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Economic evaluation of an e-mental health intervention for patients with retinal exudative diseases who receive intraocular anti-VEGF injections (E-PsEYE): protocol for a randomised controlled trial

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ABSTRACT

Introduction Because of the great potential of vascular endothelial growth factor inhibitors (anti-VEGF) for retinal exudative diseases, an increased number of patients receives this treatment. However, during this treatment, patients are subjected to frequent invasive intravitreal injections, and the effects on reversing the process of vision loss are uncertain, which may have negative consequences for patients' mental health. One in three patients experience at least mild symptoms of depression/anxiety. To support patients in dealing with these symptoms, an e-mental health intervention (called E-PsEYE) has been developed. E-PsEYE is based on cognitive–behavioural therapy (CBT) and contains nine modules. A stepped-care model with three steps will be used to deliver the intervention: (1) providing information and psychoeducation, (2) when symptoms of depression/anxiety persist, guided CBT is offered and supported by social workers from low vision rehabilitation services and (3) when symptoms still persist, patients are referred to their general practitioner.

Methods and analysis An economic evaluation from a healthcare and societal perspective will be conducted alongside a multicentre randomised controlled trial in two parallel groups to evaluate whether E-PsEYE is cost-effective in comparison with usual care. Participants (n=174) will be 50 years or older, have retinal exudative diseases, receive anti-VEGF treatment and have mild symptoms of depression/anxiety (assessed prior to randomisation). Main outcome measures are: depression (Patient Health Questionnaire-9), anxiety (Hospital Anxiety and Depression Scale-Anxiety) and quality-adjusted life-years (determined with the Health Utility Index-3 and the EuroQol-5 dimensions). Five measurements take place: at baseline and after 3, 6, 9 and 12 months.

Ethics and dissemination The study has been approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam. It will provide new and essential information on the cost-effectiveness of an innovative intervention for a vulnerable population.

Strengths and limitations of this study

► This is the first randomised controlled trial to investigate e-mental health in people with eye diseases/vision loss.
► The outcomes will provide new and essential information on the cost-effectiveness of an innovative intervention for a vulnerable population.
► The pragmatic design of the study provides a good representation of clinical practice that enables measuring all possible effects of the intervention and good external generalisability of the outcomes.
► Feasibility and implementability have a high priority in the study design, which is especially relevant in this vulnerable population.
► Participants and therapists cannot be masked due to the nature of the intervention, and some selection bias may be expected for which a non-response analysis will be performed.

Outcomes will be disseminated through peer-reviewed publications and conference presentations.
Trial registration http://www.trialregister.nl, identifier: NTR6337.

INTRODUCTION

Retinal exudative diseases (ie, age-related exudative macular degeneration, diabetic retinopathy and macula oedema) are the leading causes of vision loss in older adults.[1 2] They cause pathologically changed and newly formed blood vessels to leak and damage the retina, reducing vision. There is currently no cure for these diseases, but pharmacological inhibition of the vascular endothelial growth factor (anti-VEGF) in the eye can have a beneficial effect. Anti-VEGF drugs that reduce the

leakage and slow the growth of new blood vessels are injected into the eye at various intervals (often monthly). For approximately one-third of the patients, these injections lead to a substantial improvement in vision.[3] Therefore, anti-VEGF treatment is increasingly being offered in ophthalmic practice. However, about one-third has to deal with further vision loss despite treatment.[1–3]

The uncertainty on reversing the process of vision loss and the frequently repeated invasive intravitreal injections that patients have to endure can have a great impact on patients' mental health.[4] Studies show that about one in three patients experience at least mild symptoms of depression and/or anxiety.[4–6] These symptoms are the most important predictors of developing major depressive or anxiety disorders[7] and can lead to increased vision-specific disability,[8] decreased health-related quality of life[9] and increased mortality.[10] Moreover, depression and anxiety generate substantial economic burden due to increased healthcare utilisation (ie, public mental healthcare use) and productivity losses.[11–13]

Research shows that e-mental health interventions are promising in reducing depression and anxiety in patients with chronic somatic disorders.[14 15] Such interventions stimulate patient empowerment, are independent of time and place (which may lower barriers for receiving mental health services) and relatively little effort from professionals is needed, reducing healthcare costs.[14 15]

