RESEARCH STUDY PROTOCOL

PROTOCOL TITLE: The effectiveness of multidisciplinary protocolised interventions to reduce non-adherence rates (ADHERE) in patients with chronic macula diseases receiving intravitreal injections: A randomised controlled trial

PROTOCOL NUMBER: **R2146/40/2025**

VERSION NUMBER: 4

VERSION DATE: 24/01/2026

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PROTOCOL SIGNATURE PAGE

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Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described study in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Tan Cheng Sim Anna

Name of Principal Investigator:

Signature of Principal Investigator:

24/01/2026

Date:

Singapore National Eye Centre

Name of Study Site:

Note:
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1. BACKGROUND AND RATIONALE

Chronic macular diseases, such as age-related macular degeneration (AMD) and diabetic macular edema (DME) affect more than 28 million people worldwide and are currently the most common cause of irreversible vision loss and blindness in older adults in developed countries[1-5]. Vision loss from macular diseases has been related to loss of independence in activities of daily living (ADLs) and a reduced quality of life (QoL)[6,7]. For both neovascular AMD (nAMD) and DME, intravitreal injection treatment (IVT) of anti-vascular endothelial growth factor (anti-VEGF) is the gold standard treatment with excellent visual functional improvements in a large majority of patients[8-12]. An intensive IVT regimen, especially in the first 2 years of the diagnosis, should be prioritized for optimal treatment outcomes[13-15]. However, real-world studies looking at long term IVT treatment in nAMD and DME have shown that visual outcomes compared to clinical trials are inferior, largely driven by a lower number of intravitreal injections administered[16-18]. Especially, non-adherence to long-term treatment and follow-up regimens in the management of patients with nAMD and DME in real-world ophthalmic care is common, with an estimated prevalence of 30-95%, and reduces the effectiveness of clinical treatment outcomes, conferring a higher risk for significant, permanent vision loss[19-23]. Frequent and long-term IVT imposes a substantial burden on patients, and caregivers[24,25], with the most common reasons for non-adherence including patients' dissatisfaction with their vision, treatment-related anxiety, financial considerations, transport burden and access to appointments[19]. ***No studies to our knowledge have assessed the effectiveness of personalized patient-centred interventions to improve adherence to long term IVT treatment[19,22,26]***.

Patient reported outcome measures (PROMs) can be used to measure various aspects of QoL, including emotional reactions to vision loss and treatment, financial concerns and treatment burden, similar issues that influence non-adherence to IVT[19]. ***Currently, PROMs are not part of standard clinical care, and there is currently a lack of standardised guidelines for clinicians to effectively manage QoL concerns and recommend appropriate interventions.*** Moreover, traditional PROMS are fixed length and burdensome to complete, hence posing significant barriers to widespread clinical implementation. Item banking and artificial intelligence (AI)-driven ***computerised adaptive testings (CATs) offer a promising and novel solution to feasibly assess QoL in a clinical setting[27]***. A critical component of a CAT is an item bank (IB), which is a repository of items (questions) measuring a patient-reported construct (e.g., activity limitation) that have been calibrated on an interval-level scale using psychometric methods like Rasch analysis[27]. Thereafter the CAT algorithm chooses items from the IB that are most informative at that particular point of the test and continues to offer similar items until a stopping criterion (e.g. measurement precision, based on standard error of measurement [SEM] or an item cap) is reached[28], to obtain a precise score with less time. Additionally, CATs can be administered in-clinic or self-administered remotely on a patient's phone, tablet or computer, offering an efficient and flexible means of estimating patients' level of QoL[29,30]. Singapore Eye Research institute (SERI)/Singapore National Eye Centre (SNEC) have developed and validated several QoL CATs for nAMD[31,32] and DME[33-36] and, using our online end-to-end MoH/Synapxe approved platform, customized CAT reports are available in real-time and deposited in the EMR system at SNEC.[37]

