

# Technology Assessment



**Technology  
Assessment Program**

## **Measuring Health-Related Quality of Life for Patients With Diabetic Retinopathy**

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# **Measuring Health-Related Quality of Life for Patients with Diabetic Retinopathy**

Technology Assessment Report

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## **University of Alberta Evidence-based Practice Center**

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## Structured Abstract

**Objectives:** To identify and evaluate the psychometric properties of tools used to measure health-related quality of life (HRQL) in patients receiving treatment for diabetic retinopathy (DR), and to assess the effectiveness of interventions for DR to improve HRQL.

**Data Sources:** We conducted a systematic and comprehensive search in six electronic databases and hand searched reference lists of reviews and included studies.

**Review Methods:** Study selection, quality assessment, and data extraction were completed by reviewers independently and in duplicate. We included articles that presented data on HRQL outcomes following an intervention for DR (including diabetic macular edema (DME). Mean differences and 95 percent confidence intervals were calculated for continuous outcomes. We did not conduct any meta-analyses due to heterogeneity.

**Results:** We identified four validated HRQL measures: 36-Item Short Form Health Survey (SF-36), National Eye Institute Visual Functioning Questionnaire (VFQ-25 and -51), Visual Function Index (VF-14), and Diabetes Treatment Satisfaction Questionnaire (DTSQ). We also identified two tools that are currently undergoing evaluation: the Retinopathy Treatment Satisfaction Questionnaire (RetTSQ) and the Retinopathy Dependent Quality of Life (RetDQoL).

Two randomized controlled trials (RCTs) reported on HRQL outcomes following anti-vascular endothelial growth factor (anti-VEGF) treatment for DME. Seven observational studies reported on HRQL outcomes following: laser photocoagulation (two), vitrectomy (two), panretinal photocoagulation versus vitrectomy (one), and phacoemulsification cataract surgery (two). The RCT comparing pegaptanib sodium versus sham reported a statistically significant improvement from baseline for the composite score of the VFQ-25 at 2 years (but not at 1 year). The three-arm RCT comparing ranibizumab monotherapy versus ranibizumab plus laser versus laser showed a statistically significant difference for the composite score of the VFQ-25 for both anti-VEGF arms versus laser at 1 year. The strength of evidence for anti-VEGF was assessed as low.

For the remaining interventions, the studies were at high risk of bias due to weak study designs (before-after and cohort studies) and poor implementation. There is insufficient evidence to determine whether one of these treatments for DR is more effective than another in improving HRQL in this patient population.

**Conclusions:** We identified few HRQL measurement instruments that have been used to assess the impact of treatment in patients with DR or DME; however, the tools that have been used have been adequately evaluated. Two tools developed specifically for patients with DR are currently undergoing evaluation. In general, HRQL was improved following interventions for DR. Further research on HRQL following anti-VEGF treatment for DME is needed to confirm the results of two RCTs. The current research on the impact of other interventions for DR on HRQL is insufficient to draw conclusions about the relative effect of one intervention versus another. RCTs that assess the impact of treatments for DR should include HRQL as an outcome.

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# Executive Summary

## Introduction

### Diabetic Retinopathy

Diabetic retinopathy (DR) is a leading cause of vision loss in the United States and occurs as a result of pathologic changes of the retinal vasculature.<sup>1</sup> In 2005–2008, the estimated crude prevalence among Americans over the age of 40 with diabetes was 28.5 percent. Although the prevalence of vision-threatening DR is approximately 4.4 percent,<sup>2</sup> the number of affected Americans 40 years or older is expected to triple from 1.2 million in 2005 to 3.4 million in 2050.<sup>3</sup> The prevalence and severity of DR increases with the duration of diabetes; however, it is inversely correlated to glycemic and blood pressure control.<sup>4,5</sup> Moderate vision loss is most commonly related to retinal leakage within the macula, while severe vision loss usually occurs as a result of neovascularization (proliferative diabetic retinopathy; PDR) with subsequent hemorrhage or fibrosis.<sup>6</sup>

Early identification and treatment of DR is important since treatment is both cost-effective and reduces vision loss.<sup>7</sup> The American Academy of Ophthalmologists, the American Optometric Association, and the American Diabetes Association recommend an annual dilated eye examination for all people with diabetes, and more frequent eye examinations for people with known DR.<sup>8-10</sup> Other researchers argue that the frequency of examinations should be stratified to an individual's risk of progression and vision loss.<sup>11</sup>

The mainstay of DR treatment is aimed at reducing the risk of onset and limiting the progression of the disease. Therefore, retinal assessments should be performed on a regular basis to determine the presence and degree of DR, glycemic control should be optimized, and known risk factors such as blood pressure, dyslipidemia, elevated cholesterol, renal disease and abdominal obesity should be controlled. Direct ocular therapy should be prescribed when indicated, while vision rehabilitation and low vision aids should be used to maximize vision if there is a loss.<sup>4,5</sup>

Until recently, the primary treatment for DR has been focal or grid laser of the retina.<sup>12,13</sup> Serial intravitreal injections of triamcinolone have been introduced as a treatment option as they have been shown to be effective at reducing diabetic macular edema (DME); however, their use is becoming less common due to significant adverse effects including elevated intraocular pressure and cataract formation.<sup>14,15</sup> Ranibizumab and bevacizumab are being used with increasing frequency for the treatment of DME; however they have not yet been approved for use in this condition by the Food and Drug Administration. The recommended treatment of PDR remains panretinal photocoagulation<sup>16</sup> with vitrectomy surgery performed when necessary.<sup>14</sup> It is important to note that treatment of DR is not always aimed at restoration of pre-disease visual acuity, but rather at limiting further deterioration. Patients may report a decrease in visual acuity immediately after therapy, which may manifest in low initial perceptions of treatment satisfaction. However, results from the Early Treatment Diabetic Retinopathy Study demonstrate that early treatment with either panretinal photocoagulation or vitrectomy prevents long-term disability due to blindness.<sup>12-14</sup>

Diabetic patients with retinopathy have reported that vision loss impacts multiple areas of well-being including: independence, mobility, leisure, and self-care.<sup>7,17,18</sup> Additionally, DR has been found to impair functioning and overall health-related quality of life (HRQL).<sup>19,20</sup>

## Health Related Quality of Life

**Patient Reported Outcomes.** Patient reported outcomes (PROs) measure a variety of aspects of care including HRQL, patient illness perceptions, and treatment satisfaction or adherence.<sup>21</sup> PROs are distinguished from other outcomes because the report is from the patient's perspective, usually without interpretation by another individual.<sup>22</sup> PROs include: health status, functional status, and quality of life (QOL) or HRQL.<sup>23,24</sup> Health status refers to the identification and assessment of the changes in patients' activities and perceptions compared with normal life.<sup>24</sup> Functional status focuses on the physical capacity to complete everyday activities at home or work. QOL covers a range of experiences related to patients' well-being based on their subjective experiences.<sup>25</sup> Many variables, both objective and subjective, interact to define QOL,<sup>26</sup> but it is dependent upon individual patient experiences, states, and perceptions of their illness.<sup>25</sup> HRQL allows clinicians and researchers to measure the impact of chronic diseases such as diabetes mellitus on the lives of patients.<sup>23</sup> It takes into account the impact of disease and its treatments on physical, psychological, social, and somatic domains of functioning and well-being.<sup>25</sup>

**Measuring Health-Related Quality of Life/Quality of Life.** Collecting HRQL and QOL outcomes allows clinicians and researchers to take into account a wider array of information that cannot be obtained through laboratory or physical measures, and provides a subjective description of functioning alongside objective findings.<sup>27</sup> Through the collection of patient perceptions of interventions, health care providers can better understand what aspects of health patients value most highly and therefore what types of treatment may provide the greatest benefit.

Just as the definitions of HRQL and QOL vary, so too do the tools used for evaluating these outcomes. Evaluation tools may be as simple as a single question asking patients to state their QOL; however, they are more likely to take the form of a questionnaire with multiple items that investigate different domains related to HRQL.<sup>23</sup> HRQL tools can be divided into two categories: generic instruments and specific instruments.

Generic HRQL tools investigate all important aspects of HRQL and allow broad comparisons, but do not necessarily investigate a specific aspect of disease.<sup>28</sup> These tools may be less responsive to change as they provide an overall summary score of HRQL.<sup>23</sup> Specific HRQL instruments target a particular disease, population, or an outcome. Where generic tools allow broad comparisons, specific tools may be more responsive to HRQL changes in the specific patient population under investigation.<sup>23</sup>

**Psychometric Properties for HRQL Tools.** The large number of HRQL tools that are available can make it difficult for researchers and clinicians to determine what tools are the most trustworthy and appropriate for use in clinical and research settings. In recent years, a group of international researchers has undertaken the challenge of identifying what psychometric properties are of greatest importance when evaluating the quality of a HRQL tool, and what criteria should be used in judging the psychometric properties. In 2010, the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist was released for the purpose of evaluating the methodological quality of studies investigating the psychometric properties of HRQL tools.<sup>29</sup> The COSMIN researchers also reached consensus on definitions for these psychometric properties (Table ES1).

**Table ES1. Definitions of psychometric properties**

Domain	Psychometric Property	Definition
Reliability		Reliability is the degree to which the tool is free from measurement error.
	Internal Consistency	Internal consistency reliability is a reflection of the reproducibility of measurement by different items within a multi-item scale.
	Test-retest Reliability	Test-retest reliability is the degree to which the score of a patient who has not changed remains the same under repeated measurements.
Validity		Validity is defined as the degree to which an instrument measures the construct(s) it is intended to measure.
	Content Validity	Content validity is concerned with the content of the measurement tool and whether it is an adequate reflection of the construct to be measured.
	Construct Validity	Construct validity considers whether the scores produced by the instrument are consistent with the hypothesis of how the tool should behave, assuming the tool is valid.
	Criterion Validity	Criterion validity focuses on the degree to which the scores of an instrument reflect a 'gold standard'.
Responsiveness		The responsiveness of a tool demonstrates the ability of the instrument to detect changes in a patient over time when changes in the construct being measured actually occur.
Interpretability		Interpretability is considered important for the usability of the measurement tool rather than as a psychometric property. It is the degree to which a clinician or researcher can equate a qualitative meaning to an instrument's quantitative score.

## Key Questions

- 1a. What HRQL measures have been used in studies of treatments for DR?
- 1b. What are the psychometric properties of the HRQL measures used in the studies?
2. Including only studies that have used reliable and valid measures, what is the evidence that HRQL is improved for any intervention for DR? What is the comparative effectiveness of interventions to improve HRQL in patients with DR?
3. What evidence is presented in the studies about the relationship between the measured improvement in HRQL and any relevant variables, including but not limited to baseline visual acuity, age ( $\geq 65$  years), race, sex, severity, and type of DR (i.e., DME, nonproliferative diabetic retinopathy (NPDR), PDR)?

## Methods

### Literature Search

We conducted systematic and comprehensive searches in the following databases: MEDLINE®, EMBASE®, PsychINFO®, Cochrane Central Register of Controlled Trials®, CINAHL Plus full text, and Scopus to identify relevant studies to address the Key Questions. The searches were run in July 2010. An update search including PubMed was run in March 2011. A full search update was run in January 2012. No date or language restrictions were applied. We also conducted a search of ClinicalTrials.gov for recently completed or ongoing studies. To supplement the database searches, we hand searched the reference lists of review articles and included studies. We did not search for conference papers.

## Study Selection

Two reviewers independently screened titles and abstracts using broad inclusion criteria. The full text of articles identified as “include” or “unclear” were retrieved for formal review. Each article was independently assessed by two reviewers using detailed a priori inclusion criteria and a standardized form. Disagreements were resolved by consensus or by third party adjudication, as needed.

For all questions the population of interest was adults ( $\geq 18$  years) with DR including DME, NPDR, PDR, and other related conditions. For Key Question 1, we included studies that reported the use of any measurement tool that included at least one domain of HRQL, and we considered all study designs. For Key Questions 2 and 3, we included prospective comparative studies that investigated any intervention. We included studies that used a HRQL measurement tool with published data on the instrument’s psychometric properties. There were no language restrictions. We excluded studies that were only available as abstracts.

## Quality Assessment and Grading the Body of Evidence

**Quality Assessment of HRQL Tools.** We used the COSMIN<sup>29,36</sup> checklist to evaluate the psychometric properties of HRQL instruments. The following domains were assessed: content and construct validity, internal consistency, reliability, absolute measurement error, responsiveness, and interpretability.<sup>37</sup> Each domain was rated as “no data available,” “low quality,” “indeterminate,” or “high quality.” One reviewer assessed the HRQL tools in consultation with an expert in the HRQL field.

**Quality Assessment of Included Studies.** We assessed trials using the Cochrane Risk of Bias (ROB) tool for randomized controlled trials (RCTs).<sup>38</sup> The ROB includes six domains which assess sequence generation, allocation concealment, blinding (participants and personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias.

We assessed cohort studies using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies.<sup>39</sup> The NOS includes seven items assessing sample selection, comparability of cohorts, and the assessment of outcomes. The methodological quality of before-after studies was assessed using the modified NOS that assessed sample selection and the assessment of outcomes. Two reviewers independently assessed the methodological quality; discrepancies were resolved through consensus or third party adjudication, as needed.

**Grading the Evidence for Question 2.** The overall strength of evidence for HRQL was assessed using the EPC GRADE approach.<sup>40</sup> The following four domains were examined: risk of bias (including study design and study conduct), consistency, directness, and precision. The overall strength of evidence was graded as “high,” “moderate,” “low,” or “insufficient.” One reviewer rated the strength of evidence.

## Data Abstraction and Analysis

One reviewer extracted data directly into evidence tables, and a second reviewer checked the data for accuracy and completeness. Disagreements were resolved through discussion or third party adjudication, as needed.

We calculated mean differences and 95 percent confidence intervals (95% CI) for continuous variables. We did not conduct any meta-analysis due to the heterogeneity of interventions and patient characteristics.

## Results

### Literature Review

The electronic literature search identified 6,961 unique citations. Sixteen studies addressed Key Question 1a. Of these, 11 used validated HRQL measures (Key Question 1b). Nine primary studies provided data to address Key Questions 2 and 3.

### Key Question 1a. What HRQL measures have been used in studies of treatments for diabetic retinopathy?

We identified four HRQL measures that have been used in studies assessing the treatment of DR. The most commonly used measure was the National Eye Institute Visual Functioning Questionnaire (VFQ). Five studies<sup>41,42,45-47</sup> used the 25-item version (VFQ-25); one<sup>48</sup> used the 51 item version (VFQ-51). In addition, seven recently completed trials that have not yet published their results reported using the VFQ-25. One study<sup>49</sup> used both the VFQ-25 and the Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF-36). Two studies<sup>46,47</sup> used the Visual Function Index (VF-14). One study used both the VF-14 and the MOS 12-Item Short Form Health Survey (SF-12),<sup>52</sup> and another study<sup>53</sup> used the VF-14 plus a questionnaire to assess satisfaction with surgical outcomes. One study<sup>54</sup> used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) plus a questionnaire to assess the degree to which treatment outcomes corresponded to patient expectations. One study<sup>55</sup> used qualitative interviews to assess QOL but did not use a specific measure.

We also identified two HRQL measures that have been developed specifically for patients with DR: the Retinopathy Treatment Satisfaction Questionnaire (RetTSQ), and the Retinopathy Dependent Quality of Life (RetDQoL) measure. The HRQL assessment tools are described in Table ES2.

## ES2. Description of health-related quality of life assessment tools

Instrument	Administration	Domains Measured	Scoring
<b>Generic HRQL assessment tools</b>			
<b>Short Form–36 (SF–36)</b>	<p><b>Target population:</b> general pt population, aged &gt;14 yr</p> <p><b>Mode of administration:</b> self-complete questionnaire</p> <p><b>Time needed to complete:</b> 5–10 minutes</p>	<p>Physical functioning; Role limitations because of physical health problems; Bodily pain; Social functioning; General mental health; Role limitations because of emotional problems; Vitality; General health perceptions; Health transition</p> <p><b>Items:</b> 8 items (excluding health transition)</p>	<b>Possible range:</b> 0 (least favorable) to 100 (most favorable)
<b>Low-vision HRQL assessment tools</b>			
<b>National Eye Institute Visual Function Questionnaire–25 (VFQ– 25)</b>	<p><b>Target population:</b> pt with low vision</p> <p><b>Mode of administration:</b> pt interview; self- administered</p> <p><b>Time needed to complete:</b> 5 minutes</p>	<p>Overall health; Overall vision; Difficulty with: i) near vision; ii) distance vision; Limitations in social functioning; Role limitations; Dependency on others; Mental health symptoms; Driving difficulties; Pain and discomfort around the eyes; Peripheral vision; Color vision</p> <p><b>Items:</b> 25 or 26 items (versions vary between 2 and 3 questions in the driving domain)</p>	<b>Possible range:</b> 0 (most severe impairment) to 100 (no impairment)
<b>Visual Function–14 (VF– 14)</b>	<p><b>Target population:</b> pt treated with cataract surgery</p> <p><b>Mode of administration:</b> NR</p> <p><b>Time needed to complete:</b> NR</p>	<p>Vision dependent functional activities: e.g. reading; recognizing people; seeing steps, stairs or curbs; doing fine handwork; writing checks or filling out forms; playing games, taking part in sports, cooking, watching television; and driving</p> <p><b>Items:</b> 18 questions cover 14 items</p>	<b>Possible range:</b> 0 (most severe impairment) to 100 (no impairment)

DM = diabetes mellitus; DR = diabetic retinopathy; NR = not reported; pt = patient; QOL = quality of life tx = treatment; yr = year

## ES2. Description of health-related quality of life assessment tools (continued)

Instrument	Administration	Domains Measured	Scoring
<b>Diabetes-related HRQL assessment tools</b>			
<b>Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs)</b>	<p><b>Target population:</b> pt with DM</p> <p><b>Mode of administration:</b> self-completed questionnaire</p> <p><b>Time needed to complete:</b> NR</p>	<p>Treatment Satisfaction; Perceived frequency of hyperglycemia; Perceived frequency of hypoglycemia</p> <p><b>Items:</b> 8 items</p>	<p><b>Possible range:</b> <i>Treatment Satisfaction:</i> 0 (most dissatisfied) to 36 (most satisfied);</p> <p><i>Perceived frequency of hyperglycemia/hypoglycemia:</i> 0 (least frequent) to 6 (most frequent)</p>
<b>Diabetic retinopathy-related HRQL assessment tools</b>			
<b>Retinopathy Dependent Quality of Life (RetDQoL)</b>	<p><b>Target population:</b> pt with DR</p> <p><b>Mode of administration:</b> paper based questionnaire</p> <p><b>Time needed to complete:</b> NR</p>	<p>Retinopathy-dependent quality of life: e.g. household tasks; personal affairs; shopping; feelings about the future/past; working life; close personal relationship; family life; social life</p> <p><b>Items:</b> 24 items, also assesses the importance of each item to the pt</p>	<p><b>Possible range:</b> -9 (max negative impact of DR on QOL) to 3 (max positive impact of DR on QOL)</p>
<b>Retinopathy Treatment Satisfaction Questionnaire (RetTSQ)</b>	<p><b>Target population:</b> pt with DR</p> <p><b>Mode of administration:</b> paper based questionnaire</p> <p><b>Time needed to complete:</b> NR</p>	<p>Satisfaction of treatment for DR: e.g. tx satisfaction, perceived effectiveness of tx; tx side effects; discomfort or pain; unpleasantness of tx; difficulty of tx; feelings of apprehension r/t tx; feelings of satisfaction regarding influence over tx; safety of tx; time-consumed by tx;</p> <p><b>Items:</b> 13 items asking pt to rate different aspects of treatment</p>	<p><b>Possible range:</b> 0 (worst) to 78 (best)</p>

DM = diabetes mellitus; DR = diabetic retinopathy; NR = not reported; pt = patient; QOL = quality of life tx = treatment; yr = year

## Key Question 1b. What are the psychometric properties of the HRQL measures used in the studies?

The six HRQL tools can be separated into two broad groups: generic and specific. The latter category can be further divided into tools developed for use in populations with low vision, diabetes mellitus, and DR. Table ES3 presents a summary of the ratings of the psychometric properties for the measurement tools.