Therefore, E-PsEYE was developed for patients with retinal exudative diseases who receive anti-VEGF treatment and experience mild symptoms of depression and/or anxiety. E-PsEYE is an e-mental health intervention based on a guided self-help course with cognitive–behavioural therapy (CBT), developed for patients with severe vision loss and at least mild symptoms of depression and/or anxiety from low vision rehabilitation organisations and found effective as part of a stepped-care programme to prevent the onset of major depressive and anxiety disorders.[16] This self-help course was modified for patients who receive anti-VEGF treatment and adjusted to an e-health intervention. Previous research showed that CBT can be effective in reducing depression and anxiety in people with visual impairment.[16 17]

Here we provide a protocol for an economic evaluation to investigate the cost-effectiveness of E-PsEYE in reducing depression and anxiety in older patients (aged ≥50 years) with retinal exudative diseases who receive intraocular anti-VEGF injections and to investigate the cost–utility for quality-adjusted life-years (QALYs) of E-PsEYE in comparison with usual care.

METHODS

Design

An economic evaluation from a healthcare and a societal perspective will be performed alongside a single-masked, multicentre (ie, five Dutch hospitals will participate), randomised controlled trial. Measurements will take place at baseline and after 3, 6, 9 and 12 months.

Randomisation

Participants will be individually randomised according to a 1:1 ratio to usual care or E-PsEYE plus usual care. A computerised random number generator will be used to produce the allocation scheme. This will be based on random sequence block randomisation (blocks of 2, 4 and 6) and stratified by the five participating hospitals. Randomisation takes place after the baseline measurement by an independent researcher. Patients will receive the outcome of randomisation by email. Due to the nature of the intervention, participants and therapists cannot be masked. At the outset of the study and during each contact with the research team, participants are told not to divulge the nature of their treatment allocation. We will check if masking is maintained by asking the research assistant to guess which treatment arm was offered.

Intervention

E-PsEYE is based on CBT and contains nine web-based modules, which patients follow at home or at any other place they prefer during a period of up to 3 months. A stepped-care model with three steps will be used to deliver the intervention. (A) First, a welcome module, containing information about retinal exudative diseases, anti-VEGF treatment and psychoeducation will be offered. Previous studies have shown that mild symptoms of depression/anxiety may decrease by only providing psychoeducation.[18 19] If required, an Information and Communication Technology (ICT) trainer from Royal Dutch Visio (RDV; the low vision rehabilitation organisation that participates in this study) will provide a computer training explaining the software features of E-PsEYE before participants start using the intervention. (B) If mild symptoms of depression and/or anxiety persist, the eight CBT-based follow-up modules will be provided. These eight modules are aimed at: dealing with (1) uncertainty surrounding anti-VEGF treatment; (2) depression and anxiety; (3) fatigue and stress; (4) participating in pleasurable activities; (5) replacing self-defeating thoughts with healthier thoughts; (6) identifying and replacing negative thought patterns; (7) identifying and replacing negative communication styles; and (8) setting goals for the future. Guidance during step two will be provided by trained and supervised social workers (n=4) from RDV. After participants have finished exercises as part of each module, social workers will receive a notification by email. Within a week, the social worker provides feedback on the exercises (digitally or by telephone, depending on patients' preferences) with the aim to clarify information and motivate patients to persist in carrying out the course. The intensity of guidance will depend on patients' needs and will be accurately reported (max. 2 hours in total). (C) If mild symptoms of depression and/or anxiety still persist after E-PsEYE, patients are referred to their general practitioner (GP) to discuss further treatment.