Our novel proposed approach to improve adherence to IVT is ***personalized patient-centred care comprising a multidisciplinary protocolized intervention (MPI), which consists of medical consultation, to optimize the treatment regimen, and combinations of appropriate***

referrals to either (1) a nurse-directed patient education program (NE), (2) a low vision optometrist (OP), (3) an occupational therapy services (OT) and/or (4) a medical social worker (SW). CATs specific to AMD and DME will be used to measure QoL by collecting scores in various patient-informed domains. Lower scores at baseline, or a significant reduction in scores on follow-up visits in the various domains, will inform potential areas to address and tailor our MPI accordingly. For example, IVT patients who score poorly in the emotional domains will be sent to our IVT nurse counsellor to address patient expectations and treatment anxiety. Others, who may score poorly in the economic domains, will be referred to a medical SW to be assessed for financial aid. ***There are limited studies on the effectiveness of similar multi-disciplinary allied health interventions in managing and improving adherence in IVT patients***. Previous studies testing allied health interventions did show significant improvements in QoL but have been limited to only patients with significant permanent visual impairment and were non-disease specific[38-41]. ***Hence, using a randomized control trial (RCT) design, we hypothesize that the MPI, a personalized intervention based on specific sub-optimal QoL domain scores, versus standard care, will lead to improved adherence rates, as well as improved clinical and QoL outcomes as measured by disease-specific CAT scores, compared to standard care and will be an appropriate, acceptable and feasible intervention, that is cost-effective for future implementation.***

If the MPI is assessed to be an effective intervention to improve adherence (Specific aim 1), QoL (Specific aim 2A) and clinical outcomes (Specific aim 2B), it would be crucial to assess implementation outcomes such as acceptability, adoptability, appropriateness, feasibility, fidelity and cost-effectiveness to plan scaling up and incorporation into clinical practice. Interviews with key stakeholders such as clinicians, nurses, allied health professionals, patients and caregivers will be essential to understand the enablers and barriers to MPI implementation (Specific aim 3). Models used to predict the MPI effect on reducing vision loss and improving QALYs, long-term will assess the cost-effectiveness of MPI (Specific aim 4).

THE MULTIDISCIPLINARY PROTOCOLISED INTERVENTION (MPI) BASED ON SUBOPTIMAL DOMAIN CAT SCORES

The proposed MPI consists of a medical consultation to optimise patients' treatment regimen, address concerns about their disease and treatment, explain advantages and disadvantages about the type of IVT medication and potential of increased treatment intervals between IVT, and address other patient and care-giver concerns.

Importantly, CAT scores will be available to the clinician to guide the consultation. Based on sub-optimal CAT scores, referral to one or a combination of services will be initiated by the study team according to a preset protocol (**Table 2**):

(1) a referral to NE, which would include a session with a trained IVT nurse educator, who would use previously validated hard copy and digital education resources to educate the patients on their disease, symptoms, progression, and need for treatment. Factors which may cause anxiety for IVT patients such as side effects and adverse events will be addressed and the need for IVT adherence to maintain long-term vision will be reinforced. The patients would be reminded about the availability of the IVT hotline to address concerns and appointment issues.

(2) a referral to OP who, after a needs assessment, would then carry out a comprehensive low vision assessment that includes refraction, CS, reading acuity, determination of reading goals and prescribing of suitable optical aids. OPs will assess and address any vision-related issues that may hinder reading specific tasks, navigation and other ADLs, which may be barriers to IVT adherence. They can further discuss the patient's expectations about their visual recovery and the need for IVT to maintain vision.

(3) a referral to OT who, after a needs assessment, would provide advice about optimal lighting and, contrast perform activities of daily living retraining and functional/community mobility training, provide patient/family education and, if required, home modification to facilitate independence in ADLs, which may may allow better access to IVT appointments promoting adherence.