**ES3. Rating of the psychometric properties of health-related quality of life assessment tools used in studies of treatment of diabetic retinopathy**

Measure	Content validity	Construct validity	Internal consistency	Test re-test reliability	Measurement error	Responsiveness	Interpretability
SF-36	+	+	+	+	+	+	+
VFQ-25	+	+	+	+	0	?	?
VF-14	?	+	+	?	0	?	0
DTSQ	+	+	+	+	+	+	0
RetDQoL	+	+	+	0	0	0	0
RetTSQ	+	+	+	0	0	0	0

Method or result was rated as: + = high quality; ? = indeterminate; - = low quality; 0 = no data available

## Key Questions 2 and 3: What is the evidence that HRQL is improved by any intervention; and what is the relationship between HRQL and any relevant variables?

We identified two RCTs<sup>42,47</sup> and seven observational studies that addressed Key Questions 2 and 3. Sample sizes ranged from 55 to 345 (IQR: 77 – 293.5). Both RCTs were multicenter trials that recruited patients in Australia, North and South America, Europe, India and Turkey. Both trials were assessed as having unclear risk of bias. The primary concern was incomplete reporting and the use of the last observation carried forward approach for missing data. Both trials received industry funding.

For the observational studies, the interventions included laser photocoagulation,<sup>48,54</sup> vitrectomy,<sup>41,45,46</sup> panretinal photocoagulation,<sup>46</sup> and phacoemulsification cataract surgery for diabetic patients with cataracts.<sup>51,53</sup> Two of the four cohort studies were of good quality, and all three before-after studies were of moderate to good quality. However, overall this collection of observational studies is at high risk of bias due to weak study designs (before-after and cohort studies). We conducted a post hoc analysis of the subgroup of patients with diabetic macular edema (DME). Six studies<sup>41,42,45,47,48,54</sup> reported results for those with DME. Two studies<sup>51,53</sup> included patients with DME, but did not report separate results. Patients with DME represented less than five percent of the study sample in these studies. One study<sup>46</sup> did not report whether patients with DME were included in their study.

## Results

**Anti-Vascular Endothelial Growth Factor (anti-VEGF).** Two RCTs provided data (Table ES4). One RCT reported data on the administration of pegaptanib sodium versus sham injections—133 patients received 0.3 mg of pegaptanib sodium and 127 patients received a sham treatment. All patients were diagnosed with DME. The patients receiving pegaptanib sodium reported statistically significant improvements from baseline on the VFQ–25 domains for near



vision activities, distance vision activities, and social functioning at 54 weeks compared with patients treated with a sham injection. There were no statistically significant differences for the other domains or for the composite score. At 102 weeks patients receiving pegaptanib sodium reported statistically significant improvements in the composite score and the domains for distance vision activities, social functioning, and mental health. One three-arm RCT reported data on the administration of ranibizumab with and without laser treatment—116 patients received 0.5 mg of ranibizumab plus sham laser, 118 patients received 0.5 mg of ranibizumab plus laser, and 111 patients received sham treatment plus laser. All patients were diagnosed with DME. The composite score and the scores on the domains for general vision, near vision activities, and distance activities of the VFQ–25 were significantly improved from baseline to 12 months for patients treated with ranibizumab alone, or in combination with laser treatment compared with patients with laser treatment only. The strength of evidence for anti-VEGF is low. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

**Laser photocoagulation.** Two before-after studies provided data (Table ES4). In one study, 105 patients with PDR and DME reported high scores on the DTSQ at 9 months following surgery. Results were not reported separately for the two groups of patients. In the second study, 55 patients with DME reported a statistically significant improvement in HRQL at 3 months following surgery. While HRQL improved following laser photocoagulation, the strength of evidence is insufficient to draw conclusions about the effect of laser photocoagulation on HRQL.

**Vitrectomy.** One cohort study and one before-after study provided data (Table ES4). In the prospective cohort study, 99 patients with PDR reported a statistically significant improvement on the VFQ–25 (Japanese version) at 3 months following surgery. For those with DME (n = 38), the score improved, but the change was not statistically significant. The score on the VFQ–25 for the normal control group was statistically significantly higher than the preoperative and postoperative scores of patients with PDR and DME.

In the before-after study, 41 patients with vitreous hemorrhage reported statistically significant improvements on the VFQ–25 (Japanese version) at 6 months following surgery. This contrasts with patients with DME (n = 28) who reported no significant change in HRQL and fibrovascular membrane (n = 18) who only reported a statistically significant change on the general vision subscale. While HRQL improved for some subgroups of patients with DR following vitrectomy, the strength of evidence is insufficient to draw conclusions about the effect of vitrectomy on HRQL.

**Vitrectomy and panretinal photocoagulation.** One cohort study (Table ES4) provided data for 327 patients with DR. Of these, 136 underwent vitrectomy, 60 received panretinal photocoagulation, and 131 had no treatment and served as a comparison group. For the vitrectomy group, there was a statistically significant improvement in the VFQ–25 (Japanese version) composite score at 1 year following surgery. Changes in the VFQ–25 scores for the comparison group and the photocoagulation group were not statistically significant. The strength of evidence is insufficient to draw conclusions about the relative effect of vitrectomy versus panretinal photocoagulation on HRQL.

**Phacoemulsification.** Two cohort studies provided data (Table ES4). One study evaluated visual outcomes and visual function using the VF–14 after first-eye phacoemulsification cataract

surgery. Three months following surgery, 94 percent of patients reported improved visual acuity, and 93 percent reported improvements in visual function. Patients with no DR or mild retinopathy demonstrated significantly greater improvements in visual acuity and visual function compared with patients with more advanced DR.

The second study followed 89 diabetic patients with bilateral cataracts. At 12 months following surgery, patients with PDR had the lowest VF-14 scores at baseline and improved marginally over the study period regardless of whether they had cataract surgery on one or both eyes. A similar pattern was seen for patients with moderate or severe NPDR. For patients with no or mild NPDR, maximum VF-14 scores at 12 months were significantly higher than for patients with more severe DR.

The impact of first-eye cataract surgery on QOL was evident in patients with no or mild DR with the highest VF-14 scores being achieved by 91 percent of patients in the first month. In contrast, for those with more severe DR, 79 percent achieved the highest VF-14 score after 3 months. In patients with no or mild DR who underwent second-eye surgery the improved functional status achieved after first surgery was sustained. For those who did not have second-eye surgery, VF-14 scores decreased after 8 and 12 months. While HRQL improved following phacoemulsification cataract surgery, the strength of evidence is insufficient to draw conclusions about the effect of this surgery on HRQL.

**Factors associated with outcomes.** No conclusions can be drawn about factors associated with HRQL outcomes. In one study, multivariate analysis found that age <65 years, more severe level of DR, and low preoperative QOL were associated with improved HRQL following laser photocoagulation. In another study that also investigated laser photocoagulation, univariate analysis showed an association between age and treatment satisfaction, with older patients (>65 years) being more satisfied.

In a study that looked at vitrectomy, multivariate analysis showed that improvement in contrast sensitivity was significantly correlated with changes in the VFQ-25 composite score for patients with PDR and DME. There was no significant correlation between VFQ-25 and visual acuity.

## Discussion

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this review identified the evidence on the effect that interventions for DR, including DME have on HRQL. Overall we identified four measures—one generic, two vision-specific, and one diabetes-specific—that have been used to measure HRQL in studies of treatment for DR. As well, we identified two recently developed tools that are specific to patients with DR. We identified two RCTs and seven observational studies involving between 55 and 345 patients that addressed the question of whether HRQL is improved for any intervention for DR.

### HRQL Measures

Only one generic HRQL measure has been used to assess the impact that interventions for DR have on HRQL. The SF-36 gathers information about the patient's perceived health and asks about eight health concepts: physical functioning, physical role functioning, bodily pain, general health, vitality, social function, emotional role functioning, and mental health. Generic HRQL tools are generally insensitive to the presence of specific eye disease. Furthermore, the SF-36

appears to be unresponsive to changes in visual acuity in patients with DR.<sup>49</sup> The authors suggest that this may be because the SF-36 assesses a wide range of characteristics that are not directly related to visual acuity. While the SF-36 is a reasonable choice for researchers to consider if a generic health status measure is needed, other generic measures that include assessment of vision function (e.g., the Health Utilities Index<sup>76</sup>) may be worth consideration for this patient population. Generic HRQL tools can be used to make comparisons with the general population (regardless of the underlying condition), and to estimate the relative impact of various medical conditions.<sup>20,23,49</sup> The decision to use a generic measure along with a specific measure needs to be driven by the purpose of the measurement.<sup>35</sup>

Two validated and clinically responsive vision-specific measures, the VFQ-25 and VF-14, have been used to measure the impact of different interventions on HRQL in individuals with DR. Vision-specific measures have been shown to be sensitive to differences in vision status and functioning among patients with DR.<sup>50,63,64,66</sup>

The diabetes-specific tool, the DTSQ, was specifically developed to measure satisfaction with treatment regimens in individuals with diabetes. Research has shown that satisfaction with treatment is associated with compliance with treatment.<sup>77,78</sup> The DTSQ was not designed to measure satisfaction with other aspects of the diabetes care and management.<sup>67</sup> It is most useful when used as one of a profile of tools to assess other important outcomes, including QOL or HRQL.

We identified two disease-specific measures developed specifically for patients with DR – the RetDQoL and the RetTSQ. The tools have been developed in parallel, and to date, are the only measures that assess the impact of DR on different aspects of QOL. Unlike other tools identified in this review, the RetDQoL and RetTSQ have been designed to enable patients to consider specifically the impact of diabetic eye problems and their treatment, rather than health generally, vision or vision loss, or impact of diabetes.<sup>18</sup> Preliminary psychometric testing appears promising for content validity and internal consistency. Additional testing is ongoing to assess test-retest reliability, responsiveness, and interpretability.

Despite the availability of reliable and valid tools to measure HRQL,<sup>20,28,35</sup> our review identified several studies that used questions or tools whose psychometric properties have not been evaluated. In order to provide meaningful HRQL data, it is crucial that the measurement tools are reliable, valid, and responsive (i.e., sensitive to change). In this way, researchers, clinicians, and patients will be better able to assess and interpret the impact of different interventions on HRQL outcomes.

## **Impact of interventions on HRQL**

To date, two RCTs have reported HRQL outcomes.<sup>42,47</sup> More are expected as a search of Clinicaltrials.gov identified 13 ongoing or recently completed trials investigating interventions for DME or DR that indicate the intention to report HRQL outcomes. The PKC-DRS2 trial of once-daily ruboxistaurin versus placebo measured HRQL using the SF-36 and the VFQ-25;<sup>75</sup> however, results for the HRQL outcomes have not been reported. Furthermore, preliminary results from the RISE and RIDE trials<sup>79</sup> comparing ranibizumab versus sham have been presented at national meetings; however, to date, the final results for HRQL have not been published.

In general, it appears that HRQL outcomes improve following various interventions to treat DR at different levels of severity. For anti-VEGF to treat patients with DME, two RCTs with unclear risk of bias found statistically significant improvements in some domains of the VFQ-

25; however, the results were not consistent at 1 year post-treatment. We concluded that the strength of evidence was low.

For other interventions, the results are based on one or two observational studies with a high risk of bias. Therefore, we conclude that the strength of evidence is insufficient to draw any conclusions about which of these interventions for DR are effective in improving HRQL. Furthermore, there is a concern about the applicability of the results of the observational studies to patients in North America. All of these studies were conducted in Europe or Japan. In particular, the three studies that were based in Japan used the Japanese version of the VFQ-25.

This review shows that the impact of interventions for DR on HRQL has not been adequately assessed in the current literature. Research has increasingly highlighted HRQL as an important health outcome in diabetes.<sup>35</sup> Diabetic patients with retinopathy have reported that vision loss impacts multiple areas of well-being including: independence, mobility, leisure, and self-care.<sup>7,17,18</sup> However, the impact of DR is due not only to impaired vision, but also the emotional reaction to diagnosis and treatment, anxiety about the future, and advice to restrict physical activities.<sup>18</sup> For researchers and clinicians conducting trials of interventions for DR, the inclusion of HRQL outcomes will provide a better understanding how DR and its treatment affects outcomes that are important to patients.

**Table ES4. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Anti-VEGF</b>				
Mitchell 2011 <sup>41</sup>  RCT  Multicenter (73 centers in Australia, Canada, Europe, Turkey)	G1—ranibizumab 0.5 mg + sham laser G2—ranibizumab 0.5 mg + laser G3—laser + sham injection  VFQ-25  3 mo, 12 mo	G1 = 116 G2 = 118 G3 = 111  DME = 345 (100%)	<i>Median change in BCVA from baseline to 12 mo:</i> G1 = 6.1±6.43 G2 = 5.9±7.92 G3 = 0.8±8.59 <i>Median change in BCVA from baseline to 12 mo:</i> G1 = 6.1 (-10.9–25.2) G2 = 6.0 (-26.7–27.6) G3 = 1.3 (-37.8–26.8) <i>95% CI for the mean change:</i> G1 = 4.9, 7.3 G2 = 4.4, 7.3 G3 = -0.8, 2.4	VFQ-25, composite score at 12 mo G1—baseline: NR; improvement: 5.0 (p=0.014 compared to G3) G2—baseline: NR; improvement: 5.4 (p=0.004 compared to G3) G3—baseline: NR; improvement: 0.6 (NR) <i>Other domains:</i> G1—significant improvement for general vision, near vision activities, distance activities; other domains: NR G2— significant improvement for general vision, near vision activities, distance activities; other domains: NR G3—baseline: NR; no significant change from baseline
Sultan 2011 <sup>42</sup>  RCT  Multicenter (60 centers in Australia, Europe, India, North America, South America)	G1—pegaptanib 0.3 mg G2—sham injection  VFQ-25 baseline, 18, 54 & 102 wk	G1 = 133 G2 = 127  DME = 260 (100%)	<i>% improvement of ≥10 letters from baseline at 54 wk:</i> G1 = 43/133 (36.8%) G2 = 25/127 (19.7%) Odds ratio (95% CI) = 2.38 (1.32, 4.30); p=0.0047  <i>% improvement of ≥10 letters from baseline at 102 wk</i> G1 = 41/107 (38.3%) G2 = 30/100 (30%) Odds ratio (95% CI) = 1.57 (0.83, 2.97); p=0.1729	VFQ-25, composite score at 54 wk: G1—70.4; improvement 4.5 G2—69.2; improvement 1.3 <i>Between group differences—2.92; range - 0.32 to 6.16 (p = 0.077)</i> VFQ-25, composite score at 102 wk (n = 207): G1—69.8; improvement 4.6 G2—66.2; improvement 0.1 <i>Between group differences—4.47; range - 0.26 to 8.68 (p = 0.038)</i> <i>Other domains:</i> 54 wk: G1 vs. G2 had significantly more improvement for near vision activities, distance activities, social functioning; no difference for other domains 102 wk: G1 vs. G2 had significantly more improvement for distance activities, social functioning, mental health; no difference for other domains

95% CI = 95 percent confidence interval; BCVA = best corrected visual acuity; DR = diabetic retinopathy; DTSQ = Diabetes Treatment Satisfaction Questionnaire; DME = diabetic macular edema; mg = milligram; mo = month; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VF-14 = Visual Function-14; VFQ = National Eye Institute Visual Function Questionnaire; wk = week; yr = year

**Table ES4. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Laser photocoagulation</b>				
Tranos 2004 <sup>48</sup> Before-after United Kingdom	Laser photocoagulation VFQ-51 3 mo	DME = 55 (100%) Mild NPDR = 13 Moderate NPDR = 32 Severe NPDR = 10	<i>Binocular vision</i> —baseline: 48.7±6.7 <i>Distance vision</i> —baseline: 42.7±8.4 letters; improvement: 2.2±6.2 <i>Near vision</i> —baseline: 56.4±9.1 letters; improvement: 2.1±5.0	<i>Composite score</i> —baseline: 77.9±17.6; improvement: 4.9±8.9 (p<0.001); <i>Subscales</i> —statistically significant improvement on 8 of 11 vision-related domains
Mozaffarieh 2005b <sup>54</sup> Before-after Austria	Laser photocoagulation DTSQ 9 mo	Total = 105 PDR = 56 (53%) DME = 49 (47%)	24.7% reported improvement in visual acuity; 71.4% were unchanged; 3.8% were worse No difference in improvement between patients with PDR or DME	Mean± SD = 27.9±5.2 (maximum possible score = 36)
<b>Vitrectomy</b>				
Emi 2008 <sup>45</sup> Before-after Japan	Vitrectomy VFQ-25 (Japanese version) 6 mo	DR = 87 (total) G1—vitreous hemorrhage = 41 G2—DME = 28 G3—fibrovascular membrane = 18	G1—improved: 35; unchanged: 4; worse: 2 G2—improved: 9; unchanged: 16; worse: 3 G3—improved: 13; unchanged: 3; worse: 2	G1—statistically significant improvement on 10 of 12 subscales G2—no statistically significant change from baseline on any subscales G3—only the general vision subscale had a statistically significant improvement from baseline
Okamoto 2010 <sup>41</sup> Prospective cohort Japan	Pars plana vitrectomy VFQ-25 (Japanese version) 3 mo	G1—PDR = 99 G2—DME = 38 G3—normal controls = 100  <i>Note: this is part of a larger study (n = 399) of patients with vitreoretinal disorders— retinal vein occlusion (32), macular hole (42), epiretinal membrane (33), retinal detachment (55)</i>	<i>logMAR</i> G1—baseline: 1.37±0.75; 3 mo: 0.53±0.62 (p < 0.0001) G2—baseline = 0.76±0.49; 3 mo: 0.55±0.51 (p < 0.01)  <i>Contrast sensitivity</i> G1—baseline: 5.4±7.2; 3 mo: 14.0±7.9 (p < 0.0001) G2—baseline 9.2±6.5; 3 mo: 12.7±7.1 (p < 0.0001)	G1—baseline: 52.8±19.0; 3 mo: 63.6±17.5 (p <0.001); <i>Subscales</i> —statistically significant improvement on 9/11 vision-related domains G2—baseline: 53.0±20.5; 3 mo: 59.0±21.0 (p = 0.84); <i>Subscales</i> —statistically significant improvement on 4/11 vision-related domains G3—85.0±9.1