Social workers will be trained in delivering guidance (6 hours in total) by the researcher (background in social work) and the ICT expert from RDV. Training consists of
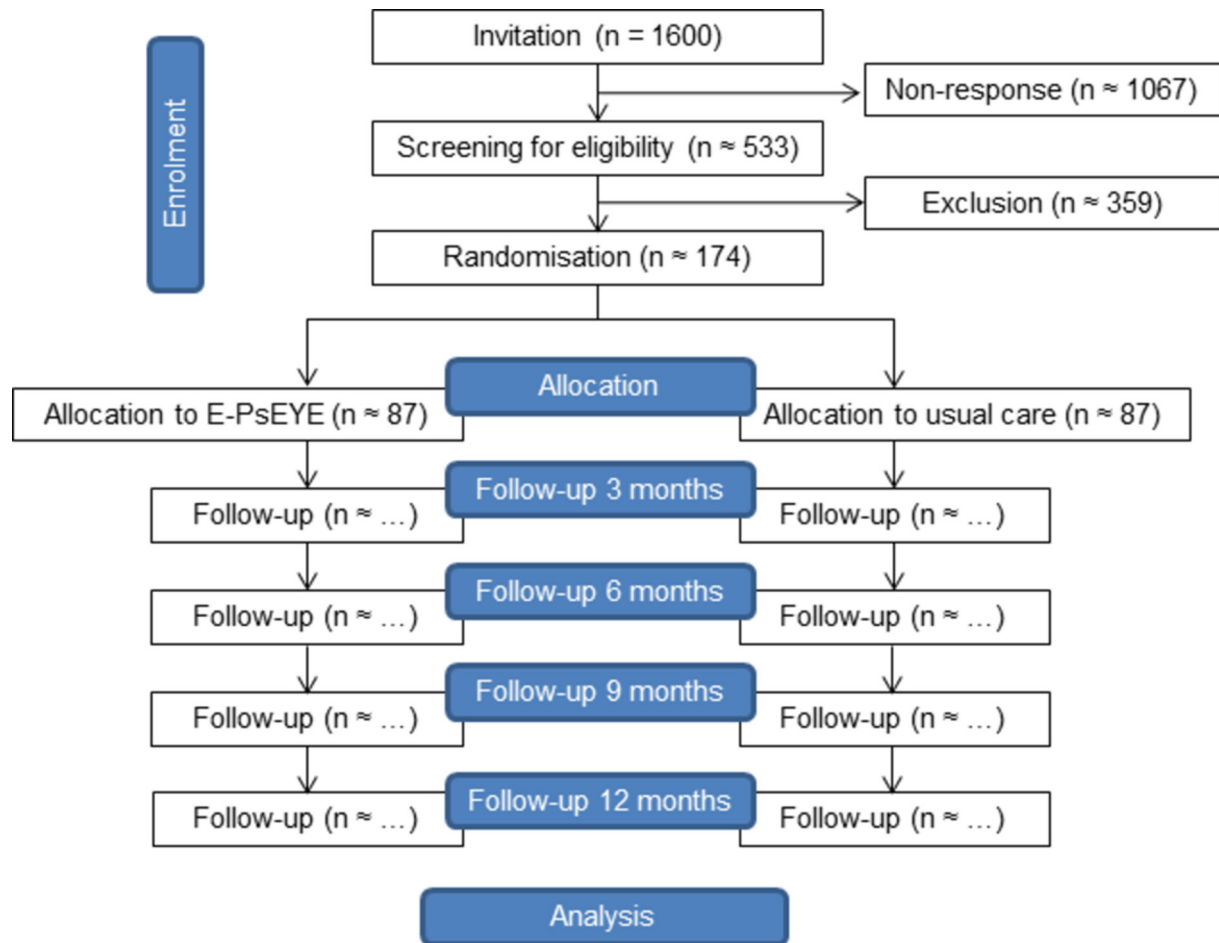
Figure 1 Overview of the study design and patient flow.

a workshop during which the study and intervention are explained, a course in providing the online intervention and the role as coach is provided (2 hours) and practice in two patient representatives while receiving intensive supervision (4 hours). Additionally, intervision sessions will be organised during the trial by social workers themselves.

Usual care

Usual care in both the intervention and control group includes care provided at the ophthalmology departments of the five participating Dutch hospitals (including intraocular anti-VEGF treatment and other care aimed at improving patients' vision or stabilising vision loss), which is reported by means of case report forms, and/or care provided by other healthcare providers (including low vision rehabilitation services), which is measured with the iMTA Medical Consumption Questionnaire (iMCQ; see www.imta.nl).