(4) a referral to medical SW who, after a needs assessment, would provide the necessary emotional counselling, financial counselling and referral to community care services and other relevant support services addressing relevant barriers related to adherence to IVT.

2. HYPOTHESIS AND OBJECTIVES

Specific aim 1: To assess the effectiveness of MPI, versus standard care, in improving adherence to IVT follow-up appointments at 6, 12 and 18 months (main timepoint for primary outcome) *in patients with nAMD and DME requiring long term management* (primary outcome).

Hypothesis 1: *Compared to those in standard care, patients in the MPI group will have higher adherence to long-term follow-up appointments and IVT therapy.*

Specific aim 2A: Assess the effectiveness of MPI, versus standard care, in improving domain-specific CAT scores at the various follow-up timepoints (secondary outcome).

Hypothesis 2A: *Compared to those in standard care, patients in the MPI group will have greater gains in domain-specific CAT scores at each follow-up time point.*

Specific aim 2B: Assess the effectiveness of MPI versus standard care in improving visual acuity (VA), contrast sensitivity (CS), disease free intervals between IVT (as measured on optical coherence tomography (OCT) (secondary outcomes).

Hypothesis 2B: *Compared to those in standard care, patients in the MPI group will have greater VA and CS gains and achieve longer disease-free intervals between IVT at each follow-up time point.*

Specific Aim 3: To assess implementation outcomes of the MPI such as acceptability, adoptability, appropriateness, feasibility, fidelity.

Hypothesis 3: *Using a mixed methodology, with quantitative and qualitative outcome measures as reported by patients, caregivers, clinicians, nurses and allied health professionals, MPI will be an appropriate, adoptable, acceptable, feasible intervention with good fidelity.*

Specific Aim 4: To assess the cost-effectiveness of the MPI for improving adherence to IVT, considering its potential impact on long term visual acuity (VA) loss and QoL adjusted years (QALYs)

Hypothesis 4: *The MPI is incrementally cost-effective relative to standard care, based on accepted willingness-to-pay thresholds*[42]*.*

3. EXPECTED RISKS AND BENEFITS

There will be minimal risks involved as this intervention consist of counselling and supportive interventions to promote adherence. The participant is encouraged to raise any queries related to the questionnaires and the proposed interventions. The standard risks that apply to a standard consultation apply. There may also be other risks associated with the study that we are currently unable to foresee. Dilation of the pupil has risks involved such as potential angle closure glaucoma, however it will be performed as part of standard clinical care.

Benefits to the patient include the chance to participate in this fully funded study that aims to assess protocolised supportive interventions to promote adherence to intravitreal therapy based on sub-optimal PROMs. Improved adherence rates will lead to reduced rates of visual impairment, better disease control and ultimately contribute to better quality of life outcomes.

4. STUDY POPULATION

4.1. List the number and nature of subjects to be enrolled.

The study population will be recruited from retinal outpatient clinics in SNEC. There are no restrictions of recruitment based on race or sex. Assuming a maximum 20% dropout in the study we estimate a sample size of 200 patients.

4.2. Criteria for Recruitment and Recruitment Process

The participants will have undergone visual acuity testing, clinical examination and optical coherence tomography screening and deemed to have nAMD or DME that requires treatment with IVT, and with no other significant vision-threatening disorders (see section on inclusion/exclusion criteria), by their treating physician as part of clinical care. The study population will be recruiting from retinal outpatient clinics in a single tertiary centre (SNEC) where retinal clinics are conducted and eligible patients will be identified by the consulting physician and referred to the clinical research coordinator (CRC) during their clinic appointment. The CRC will approach the patient and provide details of the study and further confirm the eligibility for the study before informed consent is obtained.

4.3. Inclusion Criteria

Inclusion criteria will include patients with chronic macula disease including those diagnosed with nAMD and DME, who require IVT. This would include treatment naïve patients (no IVT in either eye the last 6 months) and previously treated patients who have had IVT in either eye in the last 6 months and require further IVT treatment at the baseline study visit in either eye. All participants will be able to provide

informed consent, speak English or Mandarin, be a Singapore resident and must consent to undergoing the MPI intervention.