**Table ES4. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Vitrectomy and panretinal photocoagulation</b>				
Emi 2009 <sup>46</sup>	G1—vitrectomy G2—panretinal photocoagulation G3—no treatment	G1 = 136 G2 = 60 G3 = 131	<i>logMAR—right eye</i> G1—baseline: 0.21; 1 yr: 0.46 (p < 0.001) G2—baseline: 0.64; 1 yr: 0.52 (p = 0.272) G3—baseline: 1.09; 1 yr: 1.06 (p = 0.294)	<i>Composite score</i> G1—baseline: 67.4±17.3; 1 yr: 75.4±17.5 (p<0.001) G2—baseline: 80.7±15.7; 1 yr: 77.6±19.1 (p=0.113) G3—baseline: 91.3±7.8; 1 yr: 92.2±7.8 (p=0.169)
Japan	VFQ–25 (Japanese version)  1 yr		<i>logMAR—left eye</i> G1—baseline: 0.19; 1 yr: 0.38 (p < 0.001) G2—baseline: 0.61; 1 yr: 0.56 (p = 0.081) G3—baseline: 1.10; 1 yr: 1.09 (p = 0.704)	
<b>Phacoemulsification cataract surgery</b>				
Mozaffarieh 2005a <sup>53</sup>	Phacoemulsification cataract surgery  VF–14  3 mo	Cataracts = 67 (total) G1—no DR = 17 G2—mild NPDR = 19 G3—moderate/severe NPDR = 16 G4—PDR = 15	<i>logMAR (range)</i> G1—baseline: 0.62 (0.30–1.30); improvement 0.55 (0.30–1.15) G2—baseline: 0.60 (0.30–1.30); improvement 0.50 (0.30–1.08) G3—baseline: 0.67 (0.30–1.30); improvement 0.26 (0.15–0.48) G4—baseline: 0.71 (0.40–1.30); improvement 0.15 (-0.70–0.60)	G1—baseline: 52.21 (32.14–78.57); improvement 42.33 (21.43–60.71) G2—baseline: 55.92 (30.36–85.71); improvement 36.00 (12.50–58.93) G3—baseline: 46.65 (30.36–64.29); improvement 9.26 (1.79–25.00) G4—baseline: 40.12 (25.00–67.86); improvement 5.00 (-25.00–25.00)
Mozaffarieh 2009 <sup>51</sup>	Phacoemulsification cataract surgery  G1—first-eye surgery G2—both eyes  VF–14  12 mo	Cataracts = 89 (total) No DR = 23 Mild NPDR = 23 Moderate NPDR = 22 PDR = 21	G1 & G2—patients with no or mild NPDR had greater improvement in visual acuity	G1 baseline: no DR: 59.3±12.4; mild 39.3±5.2; severe 40.9±8.6; PDR 35.3±4.4 6 mo: no DR: 96.8±2.0; mild 86.5±13.6; severe 48.8±6.7; PDR 37.9±14.0 12 mo: no DR: 79.5±5.5; mild 72.2±8.3; severe 46.1±10.7; PDR 39.9±9.0  G2 baseline: no DR 46.8±8.7; mild 63.4±16.3; severe 54.6±8.8; PDR 50.6±11.4 6 mo: no DR: 93.0±4.3; mild 94.6±2.5; severe 60.9±6.6; PDR 53.0±10.9 12 mo: no DR: 95.3±1.9; mild 95.3±2.2; severe 47.8±16.0; PDR 47.6±15.0

## Recommendations for Future Research

- RCTs are needed to assess the impact of interventions for DR, including DME on HRQL. All RCTs investigating the effectiveness of interventions for DR should measure and report pre- and post-treatment HRQL outcomes.
- Currently, there are a number of ongoing or recently completed trials that reported the intention to capture HRQL outcomes. Future systematic reviews on this topic should followup on these studies and incorporate their findings, if appropriate.
- Researchers should use valid and reliable HRQL tools whose psychometric properties have been evaluated and reported.
- Ongoing assessment of the psychometric properties of the DR specific tools is encouraged.
- Patients should be followed for at least 6 months post-intervention in order to capture maximum improvement for visual acuity.
- Researchers should use standard protocols to assess visual acuity to allow for comparison across trials
- RCTs should be designed and conducted to minimize risk of bias where at all possible. Authors may find tools such as the CONSORT<sup>18,76</sup> statement helpful in designing and reporting on RCTs.

## Conclusions

We identified four HRQL measurement instruments that have been used to assess the impact of treatment in patients with DR. The psychometric properties of these tools have been adequately evaluated. Two tools developed specifically for patients with DR are currently undergoing evaluation. In general, HRQL was improved following interventions for DR. Further research on HRQL following anti-VEGF treatment for DME is needed to confirm the results of two RCTs. The current research on the impact of other interventions for DR on HRQL is insufficient to draw conclusions about the relative effect of one intervention versus another. RCTs that assess the impact of treatments for DR should include HRQL as an outcome.



# Introduction

The Coverage and Analysis Group at the Centers for Medicare and Medicaid Services (CMS) requested this report from the Technology Assessment Program (TAP) at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following Evidence-based Practice Center: University of Alberta Evidence-based Practice Center (Contract No. HHS A 290 2007 10021 I).

## Diabetic Retinopathy

Diabetic retinopathy (DR) is a leading cause of vision loss in the United States and occurs as a result of pathologic changes of the retinal vasculature.<sup>1</sup> In 2005–2008, the estimated crude prevalence among Americans over the age of 40 with diabetes was 28.5 percent. Although the prevalence of vision-threatening DR is approximately 4.4 percent,<sup>2</sup> the number of affected Americans 40 years or older is expected to triple from 1.2 million in 2005 to 3.4 million in 2050.<sup>3</sup> The prevalence and severity of DR increases with the duration of diabetes; however, it is inversely correlated to glycemic and blood pressure control.<sup>4,5</sup> Moderate vision loss is most commonly related to retinal leakage within the macula, while severe vision loss usually occurs as a result of neovascularization (proliferative diabetic retinopathy; PDR) with subsequent hemorrhage or fibrosis.<sup>6</sup>

Early identification and treatment of DR is an important goal for patients and health systems because treatment is both cost-effective and reduces vision loss.<sup>7</sup> Therefore, early detection is critical; the American Academy of Ophthalmologists, the American Optometric Association, and the American Diabetes Association recommend an annual dilated eye examination for all people with diabetes, and more frequent eye examinations for people with known DR.<sup>8-10</sup> Other researchers argue that the frequency of examinations should be stratified to an individual's risk of progression and vision loss.<sup>11</sup>

The mainstay of DR treatment is aimed at reducing the risk of onset and limiting the progression of the disease. Therefore, retinal assessments should be performed on a regular basis to determine the presence and degree of DR, glycemic control should be optimized, and known risk factors such as blood pressure, dyslipidemia, elevated cholesterol, renal disease and abdominal obesity should be controlled. Direct ocular therapy should be prescribed when indicated, while vision rehabilitation and low vision aids should be used to maximize vision if there is a loss.<sup>4,5</sup>

Until recently, the primary treatment for DR has been focal or grid laser of the retina.<sup>12,13</sup> Serial intravitreal injections of triamcinolone have been introduced as a treatment option as they have been shown to be effective in reducing diabetic macular edema (DME); however, their use has become less common due to significant adverse effects including elevated intraocular pressure and cataract formation.<sup>14,15</sup> Ranibizumab and bevacizumab are being used with increasing frequency for the treatment of DME; however they have not yet been approved for use in this condition by the Food and Drug Administration. The recommended treatment of PDR remains panretinal photocoagulation<sup>16</sup> with vitrectomy surgery performed when necessary.<sup>14</sup> It is important to note that treatment of DR is not always aimed at restoration of pre-disease visual acuity, but rather at limiting further deterioration. Patients may report a decrease in visual acuity immediately after therapy, which may manifest in low initial perceptions of treatment

satisfaction. However, results from the Early Treatment Diabetic Retinopathy Study demonstrate that early treatment with either panretinal photocoagulation or vitrectomy prevents long-term disability due to blindness.<sup>12-14</sup>

Vision loss is particularly debilitating for patients with diabetes because treatment success to limit progression of their diabetes depends upon their ability to read a glucometer and inject subcutaneous insulin. Diabetic patients with retinopathy have reported that vision loss impacts multiple areas of well-being including: independence, mobility, leisure, and self-care.<sup>7,17,18</sup> Additionally, DR has been found to impair functioning and overall health-related quality of life (HRQL).<sup>19,20</sup>

## **Health-Related Quality of Life**

### **Patient-Reported Outcomes**

In recent years clinicians and researchers have given greater recognition to the subjective experiences of patients diagnosed with chronic illnesses such as diabetes mellitus. This increase in attention targets a more holistic understanding of the patient and how treatments purported to curtail long-term complications of chronic illnesses, such as DR, affect daily physical and psychosocial functioning.<sup>21</sup> Patient reported outcomes (PROs) are a group of outcomes used to measure a wide variety of aspects of care including HRQL, patient illness perceptions, and treatment satisfaction or adherence.<sup>21</sup> PROs can be distinguished from other outcomes such as laboratory results and clinician or caregiver ratings because the report is from the patient's perspective, usually without interpretation by another individual.<sup>22</sup> Furthermore, PROs are dependent on disease-related dimensions, such as the degree of visual impairment caused by DR.<sup>21</sup> Researchers are more frequently including PROs as a part of clinical trials as they help demonstrate benefit, survival, and patient feelings regarding treatments.<sup>22</sup> However, PROs tend to be evaluated as a secondary outcome, and are rarely the primary outcome of a trial.<sup>21</sup>

### **Health Status/Functional Status**

Included under the umbrella of PROs are the terms: health status, functional status, and quality of life (QOL) or HRQL. These terms are frequently used interchangeably to mean "health"; however, researchers caution that they have distinct meanings and uses.<sup>23,24</sup> Health status is often used to refer to the identification and assessment of changes in patients' activities and perceptions compared with normal life.<sup>24</sup> This construct is multidimensional and represents patients' subjective evaluations of their physical and mental health.<sup>25</sup> Functional status focuses on the physical capacity to complete everyday activities at home or work, rather than patients' perceptions of how their health affects their functioning.<sup>25</sup> Health status is effective in monitoring the status of a community or local population and can be used in setting health priorities, identifying high risk groups, estimating service needs, and analyzing usage patterns.<sup>24</sup> HRQL and QOL delve further into patient perceptions of health and well-being.

### **Health-Related Quality of Life/Quality of Life**

QOL covers a range of experiences related to patients' well-being based on their subjective experiences.<sup>25</sup> Many variables, both objective and subjective, interact to define QOL,<sup>26</sup> but it is dependent upon individual patient experiences, states, and perceptions of their illness.<sup>25</sup> QOL can vary as a result of life events or changes in functional health status, with each area of QOL

impacting the others.<sup>26</sup> In the case of patients with diabetes, comorbidities and complications such as renal disease or dialysis, neuropathy, gastroparesis, amputation, impotence and erectile dysfunction all play a part in influencing QOL. Furthermore, the level of visual acuity, glycemic control, and duration of disease can impact directly on vision-related QOL.

HRQL allows clinicians and researchers to measure the impact of chronic diseases such as diabetes mellitus on the lives of patients.<sup>23</sup> As with QOL, HRQL is a multifaceted measurement. It takes into account the impact of disease and its treatments on physical, psychological, social, and somatic domains of functioning and well-being.<sup>25</sup> Therefore, in patients diagnosed with DR, treatments that improve visual acuity also have the potential to positively impact HRQL by allowing them to continue participating, or to increase their ability to participate, in the daily activities of their lives. Various domains can be included in the evaluation of HRQL including physical, psychological, and social assessments. Some definitions may include broader terms such as global perceptions of functioning and general well-being.<sup>25</sup> Several different views exist on how to measure QOL and HRQL, in large part due their subjective nature, but also due to the lack of distinction between indicator and causal variables, as well as mediating variables.<sup>26</sup>

## **Measuring Health-Related Quality of Life/Quality of Life**

As patient-centered health care grows in importance, clinicians and researchers need a way to make health care decisions that meet the needs of patients. It is critical to ensure that treatment decisions meet patient and societal values, and to recognize that perceptions of HRQL may vary between the patient and clinicians.<sup>25</sup> Furthermore, investigations into public perceptions of HRQL and QOL suggest that areas judged important by the general public have not been included in some commonly used measurement tools.<sup>26</sup> Collecting HRQL and QOL outcomes allows clinicians and researchers to take into account a wider array of information that cannot be obtained through laboratory or physical measures, and permit a subjective description of functioning alongside objective findings.<sup>27</sup> Through the collection of patient perceptions of interventions used to treat DR, health care providers can better understand what aspects of health patients value most highly and therefore what types of treatment may provide the greatest benefit.

Just as the definitions of HRQL and QOL vary, so too do the tools used for evaluating these outcomes. Evaluation tools may be as simple as a single question asking the patient to state their QOL; however, they are more likely to take the form of a questionnaire with multiple items, which investigate different domains related to HRQL.<sup>23</sup> The common thread that exists among measurement tools is that they attempt to summarize the judgments patients make about their health and illness experiences.<sup>26</sup> HRQL tools can be placed into two categories: generic instruments- and specific instruments.

Generic HRQL tools investigate all important aspects of HRQL and allow broad comparisons, but do not necessarily investigate a specific aspect of disease. Typically generic tools include questions relating to the four main domains of HRQL: physical, functional, social, and psychological health.<sup>28</sup> These tools may be less responsive to change as they provide an overall summary score of HRQL, rather than a score on a precise area of health.<sup>23</sup> Of the tools investigated in this review, one falls into the category of generic tools. The Short Form-36 (SF-36) questionnaire investigates eight health domains in patients with a variety of conditions and was developed for use in the general patient population.

Specific HRQL instruments are designed to target a disease, population, or an outcome. Where generic tools allow broad comparisons, specific tools may be more responsive to HRQL

changes in the specific patient population under investigation.<sup>23</sup> Two tools included in this review were developed specifically to evaluate patients with eye disease: the Visual Function–14 (VF–14), and the National Eye Institute Visual Function Questionnaire (VFQ) (both 25 and 51 item versions). These tools were designed for patients diagnosed with cataracts and low vision, respectively, but do not investigate the involvement of the underlying condition of diabetes mellitus on patient QOL. One tool included in this review, the Diabetic Treatment Satisfaction Questionnaire (DTSQ), evaluates treatment satisfaction in patients with diabetes mellitus. This measure is disease-specific but it does not take into account whether or not a patient is also diagnosed with DR. Two tools included in this review were developed to evaluate HRQL in patients with DR: the Retinopathy Treatment Satisfaction Questionnaire (RetTSQ), and the Retinopathy Dependent Quality of Life (RetDQoL) questionnaire. Since diabetic patients without retinopathy may have different concerns compared to those with retinopathy, these tools have the potential to provide a greater understanding of HRQL than a tool such as the DTSQ. Both of these tools have undergone a series of psychometric evaluations; however, to date neither has been used in published trials assessing the impact of an intervention for DR.

### **Psychometric Properties for HRQL Tools**

Regardless of whether a tool is generic or specific, it is helpful to accumulate evidence of its psychometric properties to ensure they provide the most reliable and valid assessment of health status in the patient population. Accompanying the growing interest in HRQL has been the increase in the number of tools available to measure such outcomes, which in turn can make it difficult for researchers and clinicians to determine what tools are the most trustworthy and appropriate for use in clinical and research settings. In recent years, researchers have undertaken the challenge of identifying what psychometric properties are of greatest importance when evaluating the quality of a HRQL tool, and what criteria should be used in judging the psychometric properties. In 2010 the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) was released as a checklist for the purpose of evaluating the methodological quality of studies investigating the measurement properties of HRQL tools.<sup>29</sup> The COSMIN researchers used a Delphi approach to reach consensus on what psychometric properties are considered the most important for high-quality HRQL measurement instruments. They also reached consensus on definitions for these psychometric properties.

**Reliability.** Reliability is the degree to which the tool is free from measurement error.<sup>29</sup> Depending on the source of measurement error and how the measurement is obtained, reliability can take different forms. Internal consistency is a reflection of the reproducibility of measurement by different items within a multi-item scale. Test-retest reliability is the degree to which the score of a patient who has not changed clinically remains the same under repeated measurements;<sup>29</sup> other groups refer to this as reproducibility.<sup>23,28,30</sup> In order to ascertain test-retest reliability, measurements should be taken over an interval that is short enough to ensure that patients remain stable, but long enough to prevent recall bias. An interval of one to four weeks is considered sufficient.<sup>23</sup> Internal consistency reliability is commonly assessed using Cronbach's coefficient  $\alpha$ . Test-retest reliability is typically presented as a correlation coefficient between the two sets of measurements, either Pearson's R or intra-class correlation. The minimum standard inter-item correlation for multi-item scales, for either reliability coefficient, is 0.70 for group comparisons, and 0.90 to 0.95 for individual comparisons.<sup>30</sup>

**Validity.** Validity is defined as the degree to which an instrument measures the construct(s) it is intended to measure.<sup>29</sup> The COSMIN panel identified three categories of validity: content validity, construct validity, and criterion validity. Content validity is concerned with the content of the measurement tool and whether it is an adequate reflection of the construct to be measured. Face validity is considered a part of this domain.<sup>29</sup> Typically, there are no formal tests of content validity, but rather a subjective assessment, based in part on the item generation process during instrument development. Construct validity considers whether the scores produced by the instrument are consistent with the hypothesis of how the tool should behave, assuming the tool is valid.<sup>29</sup> Achieving construct validity is often an iterative process.<sup>31</sup> Construct validity is further broken down into structural validity, hypothesis testing, and cross-cultural validity. The final type of validity, criterion validity, focuses on the degree to which the scores of an instrument reflect a “gold standard.” Validity can be stronger when an instrument’s results are tested against other known instruments,<sup>30</sup> however, the existence of gold standards in HRQL measurement tools is limited, therefore researchers may have to find alternate methods of demonstrating criterion validity.<sup>23</sup>

**Responsiveness.** The responsiveness of a tool demonstrates the ability of the instrument to detect changes in a patient over time when changes in the construct being measured actually occur.<sup>29</sup> Responsiveness, or a tool’s sensitivity to change, is considered a specific type of construct validation when assessing change over time.<sup>30</sup> Hypotheses regarding the relationship of the change in the instrument and how they correspond to changes in reference measures should be proposed and tested.<sup>28</sup> Changes in HRQL measures can be compared with changes in a patient’s health status, health events, interventions, or direct reports of change in QOL by patients or providers to help pinpoint the cause of variations in HRQL status.

