordance with the professional obligations described in this Ethics Application, the Principal Investigator will randomly check on the study coordinators and participants. Patients will be made fully aware of the risks and benefits of the procedures. Patients will be assessed before and after the treatment and will be closely monitored throughout the study. Complications will be managed by highly trained hospital staff including ophthalmologists, nurses, allied health professionals and technicians as per standard of care.

VIII. Funding

All aspects of clinical care, including procedures visits and exams, carried out as part of the study represent standard of care.

Support staff: Our research technicians are already salaried employees within the department. Part of the existing job description is assisting Fellow's research, and therefore no additional funds will be required.
Expenses with printing and copying will be absorbed by the principal investigator's (Dr……..) office.

VII. References:

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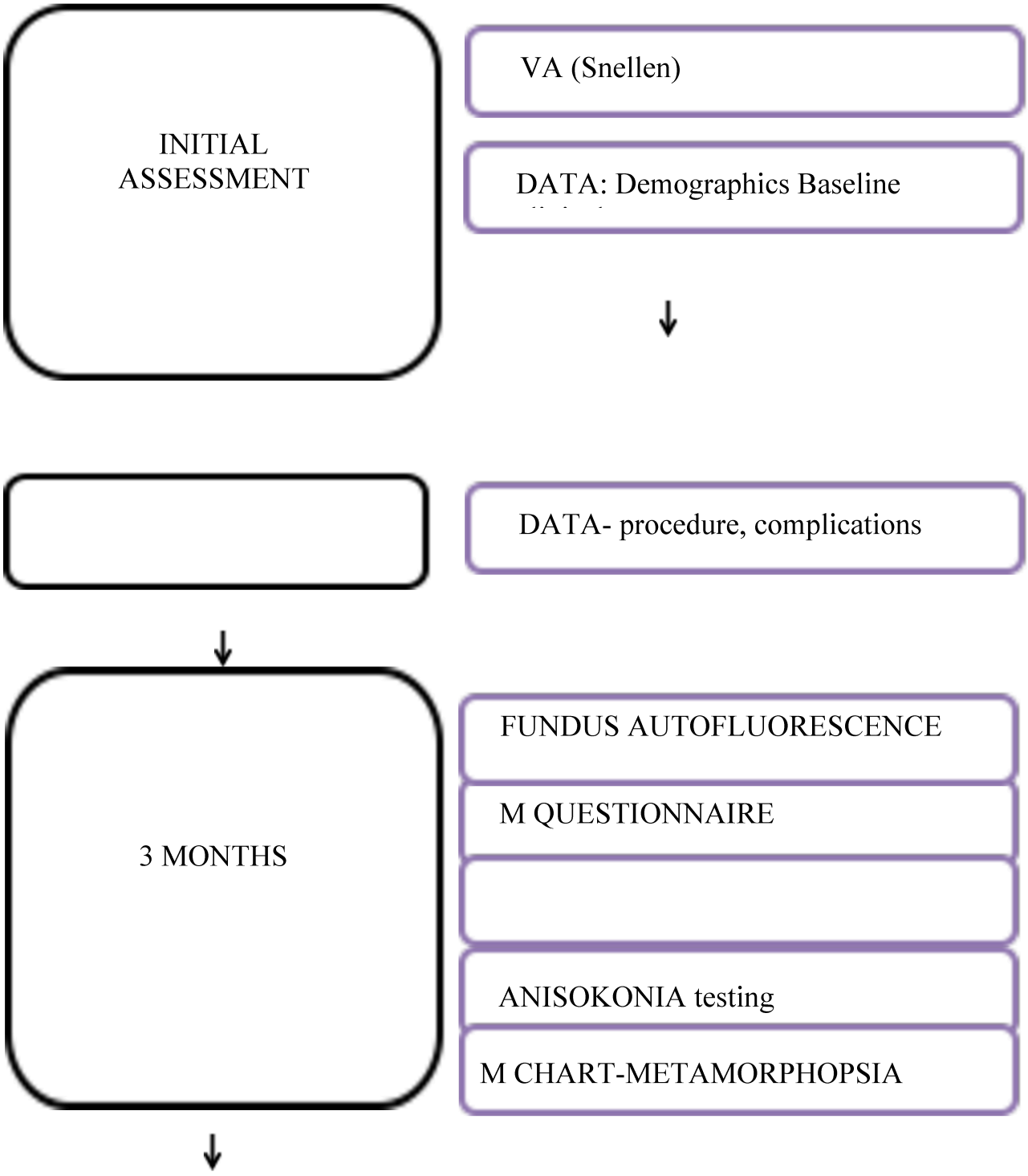
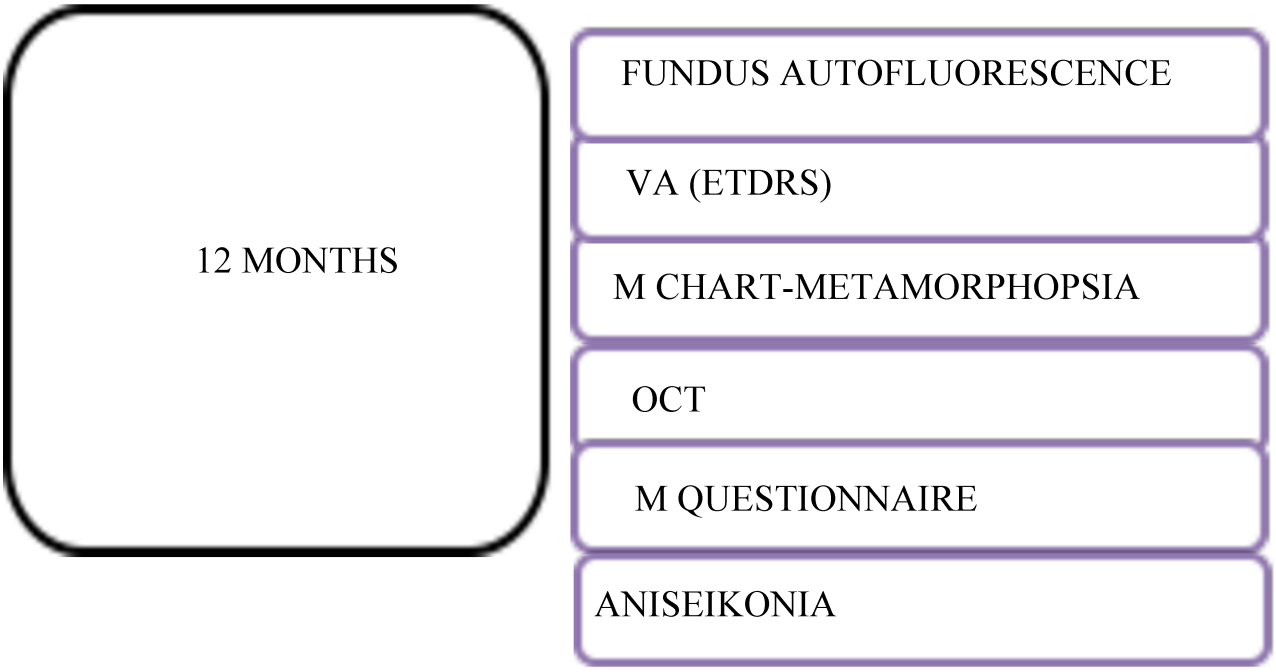
Appendix 1: STUDY FLOWCHART (ALL PATIENTS)



12 MONTHS


12 MONTHS
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M CHART-METAMORPHOPSIA
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