4.4. Exclusion Criteria

Exclusion criteria include patients who are unwilling or unable to perform CAT testing, those that are unable to provide informed consent, and those with other significant eye pathology such as cornea problems, glaucoma, or other retinal diseases that may substantially affect vision. Exclusion criteria assessed by the clinical research coordinator will include those that do not speak English or Mandarin fluently, cognitive impairment (as assessed using 6CIT of ≥8), or obvious observable physical or hearing disabilities that prevents them from completing the CAT questionnaire and undergoing MPI effectively.

5. STUDY DESIGN AND PROCEDURES/METHODOLOGY

This study comprises two study designs running in parallel: (Cohort 1) Comprises of a prospective randomized control trial (RCT) study with two arms to assess the overall effectiveness of MPI, a personalized intervention based on the use of specific sub-optimal CAT QoL domain scores, versus standard care, to improve adherence rates to IVT, and improvements in QoL, VA, and CS, and to increase disease free intervals assessed on OCT, in patients with nAMD or DME receiving IVT and having suboptimal CAT scores. atSNEC; (Cohort 2) For those patients who do not have suboptimal CAT scores, they will continue to be enrolled in a prospective observational cohort study, and undergo routine clinical care.

- Participants who meet the eligibility criteria and provide informed consent will be enrolled and assigned a unique study identification number, before proceeding with study procedures.

- CAT scores will be collected via a hybrid remote or in-clinic delivery method. At baseline, CATs will be administered in-clinic or via CAT links sent by WhatsApp to their contact number . At subsequent timepoints, relevant CAT links will be sent via a WhatsApp message to their designated contact number, to complete the questionnaire remotely on their own SMART device, before their appointment (**Figure 1**). Those who are unable to complete CAT testing remotely will be given an additional opportunity to complete them in-clinic using an internet enabled tablet in person at their clinic visit with/without CRC assistance (**Figure 1**). The CAT scores will be assessed by clinical research coordinator.

- Following baseline assessment, **participants with suboptimal CAT scores (Cohort 1-<50 in any domain)** will be included in the RCT and randomly allocated in a 1:1 ratio to either the intervention group (personalised multi-disciplinary protocolised intervention, MPI) or the control group (standard care). Randomisation will be conducted using a computer-generated random sequence created by an independent biostatistician not involved in recruitment or outcome assessment. To ensure balance across disease types, randomisation will be stratified by diagnosis (neovascular age-related macular degeneration [nAMD] vs. diabetic macular edema [DME]). Allocation concealment will be maintained using sequentially numbered, opaque, sealed envelopes prepared by an independent study coordinator. The envelopes will only be opened after baseline data collection to assign participants to their respective groups. Co-Is that are not treating clinicians and data analysts will remain blinded to group allocation, although masking of participants and principal investigator and Co-Is who are the treating clinicians will not be feasible due to the nature of the intervention.

- For the MPI arm, the CAT scores integrated into the electronic medical records will be used to formulate **an automated protocolized standardized MPI for all patients based on the domain specific scores that are sub-optimal** (See **Table 2**). All MPI patients will receive *a medical consultation (compulsory) and an addition of Intervention 1-4 (electives, 1) NE, 2) OP, 3) OT, 4) SW)*. In the MPI arm, these referrals would be automatically triggered by the study team based on baseline CAT scores and the treating clinician will be informed. The MPI visits will take place on the same day as standard clinical visits where possible, however additional MPI study visits may be needed if there are scheduling challenges. Referral adherence to the MPI appointments and intervention will be assessed.

Sub-optimal scores are defined as any domain where the scores are below 50 at baseline or have reduced by 25% from the baseline visit. Table 2 summarizes the MPI interventions that are relevant to each CAT domain. A tailored MPI will be formulated and recommended to the patient at baseline, or at a follow-up time-points where domain scores decrease, and the MPI should be completed within 4 months.