**Interpretability.** The final domain considered by the COSMIN panel is interpretability. Interpretability is not seen as a psychometric property; rather it is important to assess the usability of the measurement tool. This domain is defined as the degree to which a clinician or researcher can equate a qualitative meaning to an instrument’s quantitative score.<sup>29</sup> In other words, interpretability is concerned with whether or not an instrument can easily be understood and be made meaningful to clinicians and their patients.<sup>30</sup> Furthermore, interpretability is concerned with whether or not the score indicates that a patient is functioning normally, is experiencing moderate to severe impairment, or whether changes associated with treatments are small, medium or large.<sup>23</sup>

## Key Questions

The Centers for Medicare and Medicaid Services (CMS) requested a technology assessment on the effectiveness of interventions for DR to improve HRQL. Four questions were posed:

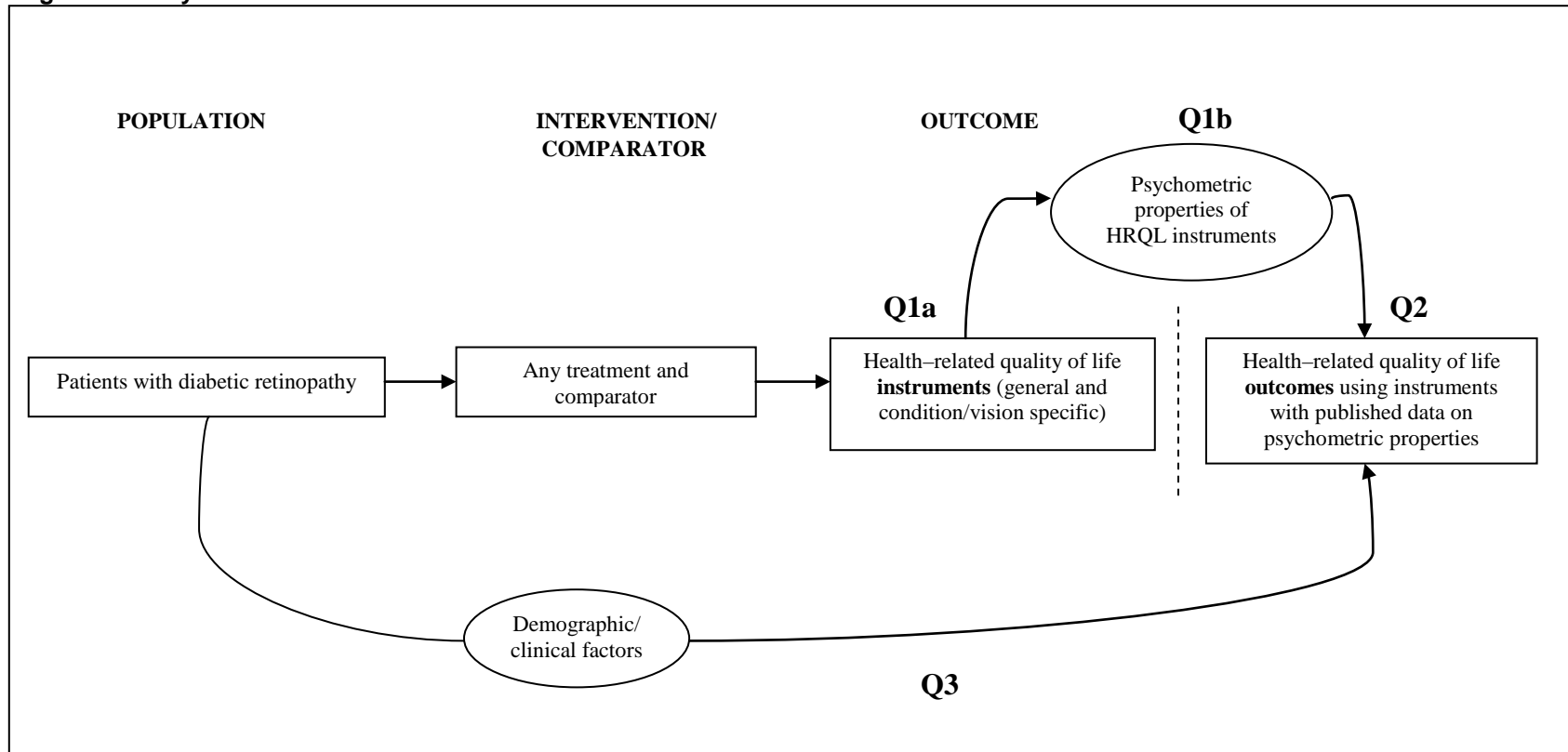
- 1a. What HRQL measures have been used in studies of treatments for DR?
- 1b. What are the psychometric properties of the HRQL measures used in the studies?
2. Including only studies that have used reliable and valid measures, what is the evidence that HRQL is improved for any intervention for DR? What is the comparative effectiveness of interventions to improve HRQL in patients with DR?
3. What evidence is presented in the studies about the relationship between the measured improvement in HRQL and any relevant variables, including but not limited to baseline visual

acuity, age ( $\geq 65$  years), race, sex, severity and type of DR (i.e. DME, nonproliferative diabetic retinopathy (NPDR), PDR)?

## **Analytic Framework**

Figure 1 depicts the four key questions and the linkages between the population of interest, the interventions, and outcome measures. It demonstrates the chain of logic that the evidence obtained must support the link between the interventions, modifying variables, and patient outcomes. This technology assessment focuses primarily on the effect of interventions for DR on HRQL (Q2). HRQL instruments may differ in their psychometric properties, and these differences could be a source of variation in outcomes among studies that use different instruments (Q1a and Q1b). HRQL outcomes may be modified by demographic and clinical factors due to the variation in baseline prevalence of these factors in different populations (Q3). The specific HRQL instruments that have been used in studies and their psychometric properties will be reported separately from the patient outcomes.

Figure 1. Analytic Framework.



# Methods

## Literature Search

In consultation with a research librarian we conducted a comprehensive search of the literature to identify relevant studies to answer the Key Questions. A single search strategy was developed to locate literature to address all four questions and was run in July 2010 in the following databases: MEDLINE®, EMBASE®, PsychINFO®, Cochrane Central Register of Controlled Trials®, CINAHL Plus full text, and Scopus. The search was updated in March 2011 in MEDLINE®, EMBASE®, Cochrane Central Register of Controlled Trials®. PubMed was also searched at this time to ensure that all current literature was captured. A final updated search of all databases was conducted in January 2012. No date or language restrictions were applied. In all databases both subject headings and key word terms for “diabetes,” “diabetic retinopathy,” “quality of life,” and “health-related quality of life” were included in the search. Appendix A contains a detailed description of the search strategy. We also conducted a search of clinicaltrials.gov for recently completed or ongoing studies of interest. The search was run in November 2010 then updated in April 2011 and used “diabetic retinopathy” as the main search term. The search was limited by study type (interventional studies) in adult participants.

To supplement the database searches we hand searched the reference lists of included studies and recently published review articles.<sup>20,32-35</sup>

## Study Selection

We used a two-step process for study selection. First, three reviewers (AM, ES, KR) independently screened the titles and abstracts (when available) located through the literature search to determine if an article met broad inclusion criteria. Studies were classed as “include,” “exclude,” or “unsure.” We retrieved the full-text of studies identified as “include,” or “unsure,” by at least one reviewer. Second, two reviewers (AM, KR) independently assessed each study using a standard inclusion-exclusion form (Appendix B). Disagreements were resolved through discussion between reviewers, or third party adjudication, as needed.

Our inclusion criteria are described below. Only articles published in full were considered for inclusion in this review (i.e., conference abstracts were not considered). We did not exclude studies based on their language of publication.

## Study Design

For Key Question 1a and b all study designs were included.

For Key Questions 2 and 3, only prospective study designs with a comparator (i.e., randomized controlled trials (RCT), nonrandomized controlled trials (NRCT), quasi-experimental studies—including, but not limited to, controlled before-after studies—and prospective cohort studies) were included. Retrospective studies were excluded.

## Population

For all questions, we included studies that recruited adults ( $\geq 18$  years) who had been diagnosed with diabetic retinopathy (DR) including diabetic macular edema (DME), nonproliferative diabetic retinopathy (NPDR), proliferative diabetic retinopathy (PDR), and other related conditions.



## **Intervention and comparator**

For all questions, we considered any intervention and comparator including comparisons of different types of interventions, different doses, or different formulations.

## **Outcome**

For Key Questions 1a and 1b, any measurement instrument that included at least one domain of HRQL (i.e., physical, mental, emotional, social functioning) was considered.

For Key Questions 2 and 3, only outcomes based on measurement instruments with published data on the instrument's psychometric properties were included.

## **Data Extraction**

Data were abstracted directly into evidence tables in a Microsoft Word™ document (Microsoft Corp., Redmond, WA). One reviewer abstracted data which was then checked for accuracy and completeness by a second reviewer. Disagreements were resolved through discussion or third party adjudication, as needed. The following data were extracted for Key Questions 1a and 1b: title of HRQL instrument, author(s), year of publication, instrument characteristics (target population, QOL domains measured, number of items, number of response options, scoring algorithm, time needed to complete, and mode of administration), and quality assessment for measurement properties.

The following data were extracted for Key Questions 2 and 3: author(s), year of publication, date of study, study setting, study characteristics (study design, inclusion/exclusion criteria, intervention, and comparator), study population (age, sex, type of diabetes, visual acuity, type of DR, and other retinal diseases), HRQL instrument(s) used, and results for the outcomes of interest.

## **Assessment of Methodological Quality**

### **Quality Assessment of HRQL Tools**

For Key Question 1b, we used the COSMIN<sup>29,36</sup> checklist to assess the quality of the HRQL instruments. The checklist includes seven items: content and construct validity, internal consistency, reliability, absolute measurement error, responsiveness, and interpretability.<sup>37</sup> Each item is rated with the following options: “not done,” or “low,” “indeterminate,” or “high” quality. Validity, reliability, and responsiveness depend on the setting and the population in which they are assessed. Therefore, descriptions of the study population characteristics, measurements, settings, and data analysis of every individual study were rated. If a description was lacking, the item was rated as indeterminate. One reviewer assessed the HRQL instruments in consultation with an expert in the HRQL field.

### **Quality Assessment for Included Studies**

For Key Question 2, we assessed trials using the Cochrane Risk of Bias (ROB) tool for RCTs.<sup>38</sup> The ROB includes six domains which assess sequence generation, allocation concealment, blinding (participants and personnel, and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias. Each domain is assessed as “low,” “unclear,” or “high” based on the predefined criteria laid out the Cochrane Handbook, and the study is given an overall rating based on the assessment of each domain.

We used a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies.<sup>39</sup> The NOS includes seven items assessing sample selection, comparability of cohorts, and the assessment of outcomes. One star was allotted for each item that was adequately addressed in the study, with the exception of the comparability of cohorts, for which a maximum of two stars could be given. The overall score was calculated by tallying the stars, with a total possible score of eight stars.

The methodological quality of before-after studies was assessed using a modified version of the NOS that assessed sample selection and the assessment of outcomes. One star was allotted for each item that was adequately addressed in the study. The overall score was calculated by tallying the stars, with a total possible score of five stars.

Two reviewers (AM, CS, DD) independently assessed the methodological quality of the included studies. Decision rules were developed a priori through discussions with content and methodology experts. Discrepancies in quality assessment were resolved through consensus.

## **Data Analysis**

For Key Question 1, we developed summary tables of the HRQL instruments, their characteristics, and their psychometric properties. For Key Question 2, we developed summary evidence tables of the study and population characteristics, and outcomes. Key Question 3 is presented in a descriptive analysis.

Mean differences (MD) and 95 percent confidence intervals (95% CI) were calculated for continuous variables. Missing means were approximated by medians. Missing standard deviations were computed from standard errors, confidence intervals, or p-values. If none of these were available, they were estimated from ranges or interquartile ranges, or imputed from other similar studies with the same outcome. We did not conduct any meta-analyses due to the heterogeneity of interventions and patient characteristics.

## **Grading the Evidence for Key Question 2**

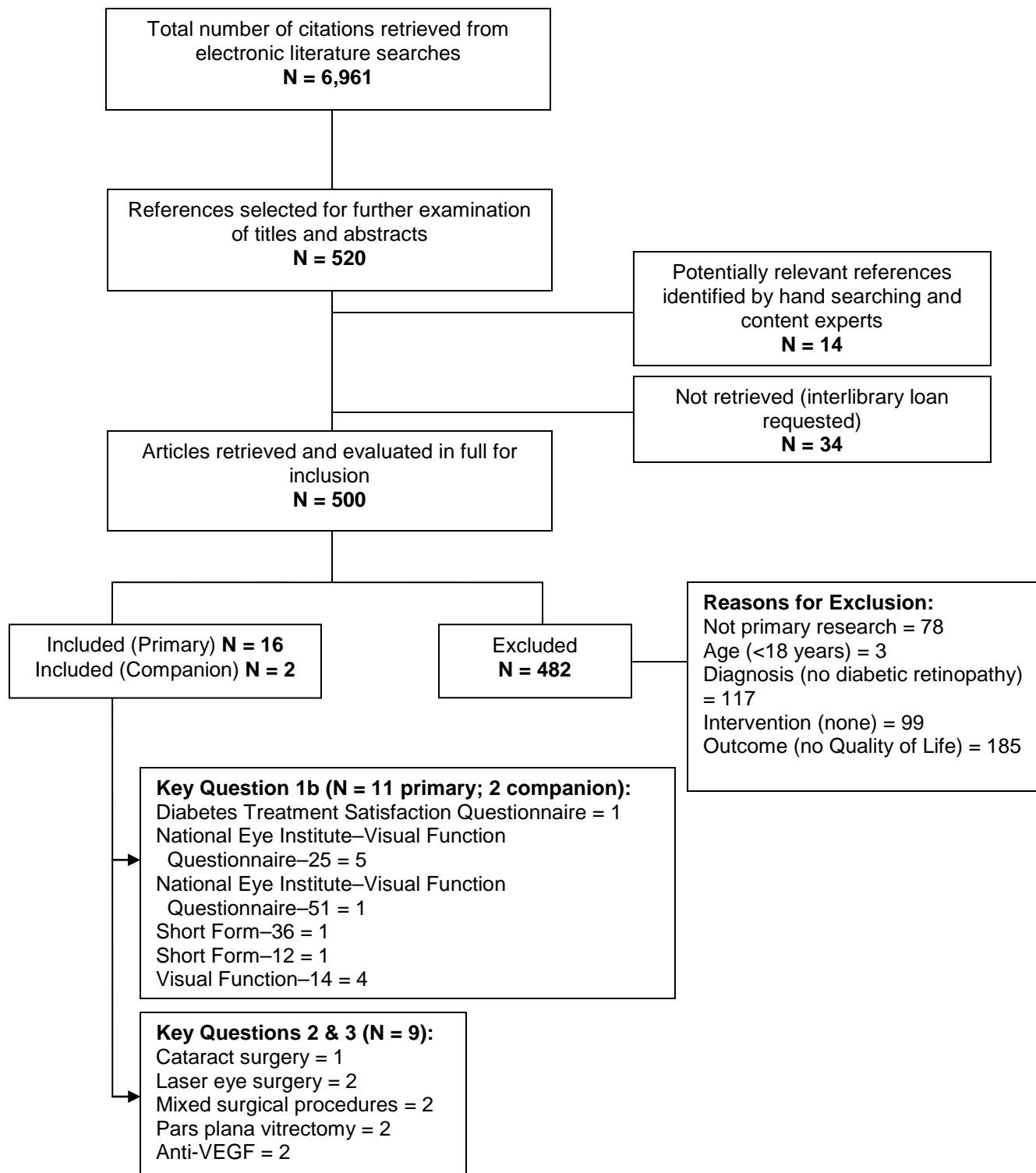
We used the EPC GRADE approach<sup>40</sup> to assess the strength of evidence for HRQL. The following four major domains were examined: risk of bias (incorporating both study design and study conduct), consistency, directness, and precision. An overall evidence grade based on the ratings for the individual domains was assigned. The overall strength of evidence was graded as “high” (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); “moderate” (indicating moderate confidence that the evidence reflects the true effect and further research may change our confidence in the estimate of effect and may change the estimate); “low” (indicating low confidence that the evidence reflects the true effect and further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); and “insufficient” (indicating that evidence is either unavailable or does not permit estimation of an effect). The strength of evidence was graded by one reviewer.

# Results

## Literature Review and Screening

The electronic literature search identified 6,961 unique citations. After the first level of screening based on title and abstract 6,441 articles were excluded from further review, leaving 520 articles for full-text retrieval. We identified an additional 14 studies through hand searching and contact with content experts. Of the 534 articles identified, 34 could not be located in either the University of Alberta libraries' holdings or through interlibrary loan requests. Of the 499 articles reviewed at the second level of screening, 16 addressed Key Question 1a. Eleven of these studies used validated measures to evaluate health-related quality of life (HRQL) and were applicable to Key Question 1b. Nine unique studies met our inclusion criteria to address Key Questions 2 and 3. Two of these studies<sup>41,42</sup> each had a related publication.<sup>43,44</sup> Figure 2 depicts the flow of the studies through the screening process and provides a breakdown of reasons for exclusion (see Appendix C for a list of excluded studies).

**Figure 2. Flow diagram for study retrieval and selection**



## Key Question 1a. What HRQL measures have been used in studies of treatments for diabetic retinopathy?

We identified four HRQL measures that have been used in studies assessing the treatment of diabetic retinopathy (DR). The most commonly used measure was the National Eye Institute Visual Functioning Questionnaire (VFQ), which is available in two versions. Five studies<sup>41,42,45-47</sup> used the 25 item version (VFQ-25); one<sup>48</sup> used the 51-item version (VFQ-51). In addition, seven recently completed trials that have not yet published their results reported using the VFQ-25 (See Appendix A for trial registration numbers). One study<sup>49</sup> used both the VFQ-25 and the Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF-36). Two studies<sup>50,51</sup> used the Visual Function Index (VF-14). One study used both the VF-14 and the MOS 12-Item Short Form Health Survey (SF-12)<sup>52</sup>, and another study<sup>53</sup> used the VF-14 plus a questionnaire to assess satisfaction with surgical outcomes. One study<sup>54</sup> used the Diabetes Treatment Satisfaction Questionnaire (DTSQ) plus a questionnaire to assess the degree to which treatment outcomes corresponded to patient expectations. One study<sup>55</sup> used qualitative interviews to assess quality of life but did not use a specific measure.

In addition to the measures used in studies of treatment for DR, we also identified two HRQL measures that have been developed specifically for patients with DR: the Retinopathy Treatment Satisfaction Questionnaire (RetTSQ), and the Retinopathy Dependent Quality of Life (RetDQoL) measure. Currently there is no literature describing their use in the evaluation of treatments for DR.

## Key Question 1b. What are the psychometric properties of the HRQL measures used in the studies?

The six HRQL tools can be separated into two broad groups: generic tools and specific tools. The latter category can be further divided into tools developed for use in populations with: low vision, diabetes mellitus, and DR. See Appendix D for a description of the six measurement tools. Table 1 presents the psychometric properties of the measures. The ratings of the measurement properties based on the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist are shown in Table 2. Below is a summary description of each tool.

### Generic Assessment Tools

#### Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)

The SF-36 is a 36 item questionnaire designed for use as a generic indicator of health status in clinical use, research, population surveys, and evaluative studies of health policy.<sup>56</sup> It incorporates physical, social, and mental concepts of both positive and negative aspects health. A higher score on the SF-36 represents better health. It has been used for evaluation in a variety of conditions and for comparisons of different populations including the general public.<sup>57</sup>

Reliability and validity of the SF-36 have been examined in both healthy and patient populations. Construct validity is good, and when compared with other health instruments (*Sickness Impact Profile*, *Quality of Well-being Scale*, *Nottingham Health Profile*), the SF-36 was more sensitive to change of community dwelling elderly persons, elderly patients, and patients with joint replacements.<sup>58-60</sup> However, the study by Matza<sup>49</sup> found that the SF-36

was unable to differentiate changes in visual acuity after treatment for DR, especially when compared with the VFQ–25.

Advantages of the SF–36 as compared to other generic instruments are its brevity and comprehensiveness. Limitations have been identified with validity pertaining to chronic disabilities, the severely ill, and the elderly. Some experts question the responsiveness of scores to changes in health status with certain populations, particularly: potential floor effects in the severely ill<sup>56</sup> and ceiling effects in healthy elderly people residing in the community.<sup>60</sup> Finally, the appropriateness of the SF–36 in the elderly is unclear<sup>61</sup> due to evidence that shows high percentages of missing data in this population.<sup>59,62</sup> Hayes and colleagues reported missing data in 70 percent of 122 respondents who were 75 years of age and older; however, they hypothesized this was likely related to visual or writing problems.<sup>62</sup>

## Low-Vision Related Assessment Tools

### **National Eye Institute Visual Function Questionnaire-25-item version (VFQ–25)**

The VFQ–25 is a reduced version of the National Eye Institute’s 51-item VFQ developed to elicit patient perceptions of their visual impairment and its relation to HRQL. The VFQ–25 includes 1 general health item in addition to 11 visual subscale scores of: general vision, ocular pain, near vision, distance vision, social function, mental health, role limitations, dependency, driving, color vision, and peripheral vision. A high score on the VFQ–25 indicates better visual function and HRQL.<sup>63</sup> The reliability and validity of the VFQ–25 has been demonstrated in a variety of eye conditions including: cataracts, age-related macular degeneration, DR, primary open-angle glaucoma, and cytomegalovirus retinitis.<sup>63</sup> Furthermore, a strong association between the VFQ–25 and visual acuity has been demonstrated, independent of the degree of retinopathy.<sup>64</sup> A Japanese version of the VFQ–25 was used in the studies by Okamoto et al.<sup>41,43</sup> and Emi et al.,<sup>45,46</sup> and has been shown to be reliable and valid in the Japanese population.<sup>65</sup>

### **Visual Function–14 (VF–14)**

The VF–14 asks patients to assess their ability to perform 14 everyday activities that can be affected by cataracts. There are 18 items related to visual acuity including: reading, recognizing people, seeing steps, stairs or curbs, doing fine handwork, writing checks or filling out forms, playing games, taking part in sports, cooking, watching television, and driving. A higher score on the VF–14 indicates that the patient is better able to complete the everyday activities included in the questionnaire.<sup>66</sup> Boisjoly<sup>50</sup> found that in a variety of eye conditions, the VF–14 was more strongly correlated with changes in patients’ self-reported visual trouble and satisfaction with vision than with changes in visual acuity and general outcome measures.