Sample size

The sample size calculation was based on our former study on the effectiveness of a stepped-care intervention in older patients from low vision rehabilitation organisations,[16] since E-PsEYE was based on the second step of this intervention. In the current study, we aim to reduce

both depressive and anxiety symptoms. Therefore, our sample size calculation was based on the outcomes of the Centre for Epidemiologic Studies Depression Scale (CES-D), which covers both depressive and anxiety symptomatology.[20 21] Twelve months after the guided self-help course (on which E-PsEYE was based), we found a mean difference of 2.5 on the CES-D. In our current study design with four follow-up measurements (after 3, 6, 9 and 12 months), sample sizes of 65 per arm achieve 80% power to detect a difference of 2.5, having a compound symmetry covariance structure when the SD is 6.4, the correlation between observations within the same subject is 0.5 and the alpha level is 0.05 (two sided). Taking into account, a drop-out rate of 25% after 12-month follow-up[16]; sample sizes of 87 per arm (total: n=174) are needed.

Recruitment and study proceedings

A total of 1600 patients from the five participating Dutch hospitals (±320 patients per hospital) who receive intraocular anti-VEGF injections will be addressed by letter to participate in the RCT in two waves (July 2017 and November 2017) to be able to include enough participants. Since we expect that about one-third has mild symptoms of depression and/or anxiety, about 40% will be willing to participate, and 83% has access to the

internet (based on unpublished pilot data), we expect to be able to include 174 eligible participants. If our expectations are incorrect, we will be able to address more patients at the participating hospitals to take part in our study. Patients will receive a letter from their ophthalmologist, in which all necessary information regarding the study, as well as an invitation to participate is included. When patients consider participating, they will receive additional information from the research team. Based on this information, written informed consent is obtained. Baseline measurements (ie, digital questionnaires, with guidance by telephone if needed) will be performed to determine eligibility. Subsequently, eligible patients are either enrolled in the E-PsEYE intervention in addition to receiving usual care or will receive usual care only (see figure 1 for an overview of the study design and patient flow).

Digital questionnaires will be used to collect the data. Guidance by telephone will be provided by the research team if needed. Data will be entered into Castor (data entry software) and converted into the statistical software package SPSS for Windows V.22 and R Studio, V.0.99.896. For each participant, a code (from 1000 to 5999) is used. A 'key file' (in which these codes are linked the patients' names, addresses and phone numbers) will be saved separately and will be deleted after the study has ended. Data will be stored at the VU University Medical Centre computer network with password. Written questionnaires and signed consent forms will be kept in a locked cabinet in a locked room, only accessible to the research team. Data will be stored for 15 years before being destroyed.

Participating in this study is with negligible risk. Therefore, appointing a data monitoring committee is not needed. However, it is possible that the intervention will cause adverse events (ie, undesirable experiences occurring to a participant during the study). All adverse events will be recorded by the research team. All serious adverse events (ie, any untoward medical occurrence or effect that results in death, is life threatening, requires hospitalisation, results in significant disability or incapacity or any other important medical event) will be reported by the research team to the accredited medical ethics committee within 7 days. All events will be followed until they have abated, or until a stable situation has been reached and the patient's GP is contacted.

Participants

In order to be eligible to participate in this study, patients must meet all of the following criteria: (1) they should be 50 years or older; (2) they should be diagnosed with a retinal exudative disease (ie, macular degeneration, diabetic retinopathy and/or macula oedema caused by retinal vein occlusion); (3) they should be treated with anti-VEGF injections; (4) they should have at least mild symptoms of depression and/or anxiety (a score of 5 or higher on the Patient Health Questionnaire (PHQ)-9[22] and/or a score of 3 or higher on the Hospital Anxiety and Depression Scale-Anxiety (HADS-A))[23]; (5) they should

be able to speak the Dutch language adequately; and (6) they should have access to the internet.

Patients are excluded from participation in this study if: (1) they are cognitively impaired, which is assessed by telephone with a score <3 on the six-item Mini Mental State Examination[24]; (2) have a score of 20 or higher on the PHQ-9, indicating severe symptoms of depression because the E-PsEYE intervention would then not be suitable; (3) indicate to be suicidal (ie, patients respond positively on the PHQ-9 suicide item); and (4) are heavy drinkers (score of 8 or higher on the Alcohol Use Disorders Identification Test.[25] These patients will be referred to their GP to discuss other (more intensive) treatment options. Subjects who have a score of 20 or higher on the PHQ-9 or who indicate to be suicidal during the follow-up measurements will also be contacted by telephone by the research team to discuss if a direct referral to their GP is necessary.