Table 2: Standardised personalised MPI based on sub-optimal CAT domain-specific scores

Ret CAT		MacCAT	
Item Bank	Interventions	Item Bank	Interventions
Visual symptoms	(2)	Activity Limitation	(2), (3)
Activity Limitation	(2), (3)	Lighting	(2)
Emotional	(1), (4)	Emotional	(1), (4)
Health Concerns	(1), (4)	Concerns	(1), (4)
Convenience	(1), (4)	AMD management	(1), (4)
Lighting	(2),		
Social	(4)		
Economic	(4)		

- In the standard care arm, the treating clinician will be masked from the CAT scores and willuse his/her own discretion when recommending the treatment regimen or when making any appropriate nurse or allied health referrals, independent of the CAT scores. The CAT scores will be recorded by the clinical research coordinator at baseline and follow-up visits for comparison to the MPI arm.

- For those patients who do not have sub-optimal CAT scores at baseline, they will be assigned to an observational study group (Cohort 2) to continue to undergo routine clinical care and at the assigned study time points, they will be reassessed for any changes in their CAT scores and will undergo randomisation into the RCT if their scores have dropped below 50 or have reduced by 25% from the baseline visit. For those patients who do not experience sub-optimal CAT scores or a significant drop in their CAT scores during the duration of the study, they will still have their data collected at

all study visits based on the protocol but will not undergo randomisation. If any of these cohort patients show non-adherence to clinic visits during the duration of the study, they will be eligible for "rescue" MPI according to the clinician's discretion at their next study visit and will be analysed as a separate sub-group.

Study schedule and outcome measures

The primary outcome is the comparison of adherence rates to IVT treatment between the MPI arm versus standard care (Cohort 1) at 6, 12 and 18 month time points (+/- 8 weeks) (main outcome) (Specific aim 1). The follow-up study visits will be coordinated with the planned clinical standard care visits, only if the patient does not have a routine clinical care visit scheduled within the range of the follow-up time-points will an additional study visit be scheduled.

Adherence is defined as
1) patient attends all follow-up appointments within 1 month of the planned follow up date, and
2) patient receives IVT within 1 month of when the doctor recommends IVT.

At each follow up time point, based on the previous scheduled follow-up appointments and recommended IVT schedule, the study team will assess if the patient has been "adherent" or "non-adherent". If the patient does not visit the clinic within the range of the follow-up time points or does not attend the scheduled study visit, phone calls will be made to determine reasons or barriers for adherence. A remote invitation to complete the CAT questionnaire will also be sent to these patients or if uncontactable, they will be approached and interviewed at their next clinical visit. For previously treated patients, previous adherence status up to 2 years prior to study enrolment for the time of IVT treatment will be recorded by the study team from medical records.

Secondary outcome measures will be assessed at baseline and 6, 12, and 18 month follow up visits (+/- 8 weeks) including:

- CAT scores (Specific aim 2A) from the CAT questionnaire database
- Visual function -Monocular and binocular presenting corrected VA and CS (Specific aim 2B) will be collected from the clinical records. If data are not present, the CRCs will conduct these tests on participants using standardized protocols.
- Disease free intervals as defined by the maximum IVT treatment interval where no disease activity recurrence is detected on OCT will be collected from clinical records and OCT images from the clinical database (Specific aim 2B)
- Tertiary outcome measures include the acceptability, adoptability, appropriateness, feasibility, fidelity through mixed method testing with interviews and questionnaires (Specific aim 3).
- The costs of MPI, baseline and 18-month assessment of Euro-quality of life (EQ-5D) to assess QALYs (Specific aim 4)

<u>Qualitative and quantitative analysis of key stakeholders (Specific aim 3)</u>