## Diabetes-Related HRQL Assessment Tools

### **Diabetes Treatment Satisfaction Questionnaire (DTSQ)**

The DTSQ measures patients’ satisfaction with the treatment they receive for their diabetes. It has been designed for use only with persons with either type 1 or type 2 diabetes mellitus and has not been validated for use in the narrower population of patients with DR. Six items on the questionnaire are combined to provide a measure of treatment satisfaction; the remaining two

items evaluate the perceived frequency of hyperglycemia and hypoglycemia. A high score on the DTSQ indicates the patient has a high level of satisfaction with their treatment.<sup>67</sup> The DTSQ can effectively measure psychological outcomes related to diabetes treatment and has demonstrated sensitivity to changes in patient satisfaction related to changes in diabetic interventions.<sup>68</sup>

## **Diabetic Retinopathy Related HRQL Assessment Tools**

### **Diabetic Retinopathy Dependent Quality of Life (RetDQoL)**

The RetDQoL is a recently developed tool designed to evaluate the QOL of patients diagnosed with DR and is modeled on the Audit of Diabetes-Dependent QoL.<sup>69</sup> The questionnaire begins with two broad questions related to present quality of life and what the patient's perceived QOL would be if they did not have diabetic eye problems. The remaining 24 items are specific questions related to aspects of QOL. Each item is split into two parts: part "a" asks the patient to evaluate the impact of the domain on their QOL; part "b" asks the patient to rank how important each domain is in their life. The RetDQoL has demonstrated high internal consistency and good construct validity.<sup>70</sup> The RetDQoL has not yet been used in clinical trials investigating the impact of an intervention for DR.

### **Diabetic Retinopathy Treatment Satisfaction Questionnaire (RetTSQ)**

The RetTSQ is a recently developed tool designed to evaluate patients' satisfaction with the treatment they receive for their DR. The DTSQ was used as a model for the development of this questionnaire. The RetTSQ is comprised of 13 items relating to patient satisfaction with different areas of treatment for DR. The 13 items are split into two subscales: one used to evaluate positive aspects of treatment, and the other to evaluate negative aspects. A high score on the RetTSQ indicates a high level of satisfaction with treatment. The internal consistency of the RetTSQ has been demonstrated to be high, and construct validity to be good. The RetTSQ has not been used in any clinical trials to evaluate the impact of an intervention for DR.<sup>71</sup>

**Table 1. Psychometric properties of health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy**

Measure	Study population	Construct validity	Internal consistency	Test-retest reliability	Responsiveness
<b>Generic HRQL assessment tools</b>					
SF-36 <sup>56,57,72</sup>	Patients who participated in the Medical Outcomes Study (1986) (US); differed in SES, medical and psychiatric dx and disease severity	7 scales (excluding general health) explain two-thirds of reliable variance in evaluations of current health status in UK, U.S., and Sweden; Scales have demonstrated 80–90% empirical validity in studies involving physical and mental health criteria compared with the longer MOS; Validity of each scale has been shown to differ from other scales: Physical functioning (r = 0.85), role-physical (r = 0.81) and bodily pain scales (r = 0.76) correlate most strongly with the PCS score, and are the most valid physical health measures; Mental health (r = 0.87), role-emotional (r = 0.78) and social functioning (r = 0.67) correlate most strongly with the MCS score and are the most valid mental measures	Median item-scale correlation (corrected for overlap) for each of the 8 scales ranged from 0.63 (general health) to 0.79 (mental health); all items except for general health (r = 0.38) exceeded the 0.40 standard for item-internal consistency; overall trends in item-internal consistency were replicated across patient subgroups; Median-item scale correlations for the 8 scales remained high across subgroups ranging from: 0.39 to 0.80	Each scale exceeded the minimum reliability standard of 0.70 for group comparisons; most reliability estimates for physical and mental summary scores exceed 0.80, and 0.90 for the PCS and MCS; Reliability ranged from 0.78 (general health) to 0.93 (physical functioning); Range for subgroups was 0.65 to 0.94	Mental health scale and MCS are useful in screening for psychiatric disorders (e.g. with a cut off score of 42, MCS has a sensitivity of 74% and a specificity of 81% to detect depressive disorder); 3 physical scales are the most responsive to benefits of knee and hip replacement, and heart valve surgery; 3 mental health scales are the most responsive in comparisons of pt before and after recovery from depression, change in severity of depression and treatment for depression

ADVS = Activities of Daily Vision Scale; BCVA = best corrected visual acuity; DR = diabetic retinopathy; dx = diagnosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQL = health-related quality of life; ICC = interclass correlation coefficient; MCS = mental component summary; mo = month; MOS = Medical Outcomes Study; PCS = physical component summary; pt = patient; QoL = quality of life; RetDQoL = Diabetic Retinopathy Dependent Quality of Life; RetTSQ = Diabetic Retinopathy Treatment Satisfaction Questionnaire; r/t = related to; SES = socioeconomic status; SIP = sickness impact profile; tx = treatment; US = United States; U.K. = United Kingdom; VA = Visual Acuity; VF = visual function; VFQ = National Eye Institute Visual Function Questionnaire



**Table 1. Psychometric properties of health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

Measure	Study population	Construct validity	Internal consistency	Test-retest reliability	Responsiveness
<b>Low vision-related HRQL assessment tools</b>					
VFQ-25 <sup>63,73</sup>	VFQ-51—visually impaired persons with diverse eye conditions (N = 598 total; N with DR = 123; N pt included in test-retest reliability analysis = 96); VFQ-25—visual impaired persons with diverse eye conditions (N=859 [597 pt from previous study]; N with DR = 181)	VFQ-51—high correlations between VFQ scales and the VF-14 and ADVS: activity-oriented scales (near, distance vision and driving scale) and other vision-targeted scales: r = 0.9 to 0.6, p = 0.01; general vision ratings : r = 0.7, p < 0.001; mental distress ratings: r = 0.7, p = 0.001; significant correlation for peripheral and color vision with Visual Activities Questionnaire; poor correlation with most SF-36 scales, highest correlation between SF-36 mental component and VFQ-51 mental distress ratings: r = 0.4, p=0.001; correlations between VFQ-51 and ETDRS VA were moderate for scales that reflected the difficulty pt had with visual activities. VFQ-25—Correlations between the VFQ-25 subscales and VFQ-51 counterparts >0.90; correlations between responses on VFQ-25 and ETDRS visual acuity were in the range of 0.65 to 0.70 for subscales that reflected the degree of difficulty with visual activities related to general vision, near vision and distance vision; remaining subscales showed lower correlations ranging from 0.39 to 0.69 with the exception of the ocular pain subscale (lowest) between 0.06 to 0.11	VFQ-51—Cronbach's α for subscales range from 0.66 to 0.94; 86% of internal consistency estimates ≥ 0.7; VFQ-25—Subscale ranges from 0.71 to 0.85; among persons with eye disease, all 8 multi-item subscales had an internal consistency ≥0.70	VFQ-51—ICC for the 11 subscales range from 0.68 to 0.91	Scale scores improve with intervention; greater improvement in visual function is associated with greater improvement in HRQL; Correlations between responses on the VFQ-51 and ETDRS visual acuity were moderate for scales that reflect the degree of difficulty that a person has with common visual activities; Correlations between each of the scales and visual acuity in the better and worse eyes were similar in magnitude

ADVS = Activities of Daily Vision Scale; BCVA = best corrected visual acuity; DR = diabetic retinopathy; dx = diagnosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQL = health-related quality of life; ICC = interclass correlation coefficient; MCS = mental component summary; mo = month; MOS = Medical Outcomes Study; PCS = physical component summary; pt = patient; QoL = quality of life; RetDQoL = Diabetic Retinopathy Dependent Quality of Life; RetTSQ = Diabetic Retinopathy Treatment Satisfaction Questionnaire; r/t = related to; SES = socioeconomic status; SIP = sickness impact profile; tx = treatment; US = United States; U.K. = United Kingdom; VA = Visual Acuity; VF = visual function; VFQ = National Eye Institute Visual Function Questionnaire

**Table 1. Psychometric properties of health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

Measure	Study population	Construct validity	Internal consistency	Test-retest reliability	Responsiveness
VF-14 <sup>66,74</sup>	Patients undergoing cataract surgery (N = 766); 522 pt of original population used to test responsiveness (had not received second surgery by 4 mo followup); 383 pt of original population used to test reproducibility (had not received second surgery by 12 mo followup)	Criterion validity assessed by examining the correlation between VF-14 scores and other measures of vision included visual acuity and global self-rating of the overall difficulty and satisfaction patients had with their vision; VF-14 with pt self-reported trouble with vision ( $r = -0.45$ ) and overall satisfaction with vision ( $r = 0.34$ ) higher than correlations with other vision measures; correlation between VF-14 score and visual acuity was strongest in the better eye ( $r = 0.27$ ); VF-14 moderately correlated with SIP score ( $r = -0.39$ ); and strongly correlated with VR-SIP score ( $r = -0.57$ )	Cronbach's $\alpha$ for total scale = 0.85; Cronbach's $\alpha$ for subscales ranged from 0.32 to 0.61	In pt whose 12 mo followup BCVA in each eye remained within 1 Snellen line of 4 mo followup value ( $n = 249$ ) (mean VF-14 scores at 12 mo 1.5 points lower than 4 mo scores): ICC = 0.57; In pt with no difference between 12 mo and 4 mo followup BCVA ( $n = 96$ ) (mean difference between 4 and 12 mo followup VF-14 scores = 1.7 points; $p < 0.05$ ): ICC = 0.71; In pt with no complications ( $n = 47$ ) (no significant difference in mean 4 and 12 mo followup scores): ICC = 0.76; Pt who had identical answers to 2 global questions r/t trouble and satisfaction with vision ( $n = 119$ ) (mean VF-14 scores at 12 mo followup 1.1 points lower than 4 mo followup score; $p < 0.05$ ): ICC = 0.79; After adjusting for pt who scored 100 points on VF-14 at both 4 and 12 mo: ICCs = 0.50 to 0.73	Pts who underwent cataract removal in one eye (up to 4 mo followup) ( $n = 522$ ): effect size 1.02 for VF-14, -0.26 for SIP; Pt whose VA in operated eye improved by $\geq 2$ Snellen lines: effect size 1.07 (VF-14), -0.29 (SIP)—results did not differ when patients stratified by baseline VA; Pt whose functional status improved at 4 mo followup ( $n = 510$ ): effect size 1.06 (VF-14), -0.27 (SIP); Pt who reported an improved rating of amount of trouble with vision at 4 mo followup ( $n = 438$ ): effect size: 1.17 (VF-14), -0.28 (SIP); Pt who reported improved rating of satisfaction with vision at 4 mo followup ( $n = 470$ ): effect size: 1.14 (VF-14), -0.30 (SIP)

ADVS = Activities of Daily Vision Scale; BCVA = best corrected visual acuity; DR = diabetic retinopathy; dx = diagnosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQL = health-related quality of life; ICC = interclass correlation coefficient; MCS = mental component summary; mo = month; MOS = Medical Outcomes Study; PCS = physical component summary; pt = patient; QoL = quality of life; RetDQoL = Diabetic Retinopathy Dependent Quality of Life; RetTSQ = Diabetic Retinopathy Treatment Satisfaction Questionnaire; r/t = related to; SES = socioeconomic status; SIP = sickness impact profile; tx = treatment; US = United States; U.K. = United Kingdom; VA = Visual Acuity; VF = visual function; VFQ = National Eye Institute Visual Function Questionnaire

**Table 1. Psychometric properties of health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

Measure	Study population	Construct validity	Internal consistency	Test-retest Reliability	Responsiveness
<b>Diabetes-related HRQL assessment tools</b>					
DTSQ <sup>75</sup>	Pt with diabetes mellitus (n = 286); divided into 3 groups: CSII: continuous subcutaneous insulin infusion; ICT: intensified conventional therapy; CT: conventional therapy	Evidence of construct validity demonstrated in populations with diabetes mellitus (not DR) by relationships between treatment satisfaction and: being less overweight (r = 0.19; p<0.05); having better glycemic control (r = -0.28; p<0.001) and being optimistic about recent diabetes control (r = 0.56; p<0.001)	Cronbach's $\alpha$ for total scale = 0.76; When item: how many hypoglycemic experiences have you experienced recent was removed, $\alpha$ = 0.79 for total scale	No data	Low score indicates that level of satisfaction has increased during the year; if no change occurred, a score of 21 would be obtained; Significantly different scores on the 3 subscales obtained between CSII, ICT and CT: F = 30.4; df 2, 123; p<0.001; Significant interaction between CSII, ICT, and CT, and magnitude of sub-scale score: F = 4.81; df 4, 246; p<0.001)
<b>Diabetic retinopathy-related HRQL assessment tools</b>					
RetDQoL <sup>70</sup>	Patients with DR (N = 207)	Predefined hypotheses were tested: Greater visual impairment, advanced stages of DR, & additional impact of DME will lead to more negative impact on QoL: <i>confirmed</i> ; Significant correlation with clinical variables for overview items I (present QoL) and II (retinopathy-specific QoL), and the AWI of domain-specific items: <i>confirmed with exception of stage of DR and item I</i> ; Significant correlations between AWI and overview items I and II, with the strongest positive relationship between AWI and overview item II: <i>confirmed</i> ; Small significant correlations with subscales of SF-12: <i>confirmed</i> ; Small significant correlation with tx satisfaction as measured by RetTSQ: <i>confirmed</i> ; No significant correlations with sociodemographic variables: <i>not confirmed for item I (living alone, employment, age, sex); confirmed for item II</i>	Cronbach's $\alpha$ weighted impact scores for all domains = 0.958; Cronbach's $\alpha$ for unweighted impact scores and the importance ratings = 0.96, 0.84, respectively	No data	No data

ADVS = Activities of Daily Vision Scale; BCVA = best corrected visual acuity; DME = diabetic macular edema; DR = diabetic retinopathy; dx = diagnosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQL = health-related quality of life; ICC = interclass correlation coefficient; MCS = mental component summary; mo = month; MOS = Medical Outcomes Study; PCS = physical component summary; pt = patient; QoL = quality of life; RetDQoL = Diabetic Retinopathy Dependent Quality of Life; RetTSQ = Diabetic Retinopathy Treatment Satisfaction Questionnaire; r/t = related to; SES = socioeconomic status; SIP = sickness impact profile; tx = treatment; US = United States; U.K. = United Kingdom; VA = Visual Acuity; VF = visual function; VFQ = National Eye Institute Visual Function Questionnaire

**Table 1. Psychometric properties of health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

Measure	Study population	Construct validity	Internal consistency	Test-retest Reliability	Responsiveness
RetTSQ <sup>†1</sup>	Patients with DR (N = 207)	Predefined hypotheses were tested: Greater visual impairment, advanced stages of DR, & additional impact of DME are associated with less tx satisfaction: <i>confirmed</i> ; Moderate significant correlations with subscales of SF-12: <i>confirmed</i> ; Positive correlations between tx satisfaction and QOL scores on RetDQoL: <i>confirmed</i> ; No significant correlations with sociodemographic variables: <i>confirmed</i>	Cronbach's $\alpha$ of total scale = 0.90; Cronbach's $\alpha$ for both of the subscales = 0.85	No data	No data

ADVS = Activities of Daily Vision Scale; BCVA = best corrected visual acuity; DR = diabetic retinopathy; dx = diagnosis; DTSQ = Diabetes Treatment Satisfaction Questionnaire; ETDRS = Early Treatment of Diabetic Retinopathy Study; HRQL = health-related quality of life; ICC = interclass correlation coefficient; MCS = mental component summary; mo = month; MOS = Medical Outcomes Study; PCS = physical component summary; pt = patient; QoL = quality of life; RetDQoL = Diabetic Retinopathy Dependent Quality of Life; RetTSQ = Diabetic Retinopathy Treatment Satisfaction Questionnaire; r/t = related to; SES = socioeconomic status; SIP = sickness impact profile; tx = treatment; US = United States; U.K. = United Kingdom; VA = Visual Acuity; VF = visual function; VFQ = National Eye Institute Visual Function Questionnaire

**Table 2. Rating of the psychometric properties health-related quality of life assessment tools used in studies of treatment of diabetic retinopathy**

Measure	Content validity	Construct validity	Internal consistency	Test re-test reliability	Measurement error	Responsiveness	Interpretability
SF-36	+	+	+	+	+	+	+
VFQ-25	+	+	+	+	0	?	?
VF-14	?	+	+	?	0	?	0
DTSQ	+	+	+	+	+	+	0
RetDQoL	+	+	+	0	0	0	0
RetTSQ	+	+	+	0	0	0	0

Method or result was rated as: += high quality; ?: indeterminate; -: low quality; 0: no data available

Key Questions 2 and 3: What is the evidence that HRQL is improved by any intervention; and what is the relationship between HRQL and any relevant variables?

## Description of Included Studies

We identified two RCTs and seven observational studies that addressed Key Questions 2 and 3. The population and study characteristics are summarized in Table 3. Additional population and study characteristics are available in Appendix F.

The two RCTs<sup>42,47</sup> were multicenter trials that recruited patients in Australia, North and South America, Europe, India, and Turkey. The trials examined two anti-VEGF treatments in patients with DME. The RESTORE study<sup>47</sup> was a three-arm double-masked RCT (n = 345) that compared ranibizumab monotherapy versus ranibizumab plus laser versus laser. The Macugen 1013 study<sup>42</sup> (n = 260) was a double-masked RCT comparing pegaptanib sodium versus sham.

For the observational studies, the interventions included laser photocoagulation,<sup>48,54</sup> vitrectomy,<sup>41,45,46</sup> panretinal photocoagulation,<sup>46</sup> and phacoemulsification cataract surgery for diabetic patients with cataracts.<sup>51,53</sup> Sample sizes ranged from 55 to 345 (IQR: 77 – 293.5). As a post hoc analysis, we examined the subgroup of patients with DME. Six studies<sup>41,42,45,47,48,54</sup> reported some results for those with DME. Two studies<sup>51,53</sup> included patients with DME, but did not report separate results. Patients with DME represented less than five percent of the study sample in these studies. One study<sup>46</sup> did not report whether patients with DME were included in their study.

## Methodological Quality

Both RCTs were assessed as “unclear” risk of bias. The primary concern for both trials was incomplete outcome data and the use of the last observation carried forward approach for missing data. For the Macugen 1013 study,<sup>42</sup> all other domains were assessed as low risk of bias. For the RESTORE study,<sup>47</sup> the domains for allocation concealment, blinding of HRQL assessment, and baseline balance for HRQL were assessed as unclear; the remaining domains were low risk of bias. Both trials received industry funding.