Outcome measures

Demographics and anti-VEGF treatment

Demographics and comorbid conditions will be measured at baseline, and life events in the past year (eg, getting injured or developing a serious illness, getting divorced, the death of a relative or close friend) will be measured after 12 months (self-rated). Information on anti-VEGF treatment (eg, frequency, period, monocular vs binocular) and visual acuity will be collected at baseline, and after 3 and 12 months from patient files at the participating hospitals.

Primary clinical outcomes

Symptoms of depression and anxiety are measured with the PHQ-9 and HADS-A[22 23] at baseline, and after 3, 6, 9 and 12 months. The PHQ contains nine questions on a 4-point Likert scale, ranging from 0 (not at all) to 3 (nearly every day). Total scores range from 0 to 27, with a cut-off score of ≥5 indicating mild depression. The PHQ-9 is widely used and is considered a valid and reliable tool to measure depression in older adults with vision loss.[22] The HADS-A has seven items on a 4-point Likert scale, with a total score ranging from 0 to 21 and a cut-off score of ≥3 for mild anxiety. The reliability of the HADS-A is reported to be 'good to very good' in older adults.[23] Health-related quality of life is measured at baseline, after 3, 6, 9 and 12 months with the Health Utility Index Mark 3 (HUI-3)[26] and the EuroQol-5 Dimensions with five levels (EQ-5D-5L),[26 27] which are used to determine QALYs. The EQ-5D-5L is the preferred measure to determine QALYs in economic evaluations.[27] We added the HUI-3 since it specifically covers sensory impairment, which is relevant in our study population.[26]

Secondary clinical outcomes

Adaptation to vision loss is measured with the 9-item Adaptation to Vision Loss (AVL) scale,[16 28] illness cognitions (related to helplessness, acceptance and disease benefits) are measured with the 18-item Illness Cognition

Questionnaire,[29] vision-related quality of life is measured with the 18-item Low Vision Quality of Life questionnaire,[16 30] mastery is measured with the 7-item Pearlin Mastery Scale[31] and cognitive therapy skills are measured with the Competencies of Cognitive Therapy Scale-Self Report of which two versions will be used: a 29-item patient version and a 9-item therapist version.[32] These secondary clinical outcomes are measured at baseline and after 3 and 12 months.

Cost-evaluation outcomes

The iMCQ is used to measure healthcare utilisation (eg, the number of contacts with a GP, physiotherapist, social worker, psychologist, hours of homecare received and medication use) and the iMTA Productivity Cost Questionnaire is used to measure and value absence and presenteeism from paid and unpaid work (eg, number of sick days and number of days less productive; see www.imta.nl)[33] at baseline, after 3, 6, 9 and 12 months. Standard costs for healthcare utilisation from the recently updated Dutch costing manuals will be used (see guideline at www.zorginstituut.nl). In addition, the costs of the intervention will be measured, which depends on the number of people who only follow the first module and those following the total intervention. Medication use is valued using prices from Dutch Medical costs guidelines (www.medicijnkosten.nl). Productivity losses will be valued using the friction cost approach, assuming that after a certain period of time (ie, 161 days), the sick employee is replaced.[34] Therefore, lost productivity costs are generated only during the friction period.

Process evaluation outcomes

Compliance is operationalised in the intervention group after 3 months by patients rating their effort and social workers rating patients' compliance to the E-PsEYE intervention, based on a 10-point scale (0=no effort/compliance to 10=full effort/compliance). In addition, patients are asked to keep a diary on how often and for how long they used the intervention. Recall is operationalised after each module in step 2 by social workers rating the degree to which patients seem to remember last modules on a 10-point scale (0=patient remembers nothing to 10=patient remembers everything). Patient satisfaction is measured with the Dutch Mental Healthcare thermometer of satisfaction.[35] This is a widely used 20-item questionnaire on patients' satisfaction with provided information, their relationship with the social worker and results of the treatment. Therapist satisfaction and adherence is measured by means of evaluation forms filled out by social workers during the intervention, containing information on: time spent on guided support by email or telephone, time after responding to exercises that were performed by participants, time spent on intervision sessions and satisfaction with the intervention. An overview of all measurements and instruments is provided in table 1.