The PI, assisted by their Co-Is and collaborators, will identify eligible individuals for qualitative interviewing that will be performed with major stakeholders between 6 to 15 months timeline. These include the clinicians, nurses and the allied health specialists (OP, OT and SW) who will be involved in administering the MPI, and patients and care-givers who receive the MPI. Potential individuals will be contacted over email or phone call, and a trained study team will follow up on affirmative responses by obtaining written informed consent to carry out the following study procedures:

Qualitative protocol: Semi-structured (1-on-1) interviews with the above key stakeholders will be conducted to explore their perspectives on barriers and enablers of integrating MPI into a Singapore public hospital for the management of nAMD and DME patients receiving IVT. Purposive and snowball sampling will be used to ensure all stakeholder groups are represented. Interviews will be conducted until no new data emerges.

An interview guide will be developed, underpinned by a suitable implementation research framework such as the NASSS framework (the non-adoption, abandonment, scale-up, spread, and sustainability framework)[60] which was created for planning and investigating implementation of health interventions. We will include interview questions that help elicit stakeholder perspectives on implementation outcomes salient to future implementation success, e.g. adoption, acceptability, appropriateness, feasibility, and fidelity, as defined by Proctor et al 2011[61].

6. SAFETY MEASUREMENTS

6.1. Definitions

Serious adverse event (SAE) in relation to human biomedical research, means any untoward medical occurrence as a result of any human biomedical research which:

- results in or contributes to death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in or contributes to persistent or significant disability/incapacity or
- results in or contributes to a congenital anomaly/birth defect
- results in such other events as may be prescribed

Adverse event (AE) in relation to human biomedical research means any untoward medical occurrence as a result of any human biomedical research which is NOT serious. Adverse event can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease possibly/ probably/ definitely associated with the participant in the human biomedical research.

6.2. Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

The reporting requirements will be in accordance to the reporting requirements published on CIRB website at the time when the event took place.

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the research.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3. Safety Monitoring Plan

The study team will conduct monthly safety reviews, with adverse events reported to the Principal Investigator within 24 hours and serious adverse events requiring immediate reporting. Participants will be withdrawn if they experience Grade 3 or higher adverse events, develop an exclusion criteria, or request withdrawal.

The study will be stopped if more than 30% of participants' experience serious adverse events, interim analysis shows no possibility of achieving study objectives, or new safety information indicates unacceptable risks.

The Principal Investigator will communicate safety concerns to all study sites via email within 48 hours of identification, with monthly safety reports distributed to all study team members. The research coordinator will maintain the central log of all safety events and ensure all site investigators receive updates.

6.4. Complaint Handling

Complaints will be handled by the research co-ordinators and if required the Quality Assurance team at the Singapore National Eye Centre.

7. DATA ANALYSIS

7.1. Data Quality Assurance

Participants information(data) from medical records dating up to 10 years prior and up to 24 months after informed consent is obtained will be collected. Linkage of participant identifiers to sociodemographic and questionnaire data can only be done on the request of the PI. The Investigator(s)/ Singapore National Eye Centre will permit study-related monitoring audits, MCRC and or EC review and regulatory inspection(s), providing direct access to source data/ document.

7.2. Data Entry and Storage

Research data and participant databases will be stored in a secured SERI PHR shared drive. As for the hard copies, they will be stored in the SERI Academia office at Level 6, in a locked cabinet. The principal investigator (PI), co-investigators (Co-I) and CRCs will have access to these data, and this access can be monitored through computer records. Questionnaire data will be entered through an internet-enabled tablet and stored on an IHiS approved secure cloud server hosted in Singapore via AWS as described previously.

8. SAMPLE SIZE AND STATISTICAL METHODS

8.1. Determination of Sample Size

Specific Aim 1 and 2: The primary outcome comparison of adherence rates to IVT treatment between the MPI arm versus standard care at various follow-up time points with 18 months as the main time point. It is estimated that the baseline non-adherence rate with standard care arm is 40% (SD=2). Considering a reduction of the non-adherence rate to 20% as a clinically significant difference, and assuming a power of 80% and a two-sided level of significance at 5%, the minimum sample size

required is 79 patients per arm (rounded up to 160 patients in total). Assuming a maximum 20% dropout in the study we estimate a sample size of 200 patients (Specific aim 1).