There were four cohort studies<sup>41,46,51,53</sup> and three before-after studies.<sup>45,48,54</sup> All data were collected prospectively. The methodological quality of the cohort studies was assessed as good for one<sup>51</sup> (7/8 stars), moderate for one<sup>53</sup> (6/8 stars), and low for two (3 or 4 of 8 stars). Two studies<sup>53,54</sup> enrolled patients that were rated to be truly or somewhat representative of average patients in the community, and the nonexposed cohort was drawn from the same community. For the remaining two studies, there was no description of the derivation of the cohort. All studies ascertained the exposure status from a secure source, most commonly from patient records. Two studies<sup>53,54</sup> controlled for potential confounders through multivariate analyses. All studies used a validated tool for outcome assessment. Two studies<sup>46,51</sup> had a followup duration of at least 6 months. For all studies, the rate of followup was either complete or considered unlikely to introduce bias.

The methodological quality of the before-after studies was assessed as good for one<sup>54</sup> (5/5 stars) and moderate for two<sup>45,48</sup> (4/5 stars). Two studies<sup>45,54</sup> enrolled patients that were rated to be truly or somewhat representative of average patients in the community. All studies ascertained the exposure status from a secure source, most commonly from patient records. All used a

validated tool for outcome assessment. Two studies<sup>45,54</sup> had a followup duration of at least 6 months. For all three studies, the rate of followup was either complete or unlikely to introduce bias.

Overall this collection of observational studies is at high risk of bias due to weak study designs (before-after and cohort studies).

## Results

The results are grouped by the type of intervention (e.g., anti-VEGF, laser photocoagulation). Three observational studies<sup>41,48,54</sup> conducted multivariate analyses to identify variables associated with HRQL outcomes; these results are presented with their respective studies. Table 4 summarizes the outcomes.

### Anti-VEGF

From September 2005 to November 2009, the Macugen 1013 Study group<sup>42</sup> conducted a multicenter trial that investigated the efficacy of pegaptanib sodium versus sham injections. All patients were diagnosed with DME. Patients were randomized to receive 0.3 mg of pegaptanib sodium (n=133) or a sham treatment designed to mimic the intravitreal injection process (n=127). The primary efficacy endpoint was the number of patients who gained 10 letters or more on visual acuity compared to baseline. At 54 weeks after baseline 49 of 133 (36.8 percent) patients treated with pegaptanib had achieved an improvement of 10 or more letters, compared with 25 of 127 (19.7 percent) in the sham injection group. The odds ratio was 2.38 (95% CI, 1.32 to 4.30, p=0.0047). Additionally, patients who received pegaptanib reported statistically (p<0.05) and clinically significant (>5 point difference) improvements on the VFQ-25 at 54 weeks on the near vision, distant vision, and social functioning subscales. The change in composite score was not statistically significant. At 102 weeks after baseline, patients who received pegaptanib reported statistically (p<0.05) and clinically significant (>5 point difference) improvements on the composite score, and the distance vision, social functioning and mental health subscores compared with patients treated with a sham injection.

The RESTORE Study group<sup>47</sup> conducted a multicenter trial that investigated the efficacy of ranibizumab with and without laser treatment. All patients were diagnosed with DME. Patients were randomized to receive 0.5 mg of ranibizumab plus sham laser treatment (n=116), 0.5 mg of ranibizumab plus laser treatment (n=118), and sham treatment plus laser treatment (n=111). The mean change in best corrected visual acuity (BCVA) from baseline to 12 months was the primary outcome. For patients treated with ranibizumab alone, 22.6 percent achieved a BCVA letter score of 15 or more, and 53 percent attained a BCVA letter score level more than 73 (20/40 Snellen equivalent); whereas 22.9 percent and 44.9 percent, respectively achieved those gains among the patients treated with ranibizumab plus laser therapy. Of patients who received laser treatment, 8.2 percent improved 15 or more letters on BCVA, and 23.6 percent reached a BVCA letter score more than 73. Scores on the VFQ-25 were significantly improved from baseline to 12 months for patients treated with ranibizumab alone and patients treated with ranibizumab in combination with laser compared with patients with laser treatment only. For the ranibizumab monotherapy group the composite score increased by 5.0 points compared with an increase of 0.6 for the laser treatment group (p=0.014). Similarly for the ranibizumab plus laser treatment group, the composite score increased by 5.4 points (p=0.004). Furthermore, at 12 months ratings of good to excellent vision were reported by 46 percent of patients treated with ranibizumab alone and 50 percent of those treated with ranibizumab plus laser treatment. This compares with

22 percent of patients who received only laser treatment. The proportion of patients reporting excellent to good vision at baseline were similar across the three groups—21 percent (ranibizumab), 23 percent (ranibizumab plus laser treatment), and 24 percent (laser only).

## **Laser photocoagulation**

Tranos et al.<sup>48</sup> conducted a prospective study that followed 55 patients with DME. Best corrected visual acuity for distance vision and near vision were recorded as the number of letters read correctly on Early Treatment of Diabetic Retinopathy Study (ETDRS) charts at 4 meters and 40 centimeters, respectively. The mean baseline visual acuity was  $42.7 \pm 8.4$  (distance) and  $56.4 \pm 9.1$  (near). Patients completed the VFQ-51 prior to and 3 months following the last session of laser treatment. At the end of the followup period, DME had resolved in 46 (84 percent) patients, although improvement in visual acuity was small. Based on the VFQ-51, laser treatment resulted in an improvement in patients' perceived functional status and QOL. The composite score and the subscale scores associated with general vision, near vision, distance vision, vision-specific mental health, expectations for visual function, and dependency due to vision were significantly improved following laser treatment.

Multivariate models showed that improvement of the VFQ-51 composite score was associated with age less than 65 years ( $p = 0.04$ ), number of laser spots (indicating more extensive treatment;  $p = 0.02$ ), and worse vision-related QOL prior to laser treatment ( $p = 0.03$ ). There was no statistically significant association between change in the composite score and stage of DR or duration of diabetes.

From June 2002 to March 2004, Mozaffarieh et al.<sup>54</sup> followed 105 patients undergoing first photocoagulation treatment for DME ( $n = 49$ ) or proliferative diabetic retinopathy (PDR) ( $n = 56$ ). Patients had laser treatments at 4 and 9 months, and then a final examination 12 months after the initial laser treatment. Best-corrected visual acuity was recorded using a Snellen chart, and visual acuity improvement was defined as the difference between the pre- and post-treatment logarithm of minimal angle of resolution (logMAR) acuity. All patients completed the DTSQ after their initial and final (9 month) laser treatments. Nine months after initial photocoagulation treatment 24.7 percent of all patients reported improvement in visual acuity. Vision remained the same in 71.4 percent and worse in 3.8 percent. These values remained constant 12 months after initial treatment for all but one patient whose vision deteriorated further. There was no statistically significant difference in vision improvement between patients with DME and PDR. Based on a maximum possible score of 36, satisfaction after the final (9 month) laser treatment was high (mean score =  $27.9 \pm 5.2$ ), with 42.8 percent scoring 31 or higher. Results of the DTSQ were not reported separately for the two groups of patients.

The Spearman correlation between treatment satisfaction and the patients' visual acuity after laser treatment for patients with DME and PDR was modest ( $r = 0.28-0.33$ ,  $p > 0.2$ ). Satisfaction was associated with age, with older patients being more satisfied than younger patients (Spearman coefficient  $r = 0.41-0.56$ ,  $p < 0.001$ ).

## **Vitrectomy**

In a prospective study, Okamoto et al.<sup>41</sup> investigated vision-related QOL in 299 patients undergoing pars plana vitrectomy for various vitreoretinal disorders. The authors reported results separately for patients with PDR ( $n = 99$ ) and DME ( $n = 38$ ). The logMAR best corrected visual acuity and letter contrast sensitivity were obtained preoperatively and at 3 months postoperatively. All patients completed the VFQ-25 (Japanese version) before and 3 months



after surgery. One hundred healthy volunteers who served as normal control subjects also completed the VFQ-25. Vitrectomy significantly improved visual acuity and contrast sensitivity in both patient groups. For patients with PDR, the composite VFQ-25 score and most subscale scores improved significantly following vitrectomy. The composite score gained  $10.8 \pm 18.3$  points. For those with DME, the change in the composite score was  $6.0 \pm 20.8$ , but was not statistically significant. The only vision related subscales that showed statistically significant improvements for patients with DME were general vision, near activities, mental health, and peripheral vision. The composite score for the normal controls was  $85.0 \pm 9.1$ , which is statistically significantly higher than the preoperative and postoperative composite scores in patients with PDR and DME.

Multiple regression analysis showed that improvement in contrast sensitivity was significantly correlated with changes in the VFQ-25 composite score for patients with PDR and DME. There was no significant correlation between changes in the VFQ-25 and postoperative visual acuity.

Emi et al.<sup>45</sup> followed 87 patients with DR. Of these, 41 (47 percent) had vitreous hemorrhage, 28 (32 percent) had DME, and 18 (21 percent) had fibrovascular membrane. All patients completed the VFQ-25 (Japanese version) 1 month before and 6 months after vitrectomy. At 6 months, 35 (85 percent) patients with vitreous hemorrhage reported that their visual acuity had improved; the remaining patients reported visual acuity as unchanged ( $n = 4$ ) or worse ( $n = 2$ ). For patients with DME and fibrovascular membrane, 9 (32 percent) and 13 (72 percent) reported improved visual acuity, respectively. For all patients, the mean VFQ-25 following vitrectomy increased in all 12 subscales; however, the changes were not statistically significant. Only the subgroup of patients with vitreous hemorrhage reported statistically significant improvements for 10 of the 12 subscales of the VFQ-25. For the subgroup of patients with fibrovascular membrane, the only subscale that had a statistically significant change from baseline was general vision.

### **Vitrectomy and panretinal photocoagulation**

In a second study by Emi et al.,<sup>46</sup> 327 patients with DR were followed for 1 year. Of these, 136 (42 percent) underwent vitrectomy, 60 (18 percent) received panretinal photocoagulation, and 131 (40 percent) did not have any treatment and served as a comparison group. All patients completed the VFQ-25 (Japanese version) at the time of entry into the study and 1 year later. Visual acuity was reported as the logMAR score for the right and the left eyes. For the vitrectomy group, the VFQ-25 composite score improved by eight points and the change was statistically significant. Changes in the composite scores for the comparison group and the photocoagulation group were not statistically significant. At baseline, the VFQ-25 composite score for the vitrectomy group was significantly lower than that of either of the other groups; at 1 year followup, there was no statistically significant difference between the vitrectomy and the photocoagulation groups.

### **Phacoemulsification**

From May 2001 to May 2003, Mozaffarieh et al.<sup>53</sup> prospectively evaluated visual outcomes and visual function after first-eye phacoemulsification cataract surgery. A total of 67 patients with different stages of DR were included: 17 patients had no apparent DR (group 1), 19 had mild nonproliferative diabetic retinopathy (NPDR) (group 2), 16 had moderate/severe NPDR (group 3), and 15 had proliferative diabetic retinopathy (PDR) (group 4). Patients were followed

for 3 months after surgery. All patients completed the VF-14 prior to and 3 months after surgery. Three months postoperatively, 94.2 percent of patients reported improved visual acuity and 92.5 percent reported improvements in visual function. Improvements in both visual acuity and visual function decreased as the baseline level of retinopathy increased. Patients with no DR or mild retinopathy (groups 1 and 2) demonstrated significantly greater improvements in visual acuity and visual function compared with patients with more advanced DR (group 3 and 4).

From May 2000 to March 2004, Mozaffarieh et al.<sup>51</sup> followed 89 diabetic patients with bilateral cataracts. Of these, 66 had DR (mild NPDR: 35 percent, moderate/severe NPDR: 33 percent, PDR: 32 percent). Forty-one patients had surgery on one eye (group 1), and 48 had subsequent surgery on the second eye (group 2) at least 6 months later. Patients completed the VF-14 prior to surgery and 1, 3, 6, 8, and 12 months postoperatively. Patients with PDR had the lowest VF-14 scores at baseline and improved marginally over the study period regardless of whether they had surgery on one or both eyes (improvement of  $2.6 \pm 10.8$  points and  $2.4 \pm 5.2$  at 6 months, and  $4.6 \pm 7.3$  and  $-2.98 \pm 7.4$  (decrease) at 12 months, respectively). A similar pattern was seen for patients with moderate/severe NPDR with an increase of  $7.8 \pm 8.0$  points and  $6.2 \pm 5.6$  at 6 months and  $5.2 \pm 8.2$  and  $-6.85 \pm 15.3$  (decrease) at 12 months, respectively. For patients with no or mild NPDR, maximum VF-14 scores at 12 months followup were significantly higher than patients with more severe DR.

The impact of first-eye cataract surgery on QOL was evident in patients with no or mild DR with the highest VF-14 scores being achieved by 91.3 percent of patients in the first month. In contrast, for those with more severe DR 79.1 percent achieved the highest VF-14 score after 3 months.

In patients with no or mild DR who underwent second-eye surgery the improved functional status achieved after first surgery was sustained. For those who did not have second-eye surgery VF-14 scores decreased after 8 and 12 months. For those with more advanced levels of DR, there were no significant gains after second eye surgery at 12 months.

**Table 3. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Anti-VEGF</b>				
Mitchell 2011 <sup>47</sup>  RCT  Multicenter (73 centers in Australia, Canada, Europe, Turkey)	G1—ranibizumab 0.5 mg + sham laser G2—ranibizumab 0.5 mg + laser G3—laser + sham injection  VFQ-25  3 mo, 12 mo	G1 = 116 G2 = 118 G3 = 111  DME = 345 (100%)	<i>Median change in BCVA from baseline to 12 mo:</i> G1 = 6.1±6.43 G2 = 5.9±7.92 G3 = 0.8±8.59 <i>Median change in BCVA from baseline to 12 mo:</i> G1 = 6.1 (-10.9–25.2) G2 = 6.0 (-26.7–27.6) G3 = 1.3 (-37.8–26.8) <i>95% CI for the mean change:</i> G1 = 4.9, 7.3 G2 = 4.4, 7.3 G3 = -0.8, 2.4	<i>VFQ-25, composite score at 12 mo</i> G1—baseline: NR; improvement: 5.0 (p=0.014 compared to G3) G2—baseline: NR; improvement: 5.4 (p=0.004 compared to G3)) G3—baseline: NR; improvement: 0.6 (NR) <i>Other domains:</i> G1—significant improvement for general vision, near vision activities, distance activities; other domains: NR G2— significant improvement for general vision, near vision activities, distance activities; other domains: NR G3—baseline: NR; no significant change from baseline
Sultan 2011 <sup>42</sup>  RCT  Multicenter (60 centers in Australia, Europe, India, North America, South America)	G1—pegaptanib 0.3 mg G2—sham injection  VFQ-25  baseline, 18, 54 & 102 wk	G1 = 133 G2 = 127  DME = 260 (100%)	<i>% improvement of ≥10 letters from baseline at 54 wk:</i> G1 = 43/133 (36.8%) G2 = 25/127 (19.7%) Odds ratio (95% CI) = 2.38 (1.32, 4.30); p=0.0047  <i>% improvement of ≥10 letters from baseline at 102 wk</i> G1 = 41/107 (38.3%) G2 = 30/100 (30%) Odds ratio (95% CI) = 1.57 (0.83, 2.97); p=0.1729	<i>VFQ-25, composite score at 54 wk:</i> G1—70.4; improvement 4.5 G2—69.2; improvement 1.3 <i>Between group differences—2.92; range - 0.32 to 6.16 (p = 0.077)</i> <i>VFQ-25, composite score at 102 wk (n = 207):</i> G1—69.8; improvement 4.6 G2—66.2; improvement 0.1 <i>Between group differences—4.47; range - 0.26 to 8.68 (p = 0.038)</i> <i>Other domains:</i> 54 wk: G1 vs. G2 had significantly more improvement for near vision activities, distance activities, social functioning; no difference for other domains 102 wk: G1 vs. G2 had significantly more improvement for distance activities, social functioning, mental health; no difference for other domains

95% CI = 95 percent confidence interval; BCVA = best corrected visual acuity; DR = diabetic retinopathy; DTSQ = Diabetes Treatment Satisfaction Questionnaire; DME = diabetic macular edema; mg = milligram; mo = month; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VF-14 = Visual Function-14; VFQ = National Eye Institute Visual Function Questionnaire; wk = week; yr = year

**Table 3. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Laser photocoagulation</b>				
Tranos 2004 <sup>48</sup> Before-after United Kingdom	Laser photocoagulation VFQ-51 3 mo	DME = 55 (100%) Mild NPDR = 13 Moderate NPDR = 32 Severe NPDR = 10	<i>Binocular vision</i> —baseline: 48.7±6.7 <i>Distance vision</i> —baseline: 42.7±8.4 letters; improvement: 2.2±6.2 <i>Near vision</i> —baseline: 56.4±9.1 letters; improvement: 2.1±5.0	<i>Composite score</i> —baseline: 77.9±17.6; improvement: 4.9±8.9 (p<0.001); <i>Subscales</i> —statistically significant improvement on 8 of 11 vision-related domains
Mozaffarieh 2005b Before-after Austria	Laser photocoagulation DTSQ 9 mo	Total = 105 PDR = 56 (53%) DME = 49 (47%)	24.7% reported improvement in visual acuity; 71.4% were unchanged; 3.8% were worse No difference in improvement between patients with PDR or DME	Mean± SD = 27.9±5.2 (maximum possible score = 36)
<b>Vitrectomy</b>				
Emi 2008 <sup>45</sup> Before-after Japan	Vitrectomy VFQ-25 (Japanese version) 6 mo	DR = 87 (total) G1—vitreous hemorrhage = 41 G2—DME = 28 G3—fibrovascular membrane = 18	G1—improved: 35; unchanged: 4; worse: 2 G2—improved: 9; unchanged: 16; worse: 3 G3—improved: 13; unchanged: 3; worse: 2	G1—statistically significant improvement on 10 of 12 subscales G2—no statistically significant change from baseline on any subscales G3—only the general vision subscale had a statistically significant improvement from baseline
Okamoto 2010 <sup>41</sup> Prospective cohort Japan	Pars plana vitrectomy VFQ-25 (Japanese version) 3 mo	G1—PDR = 99 G2—DME = 38 G3—normal controls = 100  <i>Note: this is part of a larger study (n = 399) of patients with vitreoretinal disorders— retinal vein occlusion (32), macular hole (42), epiretinal membrane (33), retinal detachment (55)</i>	<i>logMAR</i> G1—baseline: 1.37±0.75; 3 mo: 0.53±0.62 (p < 0.0001) G2—baseline = 0.76±0.49; 3 mo: 0.55±0.51 (p < 0.01)  <i>Contrast sensitivity</i> G1—baseline: 5.4±7.2; 3 mo: 14.0±7.9 (p < 0.0001) G2—baseline 9.2±6.5; 3 mo: 12.7±7.1 (p < 0.0001)	G1—baseline: 52.8±19.0; 3 mo: 63.6±17.5 (p < 0.001); <i>Subscales</i> —statistically significant improvement on 9/11 vision-related domains G2—baseline: 53.0±20.5; 3 mo: 59.0±21.0 (p = 0.84); <i>Subscales</i> —statistically significant improvement on 4/11 vision-related domains G3—85.0±9.1