Table 1 Overview of all measurements and instruments					
	Baseline	3 months	6 months	9 months	12 months
Cognitive functioning: six-item MMSE[24]	x				
Alcohol use: AUDIT[25]	x				
Demographics and comorbidities	x				
Life events in the past year					x
Anti-VEGF treatment	x	x			x
Depressive symptoms: PHQ-9[22]	x	x	x	x	x
Anxiety symptoms: HADS-A[23]	x	x	x	x	x
Health-related quality of life: HUI-3 and EQ-5D[26]	x	x	x	x	x
Adaptation to vision loss: AVL[28]	x	x			x
Illness cognitions: ICQ[29]	x	x			x
Vision-related quality of life: LVQOL[30]	x	x			x
Mastery: PMS[31]	x	x			x
Cognitive therapy skills: CCTS-SR[32]	x	x			x
Healthcare utilisation: iMCQ	x	x	x	x	x
Absence/presenteeism work: iPCQ[33]	x	x	x	x	x
Process evaluation		x			

AUDIT, Alcohol Use Disorders Identification Test; AVL, Adaptation to Vision Loss; CCTS-SR, Competencies of Cognitive Therapy Scale-Self Report; EQ-5D, EuroQol-5 Dimensions; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HUI-3, Health Utility Index Mark 3; ICQ, Illness Cognition Questionnaire; iMCQ, iMTA Medical Consumption Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire; LVQOL, Low Vision Quality of Life; MMSE, Mini Mental State Examination; PHQ, Patient Health Questionnaire; PMS, Pearlin Mastery Scale; VEGF, vascular endothelial growth factor.

Statistical analysis
Clinical effectiveness analysis
The study will be conducted in adherence to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Two-sided tests will be used with a significance level of p<0.05. Linear mixed modelling will be used to compare change in all primary and secondary clinical outcome measures over time between trial arms, which will be based on the intention-to-treat principle (ie, data of all randomised patients will be included independent of treatment completion). If necessary, the models will be adjusted for confounders. Questionnaires with latent constructs will be analysed using item response theory models.

Cost-effectiveness and cost–utility analysis
Both a cost-effectiveness analysis (CEA), with the PHQ-9 and the HADS-A as primary measures of effectiveness, and a cost–utility analysis (CUA), based on QALYs, from a healthcare and societal perspective will be performed. Missing cost and effect data will be imputed using multiple imputation techniques according to the Multivariate Imputation by Chained Equations (MICE) algorithm.[36] The results of the imputed datasets will be pooled using Rubin's rules.[37] Bias-corrected and accelerated bootstrapping with 5000 replications will be used to calculate 95% CIs around the mean difference in total costs between the two groups for both perspectives. Incremental cost-effectiveness ratios (ICERs) will be calculated. Bootstrapping will be used to estimate the uncertainty surrounding the ICERs, which will be plotted graphically on cost-effectiveness planes. Cost-effectiveness acceptability curves will also be estimated. Findings will be integrated with published reports and literature to extrapolate the findings to a national level.

Budget impact analysis (BIA)
Based on the results of the clinical study, the CEA and the CUA, a BIA will be performed to inform decision makers on the financial consequences of implementing E-PsEYE in routine practice. Guidelines by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force will be used for the BIA, that is, relevant features of the healthcare system, access restrictions, anticipated uptake and the use and effect of current and new intervention(s) will be taken into account. The BIA will be performed from the perspective of: (1)society (including both direct healthcare and indirect non-healthcare costs) and (2) health service providers and health insurers (including only direct healthcare costs). The trial results will be extrapolated, by means of a simple model, from a time horizon of 2 years to 5 years, concerning the entire Dutch population. Due to a lack of registration, only an estimation of the number of people who receive anti-VEGF injections in the Netherlands can be provided based on GP registrations. The extrapolation will assume a constant incidence of clinically significant symptoms of depression and anxiety in older adults who receive anti-VEGF treatment. Also, we expect that the detection rate as found in the trial will be stable over time. Therefore, the extrapolation will be linear. A factor that is expected to change with time is the uptake of the E-PsEYE intervention. This factor will be used for scenario analysis in the BIA. For each perspective, we assess costs when 10%, 20%, 30% and 100% of the target group receive E-PsEYE. These scenarios will be compared with the baseline scenario, reflecting current care, where 0% of the target group is offered E-PsEYE. Sensitivity analyses will be performed on relevant parameters such as the uptake of E-PsEYE and unit costs. The source of the unit prices will vary with the perspective. Also, future costs will be indexed and not discounted. The precision of costs will be in accordance with the described perspectives. In addition, a modelling approach will be used to provide a wider range of estimates in which cost estimates from the trial results will be combined with data from the literature.