For secondary outcomes such as the improvement of QoL as assessed by the various CAT domain scores, we assume a modest effect size difference of 0.5 between the two arms. Using a power of 80%, a two-sided level of significance at 5%, and the maximum 20% dropout rate, we estimate the required sample size is 158 (79 per arm) (Specific aim 2A). Hence, this is included in the larger sample size calculated above.

Specific aim 3: There is no *a priori* sample size required for qualitative interviews. We will continue our semi-structured interviews until thematic saturation is reached (i.e. no new themes emerge). Based on previous studies by our group[31,67], we anticipate the need to interview between 5-10 participants for each stakeholder group to obtain data saturation, broadly: (a) clinicians using CATs and MPI, (b) NE, OP, OT and SW involved in administering MPI (c) patients involved in this study, and (d) caregivers of patients. For the purposes of estimating a budget for this grant proposal, we state an indicative sample size of 40 interview participants i.e. 10 in total for stakeholder group a and b, and 30 for stakeholder group c and d (patients and caregivers).

Specific aim 4: The sample size required for cost-effectiveness analysis is usually larger than clinical studies as it involves estimating the joint distribution of patient outcomes and costs. Furthermore, power calculations require setting a willingness-to-pay threshold, which is not known for Singapore. However, as cost-effectiveness is more concerned with estimating effect size rather than hypothesis testing, it can still provide valuable information even if underpowered. Instead of confidence intervals, sensitivity analysis will be used to assess the range of estimated values.

8.2. Statistical and Analytical Plans

Specific aim 1: Planned statistical analysis for the primary outcome measure will be the difference in percentage of adherence rate between the standard care and MPI arm assessed by the chi-square test or Fisher's exact test. Cox proportional hazards model will be used to assess the independent effect of MPI on adherence rates, after adjusting for age, baseline CAT scores, visual function, anatomical outcomes, type of IVT medication given, and disease-free intervals.

Specific aims 2A and 2B: CAT scores will be assessed with a two-sample t-test to compare the differences in mean CAT scores between the 2 arms. Linear mixed models will be used to assess the independent effect of MPI on follow-up CAT scores, after adjusting for fixed effects terms such as age, baseline CAT scores, visual function, anatomical outcomes, type of IVT medication given, and disease-free intervals, and a random slope term follow-up time (measured in months).

Specific aim 3 Interviews will be conducted in-person or online, audio-recorded, and transcribed verbatim by professional transcribers (i.e. transcriptions outsourced to third party). Designated researchers in the study team will check a random 10% sample of interview transcriptions for accuracy, prior to qualitative data analysis. If errors or inaccuracies are found in the random sample of transcripts, then 100% of the transcripts will need to be checked and edited for accuracy, prior to data analysis. We will analyse the qualitative data as per Gale et al's thematic analysis[62]. NVivo software will be used to manage qualitative data analysis. A standardised questionnaire to assess implementation outcomes will also be administered to all the stakeholders for a quantitative assessment.