**Table 3. Study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Author Year Study design Country	Intervention HRQL measure Followup	Participants	Visual acuity outcomes	HRQL outcomes
<b>Vitrectomy and panretinal photocoagulation</b>				
Emi 2009 <sup>46</sup>	G1—vitrectomy G2—panretinal G3—no treatment	G1 = 136 G2 = 60 G3 = 131	<i>logMAR—right eye</i> G1—baseline: 0.21; 1 yr: 0.46 (p < 0.001) G2—baseline: 0.64; 1 yr: 0.52 (p = 0.272) G3—baseline: 1.09; 1 yr: 1.06 (p = 0.294)	<i>Composite score</i> G1—baseline: 67.4±17.3; 1 yr: 75.4±17.5 (p<0.001) G2—baseline: 80.7±15.7; 1 yr: 77.6±19.1 (p=0.113) G3—baseline: 91.3±7.8; 1 yr: 92.2±7.8 (p=0.169)
Prospective cohort	VFQ-25 (Japanese version)		<i>logMAR—left eye</i> G1—baseline: 0.19; 1 yr: 0.38 (p < 0.001) G2—baseline: 0.61; 1 yr: 0.56 (p = 0.081) G3—baseline: 1.10; 1 yr: 1.09 (p = 0.704)	
Japan	1 yr			
<b>Phacoemulsification cataract surgery</b>				
Mozaffarieh 2005a <sup>33</sup>	Phacoemulsification cataract surgery	Cataracts = 67 (total) G1—no DR = 17 G2—mild NPDR = 19 G3—moderate/severe NPDR = 16 G4—PDR = 15	<i>logMAR (range)</i> G1—baseline: 0.62 (0.30–1.30); improvement 0.55 (0.30–1.15) G2—baseline: 0.60 (0.30–1.30); improvement 0.50 (0.30–1.08) G3—baseline: 0.67 (0.30–1.30); improvement 0.26 (0.15–0.48) G4—baseline: 0.71 (0.40–1.30); improvement 0.15 (-0.70–0.60)	G1—baseline: 52.21 (32.14–78.57); improvement 42.33 (21.43–60.71) G2—baseline: 55.92 (30.36–85.71); improvement 36.00 (12.50–58.93) G3—baseline: 46.65 (30.36–64.29); improvement 9.26 (1.79–25.00) G4—baseline: 40.12 (25.00–67.86); improvement 5.00 (-25.00–25.00)
Prospective cohort	VF-14			
Austria	3 mo			
Mozaffarieh 2009 <sup>51</sup>	Phacoemulsification cataract surgery	Cataracts = 89 (total) No DR = 23 Mild NPDR = 23 Moderate NPDR = 22 PDR = 21	G1 & G2—patients with no or mild NPDR had greater improvement in visual acuity	G1 baseline: no DR: 59.3±12.4; mild 39.3±5.2; severe 40.9±8.6; PDR 35.3±4.4 6 mo: no DR: 96.8±2.0; mild 86.5±13.6; severe 48.8±6.7; PDR 37.9±14.0 12 mo: no DR: 79.5±5.5; mild 72.2±8.3; severe 46.1±10.7; PDR 39.9±9.0 G2 baseline: no DR 46.8±8.7; mild 63.4±16.3; severe 54.6±8.8; PDR 50.6±11.4 6 mo: no DR: 93.0±4.3; mild 94.6±2.5; severe 60.9±6.6; PDR 53.0±10.9 12 mo: no DR: 95.3±1.9; mild 95.3±2.2; severe 47.8±16.0; PDR 47.6±15.0
Prospective cohort	G1—first-eye surgery G2—both eyes			
Austria	VF-14			
	12 mo			

## Summary of Findings

**Anti-VEGF.** Two RCTs provided data. In one RCT, 133 patients received 0.3 mg of pegaptanib sodium versus 127 patients who received a sham injection. All patients were diagnosed with DME. At 54 weeks there was no statistically significant difference between groups in the composite score on the VFQ–25. At 102 weeks, patients receiving pegaptanib sodium reported statistically significant improvements in the composite score. The second RCT was a three-arm trial comparing 0.5 mg of ranibizumab plus sham laser treatment (n=116), 0.5 mg of ranibizumab plus laser treatment (n=118), and sham treatment plus laser treatment (n=111). All patients were diagnosed with DME. The composite score on the VFQ–25 was significantly improved for patients treated with ranibizumab alone, or in combination with laser treatment compared with patients with laser treatment only. The strength of evidence for anti-VEGF is low. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.

**Laser photocoagulation.** Two before-after studies provided data. In one study, 105 patients with PDR and DME reported high scores on the DTSQ at 9 months following surgery. In the second study, 110 patients with DME and NPDR reported a statistically significant improvement in HRQL at 3 months following surgery. While HRQL improved following surgery, the strength of evidence is insufficient to draw conclusions about the effect of laser photocoagulation in improving HRQL.

**Vitrectomy.** One cohort study and one before-after study provided data. In the cohort study, 99 patients with PDR reported a statistically significant improvement on the VFQ–25 (Japanese version) at 3 months following surgery. For those with DME (n = 38), the score improved, but the change was not statistically significant. The score on the VFQ–25 for the normal control group was significantly higher than the preoperative and postoperative scores of patients with PDR and DME. In the before-after study, 41 patients with vitreous hemorrhage reported statistically significant improvements on the VFQ–25 (Japanese version) at 6 months following surgery. This contrasts with patients with DME (n = 28) and fibrovascular membrane (n = 18) who reported no significant change in HRQL. While HRQL improved for some subgroups of patients, the strength of evidence is insufficient to draw conclusions about the effect of vitrectomy in improving HRQL.

**Vitrectomy and panretinal photocoagulation.** One cohort study provided data for 327 patients with DR. Of these, 136 underwent vitrectomy, 60 received panretinal photocoagulation, and 131 had no treatment and served as a comparison group. For the vitrectomy group, there was a statistically significant improvement in the VFQ–25 (Japanese version) composite score at 1 year following surgery. Changes in the VFQ–25 scores for the comparison group and the photocoagulation group were not statistically significant. The strength of evidence is insufficient to draw conclusions about the relative effect of vitrectomy versus panretinal photocoagulation in improving HRQL.

**Phacoemulsification for cataract surgery.** Two cohort studies provided data. One study evaluated visual function using the VF–14 after first-eye phacoemulsification cataract surgery. Three months following surgery, 94 percent of patients reported improved visual acuity and 93

percent reported improvements in visual function. Patients with no or mild DR demonstrated significantly greater improvements in visual acuity and function compared with patients with more advanced disease. The second study followed 89 diabetic patients with bilateral cataracts. At 12 months following surgery, patients with PDR had the lowest VF-14 scores at baseline and improved marginally over the study period regardless of whether they had cataract surgery on one or both eyes. A similar pattern was seen for patients with moderate/severe NPDR. For patients with no or mild NPDR, maximum VF-14 scores at 12 months were significantly higher than for patients with more severe DR. While HRQL improved, the strength of evidence is insufficient to draw conclusions about the effect of this surgery in improving HRQL.

**Factors associated with outcomes.** No conclusions can be drawn about factors associated with HRQL outcomes. In one study, multivariate analysis found that age <65 years, more severe level of DR, and low preoperative QOL were associated with improved HRQL following laser photocoagulation. In another study that also investigated laser photocoagulation, univariate analysis showed an association between age and treatment satisfaction, with older patients (>65 years) being more satisfied. In a study of vitrectomy, multivariate analysis showed that improvement in contrast sensitivity was significantly correlated with changes in the VFQ-25 for patients with PDR and DME. There was no significant correlation between VFQ-25 and visual acuity.

**Table 4. Strength of evidence for health-related quality of life outcomes**

Design # studies (sample size)	Risk of Bias	Consistency	Directness	Precision	Strength of evidence
<b>Anti-VEGF</b>					
2 RCTs (n = 605)	Medium	Inconsistent (at 1 yr)	Direct	Not pooled	Low
<b>Laser photocoagulation</b>					
2 before-after studies (n = 160)	High	Unknown (single study)	Direct	Not pooled	Insufficient
<b>Vitrectomy</b>					
1 cohort study (n = 237) 1 before-after study (n = 87)	High	Consistent	Direct	Not pooled	Insufficient
<b>Vitrectomy and panretinal photocoagulation</b>					
1 cohort study (n = 327)	High	Unknown (single study)	Direct	Not pooled	Insufficient
<b>Phacoemulsification cataract surgery</b>					
2 cohort studies (n = 156)	Medium	Consistent	Direct	Not pooled	Insufficient

## Discussion

Using a comprehensive search strategy and concerted efforts to avoid publication and selection bias, this review identified the evidence on the effect that interventions for DR or DME have on HRQL. Overall we identified four measures—one generic, two vision-specific, and one diabetes-specific—that have been used to measure HRQL in studies of treatment for DR. As well, we identified two recently developed tools that are specific to patients with DR. We identified two RCTs and seven observational studies involving between 55 and 345 patients that addressed the question of whether HRQL is improved for any intervention for DR or DME.

### HRQL Measures

Only one generic HRQL measure has been used to assess the impact that interventions for DR have on HRQL in patients with DR. The SF-36 gathers information about the patient's perceived health and asks about eight health concepts: physical functioning (ability to perform physical activities), physical role functioning (problems with daily tasks due to physical health), bodily pain (degree of limitation due to pain), general health (personal perception of health), vitality (degree of energy—tired and worn out to full of energy), social function (ability to perform social activities), emotional role functioning (problems with daily tasks due to mental health), and mental health (overall emotional state).<sup>50</sup> Generic HRQL tools are generally insensitive to the presence of specific eye disease. Furthermore, the SF-36 appears to be unresponsive to changes in visual acuity in patients with DR.<sup>49</sup> The authors suggest that this may be because the SF-36 assesses a wide range of characteristics that are not directly related to visual acuity. Other generic measures that include assessment of vision function (e.g., the Health Utilities Index<sup>76</sup>) may be a reasonable choice for researchers to consider if a generic health status measure is needed. Generic HRQL tools can be used to make comparisons with the general population (regardless of the underlying condition), estimate the relative impact of various medical conditions, and derive a utility value summarizing health status for cost-effectiveness modeling.<sup>20,23,49</sup> The decision to use a generic measure along with a specific measure needs to be driven by the purpose of the measurement.<sup>35</sup>

Two validated and clinically responsive vision-specific measures, the VFQ-25 and VF-14, have been used to measure the impact of different interventions on HRQL in individuals with DR. Vision-specific measures have been shown to be sensitive to differences in vision status and functioning among patients with DR.<sup>50,63,64,66</sup>

The diabetes-specific tool, the DTSQ, was specifically developed to measure satisfaction with treatment regimens in individuals with diabetes. Research has shown that satisfaction with treatment is associated with compliance with treatment.<sup>77,78</sup> The DTSQ was not designed to measure satisfaction with other aspects of the diabetes care and management.<sup>67</sup> It is most useful when used as one of a profile of tools to assess other important outcomes, including quality of life (QOL) or HRQL.

We identified two disease-specific measures developed specifically for patients with DR—the Diabetic Retinopathy Dependent Quality of Life (RetDQoL) and the Diabetic Retinopathy Treatment Satisfaction Questionnaire (RetTSQ). The tools have been developed in parallel, and to date, are the only measures that assess the impact of DR on different aspects of QOL. Unlike other tools identified in this review, the RetDQoL and RetTSQ have been designed to enable patients to consider specifically the impact of diabetic eye problems and their treatment, rather



than health generally, vision or vision loss, or impact of diabetes.<sup>18</sup> Preliminary psychometric testing appears promising for content validity and reliability. Additional testing is ongoing to assess responsiveness and interpretability.

Despite the availability of reliable and valid tools to measure HRQL,<sup>20,28,35</sup> our review identified several studies that used questions or tools whose psychometric properties had not been evaluated. In order to provide meaningful HRQL data, it is crucial that the measurement tools are reliable, valid, and responsive (i.e., sensitive to change). In this way, researchers, clinicians, and patients will be better able to assess and interpret the impact of different interventions for DR on HRQL outcomes.

## **Impact of interventions on HRQL**

To date, two RCTs have reported HRQL outcomes.<sup>42,47</sup> More are expected as a search of Clinicaltrials.gov identified 13 ongoing or recently completed trials investigating interventions for DME or DR that indicate the intention to report HRQL outcomes. The PKC-DRS2 trial of once-daily ruboxistaurin versus placebo measured HRQL using the SF-36 and the VFQ-25;<sup>75</sup> however, results for the HRQL outcomes have not been reported. Furthermore preliminary results from the RISE and RIDE trials<sup>79</sup> comparing ranibizumab versus sham have been presented at national meetings; however, to date, the final results for HRQL have not been published.

In general, it appears that HRQL outcomes improve following various interventions to treat DR at different levels of severity. For anti-VEGF to treat patients with DME, two RCTs with unclear risk of bias found statistically significant improvements in some domains of the VFQ-25; however, the results were not consistent at 1 year post-treatment. We concluded that the strength of evidence was low.

For other interventions, the results are based on one or two observational studies with a high risk of bias. Therefore, we conclude that the strength of evidence is insufficient to draw any conclusions about which of these interventions for DR are effective in improving HRQL. Furthermore, there is a concern about the applicability of the results of the observational studies to patients in North America. All of these studies were conducted in Europe or Japan. In particular, the three studies that were based in Japan used the Japanese version of the VFQ-25.

This review shows that the impact of interventions for DR on HRQL has not been adequately assessed in the current literature. Research has increasingly highlighted HRQL as an important health outcome in diabetes.<sup>35</sup> Diabetic patients with retinopathy have reported that vision loss impacts multiple areas of well-being including: independence, mobility, leisure, and self-care.<sup>7,17,18</sup> However, the impact is due not only to impaired vision, but also the emotional reaction to diagnosis and treatment, anxiety about the future, and advice to restrict physical activities.<sup>18</sup> For researchers and clinicians conducting trials of interventions for DR, the inclusion of HRQL outcomes will provide a better understanding how DR and its treatment affects outcomes that are important to patients.

## **Recommendations for Future Research**

- RCTs are needed to assess the effectiveness of interventions for DR, including DME to improve HRQL. All RCTs investigating the effectiveness of interventions for DR should measure and report pre- and post-treatment HRQL outcomes.

- Currently, there are a number of ongoing or recently completed trials that reported the intention to capture HRQL outcomes. Future systematic reviews should followup on these studies and incorporate their findings, if appropriate.
- Researchers should use valid and reliable HRQL tools whose psychometric properties have been evaluated and reported.
- Ongoing assessment of psychometric properties of the DR specific tools is encouraged.
- Patients should be followed for at least 6 months post-intervention in order to capture maximum improvement for visual acuity.
- Use standard protocols to assess visual acuity to allow for comparison across trials
- RCTs should be designed and conducted to minimize risk of bias where at all possible. Authors may find tools such as the CONSORT<sup>18,80</sup> statement helpful in designing and reporting on RCTs.

## Conclusions

We identified four HRQL measurement instruments that have been used to assess the impact of treatment in patients with DR. The psychometric properties of these tools have been adequately evaluated. Two tools developed specifically for patients with DR are currently undergoing evaluation. In general, HRQL was improved following interventions for DR and DME. Further research on HRQL following anti-VEGF treatment for DME is needed to confirm the results of two RCTs. The current research on the impact of other interventions for DR on HRQL is insufficient to draw conclusions about the relative effect of one intervention versus another. RCTs that assess the impact of treatments for DR should include HRQL as an outcome.

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## Abbreviations and Acronyms

95% CI	95% confidence intervals
ADVS	Activities of Daily Vision Scale
BVCA	best corrected visual acuity
CONSORT	Consolidated Standards of Reporting Trials
COSMIN	COnsensus-based Standards for the selection of health Measurement Instruments
DME	diabetic macular edema
DR	diabetic retinopathy
DTSQ	Diabetic Treatment Satisfaction Questionnaire
dx	diagnosis
ETDRS	Early Treatment of Diabetic Retinopathy Study
HRQL	health-related quality of life
ICC	interclass correlation coefficient
logMAR	logarithm of minimal angle of resolution
MCS	mental component summary
MD	mean differences
mo	month
MOS	Medical Outcomes Study
NOS	Newcastle-Ottawa Scale
NPDR	nonproliferative diabetic retinopathy
NRCT	nonrandomized controlled trial
PCS	physical component summary
PDR	proliferative diabetic retinopathy
PRO	patient reported outcomes
Pt	patient
QOL	quality of life
RCT	randomized controlled trial
RetTSQ	Diabetic Retinopathy Treatment Satisfaction Questionnaire
RetDQoL	Diabetic Retinopathy Dependent Quality of Life
SES	socioeconomic status
SF-36	Short-Form Health Survey 36
SIP	Sickness Impact Profile
tx	treatment
UK	United Kingdom
US	United States
VA	visual acuity
VF	visual function
VF-14	Visual Function-14
VFQ-25	National Eye Institute Visual Function Questionnaire-25
yr	year



## **Appendices**

Appendix A. Search strategies

Appendix B. Inclusion/exclusion form

Appendix C. List of excluded studies

Appendix D. Summary table of included HRQL assessment tools

Appendix E. Sample HRQL assessment tools

Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL

## Appendix A. Search Strategies

### Database: Ovid MEDLINE® <1950 to July 2010>

Search Strategy:

- 
- 1 exp diabetes mellitus/
  - 2 exp hyperinsulinism/
  - 3 exp hypoglycemia/
  - 4 exp hyperglycemia/
  - 5 exp glycosuria/
  - 6 diabet\$.tw
  - 7 mellitus.tw
  - 8 ((non insulin adj depend\$ adj3 diabetes mellitus) OR (noninsulin\$ adj depend\$ adj3 diabetes mellitus)).tw.
  - 9 ((insulin adj depend\$ adj3 diabetes mellitus) OR (insulindepend\$ adj3 diabetes mellitus)).tw.
  - 10 ((type 1 OR type I) adj2 (diabetes mellitus OR DM)).tw
  - 11 ((type 2 OR type II) adj2 (diabetes mellitus OR DM)).tw
  - 12 (T1DM OR T2DM OR ((T1 OR T2) adj DM)).tw
  - 13 ((maturity OR late) adj onset adj diabet\$).tw
  - 14 IDDM.tw
  - 15 NIDDM.tw
  - 16 MODY.tw
  - 17 DM.tw
  - 18 OR/1-17 (392,571)
  - 19 exp vision disORders/
  - 20 exp diabetic retinopathy/
  - 21 exp retinal detachment/
  - 22 exp retinal degeneration/
  - 23 exp retinal hemORrhage/
  - 24 exp retinal neovascularization/
  - 25 exp retinal vein occlusion/
  - 26 exp epiretinal membrane/
  - 27 exp vitreORetinopathy, proliferative/
  - 28 exp vitreous detachment/
  - 29 exp vitreous hemORrhage/
  - 30 exp macular edema/
  - 31 (eye disease\$ OR blindness OR visual loss\$).tw
  - 32 (vis\$ adj funct\$).tw
  - 33 (retinopath\$ OR retinitis OR maculopath\$).tw
  - 34 (diabet\$ adj3 maculopath\$).tw
  - 35 macula\$ adj \$edema.tw
  - 36 macula\$ adj (defect\$ OR degenerat\$ OR swell\$).tw
  - 37 microaneurysm\$.tw
  - 38 neovascular\$.tw
  - 39 OR/19-38 (142,484)
  - 40 18 AND 39 (23,376)
  - 41 exp "quality of life"/
  - 42 exp quality-adjusted life years/
  - 43 exp health status/
  - 44 exp health status indicatORs/
  - 45 exp "value of life"/
  - 46 exp self concept/
  - 47 exp "activities of daily living"/
  - 48 exp "severity of illness index"/
  - 49 exp sickness impact profile/