Implementation
During the E-PsEYE trial, a problem analysis study on barriers and facilitators for implementation will be conducted to identify and target barriers for nationwide implementation. This will be a qualitative study including semistructured interviews with patients, ophthalmologists, heads of ophthalmology departments, social workers and managers from low vision rehabilitation organisations. The number of participants will depend on the moment when saturation of data is reached, that is, when more data will not lead to more information. All interviews will be recorded by a digital voice recorder and transcribed verbatim using F4 software.[38] Data will be analysed using Atlas.Ti software (V.7.5) and the so-called 'framework method' will be used, which combines deductive and inductive forms of analysis and is most commonly used for the thematic analysis of semistructured interview transcripts.[39] Based on the information obtained by these interviews, an implementation plan will be developed.

DISCUSSION
Older patients with retinal exudative diseases who receive anti-VEGF treatment often experience mental health problems.[4–6] These problems can lead to increased vision-specific disability,[8] decreased health-related quality of life,[9] increased mortality[10] and generate substantial economic burden due to increased healthcare utilisation and productivity losses.[11–13] Therefore, extensive research on mental healthcare for these patients is warranted.

Based on previous studies,[14–16] we expect that the CBT-based e-mental health intervention E-PsEYE may provide a solution. E-PsEYE stimulates a collaboration between ophthalmologists, who primarily focus on curing the patient in the limited time that is available to them, and low vision rehabilitation professionals, who have the means and expertise to provide the necessary mental health support. Moreover, E-PsEYE is accessible

(ie, independent of time and place: patients can use it at home), it stimulates patient empowerment and relatively little effort from professionals is needed, which may result in a cost-effective intervention.

To the best of our knowledge, this is the first randomised controlled trial to investigate e-mental health in people with eye diseases or vision loss. By testing E-PsEYE to reduce symptoms of depression and anxiety in this vulnerable population, this study is highly relevant to patients, clinicians and society in general. Moreover, because a structured evaluation of the feasibility and implementability of E-PsEYE is explicitly taken into account in the design of this study, the results will greatly contribute to the practical evidence about treatment options for depression and anxiety in patients with retinal exudative diseases who receive anti-VEGF treatment. In addition, the study covers a variety of medical fields, that is, low vision rehabilitation, ophthalmology, gerontology, epidemiology and psychology, that could benefit from the results.

Another strength of this study is the pragmatic design that was chosen in which patients, treatments and procedures are similar to daily clinical practice. This greatly enhances the generalisability of the results and possibilities for implementation.

A limitation of this study is that participants and therapists cannot be masked due to the nature of the intervention, which could lead to information bias—for instance, participants who receive E-PsEYE may have more attention on treatment outcomes, which may lead to an overestimation of the results. However, because we chose a pragmatic design for our study, we expect to be able to give a good representation of actual clinical practice. Second, although we use a well-designed randomisation procedure with allocation concealment, some selection bias may be expected because patients who volunteer and will be selected for this study may differ from other eligible individuals. We will perform a non-response analysis to examine these differences. Third, E-PsEYE will only be accessible to people who use the internet. Still, this group of people is vastly increasing, even among older adults.[40]

ETHICS AND DISSEMINATION

The study protocol was approved by the Medical Ethics Committee of the VU University Medical Centre Amsterdam, the Netherlands and will be conducted according to the principles of the Declaration of Helsinki (seventh revision 2013) and the Dutch Medical Research Involving Human Subjects Act (WMO). Results will be presented at national and international conferences and published in peer-reviewed journals.

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