Specific aim 4: To assess the cost-effectiveness analysis of the MPI, we will develop a cohort-based Markov model embedded within a decision tree to simulate the net lifetime cost and effectiveness of the MPI compared to standard care. The model's health states will be defined by VA ranges, consistent with prior cost-effectiveness studies for of macular disease treatments[63,64]. We will quantify the incremental costs of implementing the MPI using an activity-based costing approach, which includes all non-sunk costs – such as labour, materials and supplies, and amortized technology and rental costs – associated with treating each patient. These costs will be categorized by key activities, including physician/nurse/allied health training, CAT assessment, and referral to personalized programs. Treatment costs will be based on non-subsidized bill sizes, which are expected to approximate actual costs. Data on health resource utilization and costs incurred during the first 18 months will come from this study. For benefits, which are measured in terms of QALYs gained, QoL weights will be measured for month 18 using the EQ-5D instrument and validated local preference weights[65]. The key difference between the MPI and standard care will be the proportion of IVT-adherent patients, influencing costs and long-term VA outcomes. As these differences likely persist over a patient's remaining lifetime, the model will extrapolate long-term VA and corresponding quality-of-life weights based on published trajectories for treated (adherent) and untreated (non-adherent) patients[66]. With each subsequent annual cycle, the surviving cohort will accrue costs and QALYs associated with their VA and IVT adherence status. This model will be used to estimate the incremental cost-effectiveness ratio (ICER) for the MPI. We will also conduct one-way and n-way sensitivity analyses for all key model inputs and present cost-effectiveness acceptability curves showing the probability that the MPI is cost-effective at various willingness-to-pay thresholds policymakers may consider. We will also conduct scenario analyses to investigate the robustness of our results to alternative assumptions on long-run VA trajectories.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10. QUALITY CONTROL AND QUALITY ASSURANCE

The major quality control and assurance features of the study are:

- Standardised eligibility and exclusion criteria
- Adherence to protocol and follow-up
- Monthly meetings of study staff personnel (SERI) to review methods and discuss problems
- Regular meetings between PI and study staff to aid in recruitment, follow up and adherence to protocol

11. ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Study Protocol, including the final version of the Participant Information and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB of any amendments to the protocol or other study-related documents, as per local requirement.

11.1. Informed Consent

The study population will be recruited from retinal outpatient clinics in a single tertiary centre (SNEC) at various locations where retinal clinics are conducted and eligible patients will be identified first face-to-face by the consulting physician and referred to then CRC during their clinic appointment. The CRC will approach the patient and provide details of the study and further confirm the eligibility for the study before informed consent is obtained.

After the participants are given adequate time to consider participation in this study after consultation with the treating physician and study coordinator in a private, comfortable, quiet room where informed consent will then be taken. For patients participating in semi-structured interviews, verbal consent can first be obtained via phone (if patient was contacted by phone) or in person (if patient was approached at next appointment visit). Written consent will be obtained in person when patient arrives for the appointment. All consent will be obtained at time and place convenient to patient.

11.2. Confidentiality of Data and Patient Records

Research data and participant databases will be stored in a secured SERI PHR shared drive. As for the hard copies, they will be stored in the SERI Academia office at Level 6, in a locked cabinet. The principal investigator (PI), co-investigators (Co-I) and CRCs will have access to these data, and this access can be monitored through computer records. Linkage of participant identifiers to sociodemographic and questionnaire data can only be done on the request of the PI. Questionnaire data will be entered through an internet-enabled tablet and stored on an IHiS approved secure cloud server hosted in Singapore via AWS as described previously.

12. PUBLICATIONS

Please refer to the SERI publication policy.

13. RETENTION OF STUDY DOCUMENTS

Records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, results of consultations, etc.) as well as IRB records and other regulatory documentation will be retained by the PI in a secure storage facility. The records will be accessible for inspection and copying by authorized authorities. The research data will be stored for at least 15 years and then destroyed or deleted.

14. FUNDING AND INSURANCE

Funding will be provided by the NMRC HPHSR Clinician Scientist Award (INV category) Application number MOH-HCSAINV25jan-0006.

Research participants will be provided transport allowance for their visits (SGD $20 per patient) for all patients who enrol in the study (Cohort 1 and 2) to be collected at the exit visit of the study timed to

be similar to clinical visits. For the Cohort 1 patients, they will also be reimbursed at each study visit ($20/visit) and compensation for their time during the qualitative interviews (SGD $50/patient).

List of Attachments

Appendix 1 – References

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