50 exp patient satisfaction/  
51 exp questionnaires/  
52 "quality of life".tw  
53 "health related quality of life".tw  
54 (health adj status).tw  
55 (QoL OR QL).tw  
56 QALY.tw  
57 HRQL.tw  
58 (life adj3 qualit\$).tw  
59 (funct\$ adj (assess\$ OR abilit\$)).tw  
60 "patient repORted outcomes".tw  
61 ADL\$.tw  
62 OR/41-61 (607,847)  
63 SF?36.tw  
64 SF?12.tw  
65 EuroQol.tw  
66 "Quality of Well-Being".tw  
67 "National Eye Institute Visual Functioning Questionnaire".tw  
68 "Visual Function Index".tw  
69 "Activities of Daily Vision".tw  
70 "Daily Living Tasks Dependent on Vision".tw  
71 "sickness impact profile".tw  
72 RAND?36.tw  
73 RAND?12.tw  
74 "health utilities index".tw  
75 "quality of well-being scale".tw  
76 "standard gamble".tw  
77 "time-trade off".tw  
78 WHO-BREF.tw  
79 "diabetes health profile".tw  
80 "diabetes quality of life".tw  
81 "diabetes quality of life clinical trial questionnaire".tw  
82 "well-being questionnaire".tw  
83 OR 63-82 (4,196)  
84 exp depression/  
85 exp anxiety/  
86 exp anxiety disORDers/  
87 exp mental disORDers/  
88 exp mental health/  
89 exp mental fatigue/  
90 exp stress, psychological/  
91 exp social behaviOR/  
92 "life stress".tw  
93 anxiet\*.tw  
94 depress\*.tw  
95 nervous\*.tw  
96 (coping adj2 strateg\*).tw  
97 psychosocial\*.tw  
98 psychological\*.tw  
99 (mental adj health).tw  
100 (social adj2 (skill\* OR behavi?OR)).tw  
101 OR/84-100 (1,352,438)  
102 62 OR 83 OR 101 (1,789,878)  
103 40 AND 102 (1,731)

## Database: Ovid EMBASE® <1980 to July 2010>

Search Strategy:

- 1 exp diabetes mellitus/
- 2 exp hyperinsulinism/
- 3 exp hypoglycemia/
- 4 exp hyperglycemia/
- 5 exp glycosuria/
- 6 diabet\$.tw
- 7 mellitus.tw
- 8 ((non insulin adj depend\$ adj diabetes mellitus) OR (noninsulin\$ adj depend\$ adj diabetes mellitus)).tw.
- 9 (insulin adj depend\$ adj diabetes mellitus).tw.
- 10 ((type 1 OR type I) adj (diabetes mellitus OR DM)).tw
- 11 ((type 2 OR type II) adj (diabetes mellitus OR DM)).tw
- 12 (T1DM OR T2DM OR ((T1 OR T2) adj DM)).tw
- 13 ((maturity OR late) adj onset adj diabet\$).tw
- 14 IDDM.tw
- 15 NIDDM.tw
- 16 MODY.tw
- 17 DM.tw
- 18 OR/1-17 (508,740)
- 19 exp visual disORder/
- 20 exp diabetic retinopathy/
- 21 exp retina detachment/
- 22 exp retina degeneration/
- 23 exp retina hemORrhage/
- 24 exp retinal neovascularization/
- 25 exp retinal vein occlusion/
- 26 exp vitreORetinopathy
- 27 exp vitreous body detachment/
- 28 exp vitreous hemORrhage/
- 29 (eye disease\$ OR blindness OR visual loss\$).tw
- 30 (vis\$ adj funct\$).tw
- 31 (retinopath\$ OR retinitis OR maculopath\$).tw
- 32 macula\$ adj \$edema.tw
- 33 macula\$ adj (defect\$ OR degenerat\$ OR swell\$).tw
- 34 microaneurysm\$.tw
- 35 neovascular\$.tw
- 36 OR/19-35 (270,247)
- 37 18 AND 36 (33,026)
- 38 exp "quality of life"/
- 39 exp quality adjusted life year/
- 40 exp health status/
- 41 exp health survey/
- 42 exp self concept/
- 43 exp daily life activity/
- 44 exp Sickness Impact Profile/
- 45 exp patient satisfaction/
- 46 exp questionnaire/
- 47 "quality of life".tw
- 48 "health related quality of life".tw
- 49 (health adj status).tw
- 50 (QoL OR QL).tw
- 51 QALY.tw
- 52 HRQL.tw

53 (life adj3 qualit\$).tw  
54 (funct\$ adj (assess\$ OR abilit\$)).tw  
55 "patient repORted outcomes".tw  
56 ADL\$.tw  
57 health status indicatOR\$.tw  
58 value of life.tw  
59 act\$ of daily living.tw  
60 (severity adj3 (illness index OR disease index)).tw  
61 OR/38-60 (465,498)  
62 exp ShORt FORm36/  
63 exp ShORt FORm12.tw  
64 exp National Eye Institute Visual Functioning Questionnaire/  
65 EuroQol.tw  
66 quality of well-being.tw  
67 visual function index.tw  
68 activities of daily vision.tw  
69 daily living tasks dependent on vision.tw  
70 RAND-36.tw  
71 RAND-12.tw  
72 health utilities index.tw  
73 quality of well-being scale.tw  
74 standard gamble.tw  
75 time-trade off.tw  
76 WHO-BREF.tw  
77 diabetes health profile.tw  
78 diabetes quality of life.tw  
79 diabetes quality of life clinical trial questionnaire.tw  
80 well-being questionnaire.tw  
81 OR/62-80 (9,399)  
82 exp depression/  
83 exp anxiety/  
84 exp anxiety disORders/  
85 exp mental health/  
86 exp life stress/  
87 exp coping behaviOR/  
88 depress\$.tw  
89 anxiety\$.tw  
90 nervous\$.tw  
91 (coping adj2 strateg\$).tw  
92 psychosocial\$.tw  
93 psychological\$.tw  
94 (mental adj health).tw  
95 (social adj2 (skill\$ OR behavi?OR)).tw  
96 OR/82-95 (793,003)  
97 61 OR 81 OR 96 (1,396,857)  
98 37 AND 97 (2,979)

## Database: Ovid PsychINFO <1806 to July 2010>

Search Strategy:

- 
- 1 exp diabetes mellitus/
  - 2 exp hypoglycemia/
  - 3 exp hyperglycemia/
  - 4 diabet\$.tw
  - 5 mellitus.tw
  - 6 ((non insulin adj depend\$ adj3 diabetes mellitus) OR (noninsulin\$ adj depend\$ adj3 diabetes mellitus)).tw.
  - 7 (insulin adj depend\$ adj3 diabetes mellitus).tw.
  - 8 ((type 1 OR type I) adj2 (diabetes mellitus OR DM)).tw
  - 9 ((type 2 OR type II) adj2 (diabetes mellitus OR DM)).tw
  - 10 (T1DM OR T2DM OR ((T1 OR T2) adj DM)).tw
  - 11 ((maturity OR late) adj onset adj diabet\$).tw
  - 12 IDDM.tw
  - 13 NIDDM.tw
  - 14 MODY.tw
  - 15 DM.tw
  - 16 hyperinsulinism.tw
  - 17 glycosuria.tw
  - 18 OR/1-17 (13,235)
  - 19 exp vision disORders/
  - 20 (eye disease\$ OR blindness OR visual loss\$).tw
  - 21 (vis\$ adj funct\$).tw
  - 22 (retinopath\$ OR retinitis OR maculopath\$).tw
  - 23 (diabet\$ adj3 maculopath\$).tw
  - 24 macula\$ adj \$edema.tw
  - 25 macula\$ adj (defect\$ OR degenerat\$ OR swell\$).tw
  - 26 microaneurysm\$.tw
  - 27 neovascular\$.tw
  - 28 (diabet\$ adj3 retinopath\$).tw
  - 29 (retina\$ adj3 detach\$).tw
  - 30 (retina\$ adj3 degenerat\$).tw
  - 31 (retina\$ adj3 h\$emORrhage).tw
  - 32 (retina\$ adj3 neovasculari\*ation).tw
  - 33 (retina\$ adj3 vein occlusion).tw
  - 34 epiretinal membrane.tw
  - 35 vitreORetinopathy.tw
  - 36 (vitreous adj3 (detach\$ OR h?emORrhage)).tw
  - 37 OR/19-36 (17,045)
  - 38 18 AND 37 (323)
  - 39 exp "quality of life"/
  - 40 exp life satisfaction/
  - 41 exp self concept/
  - 42 exp "activities of daily living"/
  - 43 exp client satisfaction/
  - 44 exp questionnaires/
  - 45 "quality of life".tw
  - 46 "health related quality of life".tw
  - 47 (health adj status).tw
  - 48 (QoL OR QL).tw
  - 49 QALY.tw
  - 50 HRQL.tw
  - 51 (life adj3 qualit\$).tw

52 (funct\$ adj (assess\$ OR abilit\$)).tw  
53 "patient repORted outcomes".tw  
54 ADL\$.tw  
55 (health adj3 (status OR status indicatOR\$)).tw  
56 value of life.tw  
57 (severity adj3 (illness index OR disease index)).tw  
58 sickness impact profile.tw  
59 OR/39-58 (116,240)  
60 SF-36.tw  
61 SF-12.tw  
62 EuroQol.tw  
63 Quality of Well-Being.tw  
64 National Eye Institute Visual Functioning Questionnaire.tw  
65 Visual Function Index.tw  
66 Daily Living Tasks Dependent on Vision.tw  
67 RAND-36.tw  
68 RAND-12.tw  
69 health utilities index.tw  
70 quality of well-being scale.tw  
71 standard gamble.tw  
72 time-trade off.tw  
73 WHO-BREF.tw  
74 diabetes health profile.tw  
75 diabetes quality of life.tw  
76 diabetes quality of life clinical trial questionnaire.tw  
77 well-being questionnaire.tw  
78 OR 60-77 (3,135)  
79 59 OR 78 (116,961)  
80 exp majOR depression/  
81 exp anxiety/  
82 exp anxiety disORDers/  
83 exp mental health/  
84 exp mental disORDers/  
85 exp stress, psychological/  
86 exp coping behaviOR/  
87 "life stress".tw  
88 anxiet\*.tw  
89 depress\*.tw  
90 nervous\*.tw  
91 (coping adj2 strateg\*).tw  
92 psychosocial\*.tw  
93 psychological\*.tw  
94 (mental adj health).tw  
95 (social adj2 (skill\* OR behavi?OR)).tw  
96 OR/80-95 (795,694)  
97 79 OR 96 (866,765)  
98 38 AND 97 (113)

## Database: Ovid Cochrane Central Register of Control Trials <1991 to July 2010>

Search Strategy:

- 1 exp diabetes mellitus/
- 2 exp hyperinsulinism/
- 3 exp hypoglycemia/
- 4 exp hyperglycemia/
- 5 exp glycosuria/
- 6 diabet\$.tw
- 7 mellitus.tw
- 8 ((non insulin adj depend\$ adj3 diabetes mellitus) OR (noninsulin\$ adj depend\$ adj3 diabetes mellitus)).tw.
- 9 (insulin adj depend\$ adj3 diabetes mellitus).tw.
- 10 ((type 1 OR type I) adj2 (diabetes mellitus OR DM)).tw
- 11 ((type 2 OR type II) adj2 (diabetes mellitus OR DM)).tw
- 12 (T1DM OR T2DM OR ((T1 OR T2) adj DM)).tw
- 13 ((maturity OR late) adj onset adj diabet\$.tw
- 14 IDDM.tw
- 15 NIDDM.tw
- 16 MODY.tw
- 17 DM.tw
- 18 OR/1-17 (21,104)
- 19 exp vision disORders/
- 20 exp diabetic retinopathy/
- 21 exp retinal detachment/
- 22 exp retinal degeneration/
- 23 exp retinal hemORrhage/
- 24 exp retinal neovascularization/
- 25 exp retinal vein occlusion/
- 26 exp epiretinal membrane/
- 27 exp vitreORetinopathy, proliferative/
- 28 exp vitreous detachment/
- 29 exp vitreous hemORrhage/
- 30 exp macular edema/
- 31 (eye disease\$ OR blindness OR visual loss\$).tw
- 32 (vis\$ adj funct\$).tw
- 33 (retinopath\$ OR retinitis OR maculopath\$).tw
- 34 (diabet\$ adj3 maculopath\$).tw
- 35 macula\$ adj \$edema.tw
- 36 macula\$ adj (defect\$ OR degenerat\$ OR swell\$).tw
- 37 microaneurysm\$.tw
- 38 neovascular\$.tw
- 39 OR/19-38 (4,902)
- 40 18 AND 39 (1,377)
- 41 exp "quality of life"/
- 42 exp quality-adjusted life years/
- 43 exp health status/
- 44 exp health status indicatORs/
- 45 exp "value of life"/
- 46 exp self concept/
- 47 exp "activities of daily living"/
- 48 exp "severity of illness index"/
- 49 exp sickness impact profile/
- 50 exp patient satisfaction/



51 exp questionnaires/  
52 "quality of life".tw  
53 "health related quality of life".tw  
54 (health adj status).tw  
55 (QoL OR QL).tw  
56 QALY.tw  
57 HRQL.tw  
58 (funct\$ adj (assess\$ OR abilit\$)).tw  
59 "patient repORted outcomes".tw  
60 ADL\$.tw  
61 OR/41-61 (44,357)  
62 SF-36.tw  
63 SF-12.tw  
64 EuroQol.tw  
65 "Quality of Well-Being".tw  
66 "National Eye Institute Visual Functioning Questionnaire".tw  
67 "Visual Function Index".tw  
68 "Activities of Daily Vision".tw  
69 Daily Living Tasks Dependent on Vision.tw  
70 sickness impact profile.tw  
71 RAND-36.tw  
72 health utilities index.tw  
73 quality of well-being scale.tw  
74 standard gamble.tw  
75 time-trade off.tw  
76 WHO-BREF.tw  
77 diabetes health profile.tw  
78 diabetes quality of life.tw  
79 diabetes quality of life clinical trial questionnaire.tw  
80 well-being questionnaire.tw  
81 OR/62-80 (2,457)  
82 62 OR 81 (44,449)  
83 exp depression/  
84 exp anxiety/  
85 exp anxiety disORders/  
86 exp mental disORders/  
87 exp mental health/  
88 exp mental fatigue/  
89 exp stress, psychological/  
90 exp social behaviOR/  
91 "life stress".tw  
92 anxiet\*.tw  
93 depress\*.tw  
94 nervous\*.tw  
95 (coping adj2 strateg\*).tw  
96 psychosocial\*.tw  
97 psychological\*.tw  
98 (mental adj health).tw  
99 (social adj2 (skill\* OR behavi?OR)).tw  
100 OR/93-99 (64,320)  
101 82 OR 100 (96,404)  
102 40 AND 101 (71)

## Database: CINAHL Plus with full text <1937 to July 2010>

Search Strategy:

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S108=S46 AND S107 (1,651)  
S107=S67 OR S88 OR S106 (593,052)  
S106=S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101  
OR S102 OR S103 OR S104 OR S105 (552,364)  
S105=TX coping N2 strateg\*  
S104=TX social N2 behavi#OR  
S103=TX social N2 skill\*  
S102=TX mental N1 health  
S101=TX psychological\*  
S100=TX psychosocial\*  
S99=TX nervous\*  
S98=TX depress\*  
S97=TX anxiet\*  
S96=TX "life stress"  
S95=TX "life stress"  
S94=MH "Social BehaviOR+"  
S93=MH "Stress, Psychological+"  
S92=MH "Mental Health"  
S91=MH "Mental DisORders+"  
S90=MH "Anxiety DisORders+"  
S89=MH "Anxiety+"  
S88=S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR  
S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 (33,010)  
S87=TX "well-being questionnaire"  
S86=TX "diabetes quality of life clinical trial questionnaire"  
S85=TX "diabetes quality of life"  
S84=TX "diabetes health profile"  
S83=TX WHO-BREF  
S82=TX "time-trade off"  
S81=TX "standard gamble"  
S80=TX "quality of well-being scale"  
S79=TX "health utilities index"  
S78=TX RAND#12  
S77=TX RAND#36  
S76=TX "sickness impact profile"  
S75= TX "activities of daily vision"  
S74= TX "visual function index"  
S73=TX "national eye institute visual functioning questionnaire"  
S72=TX "quality of well-being"  
S71=TX EuroQoL  
S70=TX sf#12  
S69=TX sf#36  
S68=MH "Severity of Illness Indices+"  
S67=S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR  
S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 (310,508)  
S66=TX ADL\*  
S65=TX "patient reported outcomes"  
S64=TX (funct\* N1 assess\*) OR (funct\* abilit\*)  
S63=TX life N3 qualit\*  
S62=TX HRQL

S61=TX QALY  
 S60=TX QoL  
 S59=TX (health N1 status)  
 S58=TX "health related quality of life"  
 S57=TX "quality of life"  
 S56=MH "Questionnaires+"  
 S55=MH "Patient Satisfaction"  
 S54=MH "Sickness Impact Profile"  
 S53=MH "Severity of Illness"  
 S52=MH "Activities of Daily Living+"  
 S51=MH "Self Concept+"  
 S50=MH "Health Status Indicators"  
 S49=MH "Health Status+"  
 S48=MH "Quality-Adjusted Life Years"  
 S47=MH "Quality of Life+"  
 S46=S21 AND S45 (4,823)  
 S45=S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR  
 S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 (19,362)  
 S44=TX vitreous h#emORrhage  
 S43=TX vitreous detach\*  
 S42=TX vitreORetinopathy  
 S41=TX epiretinal membrane  
 S40=TX retina\* N1 neovasculari?ation  
 S39=TX retina\* N1 vein occlusion  
 S38=TX retina\* N1 detach\*  
 S37=TX retina\* N1 degenerat\*  
 S36=TX microaneurysm\*  
 S35=TX neovascular\*  
 S34=TX macula\* N1 swell\*  
 S33=TX macula\* N1 degenerat\*  
 S32=TX macula\* N1 defect\*  
 S31=TX macula\* N1 #edema  
 S30=TX (diabet\* N3 maculopath\*)  
 S29=TX (retinopath\* OR blindness OR visual loss\*)  
 S28=TX (vis\* N1 funct\*)  
 S27=TX (eye disease\* OR blindness OR visual loss\*)  
 S26=MH "Retinal Diseases+"  
 S25=MH "Eye HemORrhage"  
 S24=MH "Retinal Detachment"  
 S23=MH "Diabetic Retinopathy"  
 S22=MH "Vision DisORders+"  
 S21=S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR  
 S15 OR S16 OR S17 OR S18 OR S19 OR S20 (161,039)  
 S20=TX DM  
 S19=TX MODY  
 S18=TX NIDDM  
 S17=TX IDDM  
 S16=TX ((maturity onset N2 diabet\*) OR (late onset N2 diabet\*))  
 S15=TX (T1 N1 DM) OR (T2 N1 DM)  
 S14=TX (T1DM OR T2DM)  
 S13=TX (type II N2 diabetes mellitus) OR (type II N2 DM)  
 S12=TX (type 2 N2 diabetes mellitus) OR (type 2 N2 DM)  
 S11=TX (type I N2 diabetes mellitus) OR (type I N2 DM)  
 S10=TX ((type 1 N2 diabetes mellitus) OR (type 1 N2 DM))  
 S9=TX (insulin N1 depend\* N3 diabetes mellitus)  
 S8=TX ((non insulin N1 depend\* N3 diabetes mellitus) OR (noninsulin\* N1 depend\* N3 diabetes mellitus))

S7=TX mellitus  
S6=TX diabet\*  
S5=TX glycosuria  
S4=MH Hypoglycemia+  
S3=MH Hyperglycemia+  
S2=MH Hyperinsulinism+  
S1=MH Diabetes Mellitus+

## Database: Scopus <1823 to July 2010>

Search Strategy:

((TITLE-ABS-KEY("diabetes PRE/1 mellitus") OR (diabet\*) OR (mellitus)) AND (TITLE-ABS-KEY("diabetic PRE/1 retinopath\*") OR (blindness) OR ("visual PRE/1 loss\*") OR ("vis\* PRE/1 funct\*") OR (retinopath\*) OR (retinitis) OR (maculopath\*) OR ("macula\* PRE/1 defect\*") OR ("macula\* PRE/1 degenerat\*") OR ("macula\* PRE/1 swell\*")) AND ((TITLE-ABS-KEY("quality PRE/1 life") OR ("health PRE/1 status") OR ("value PRE/1 life") OR ("self PRE/1 concept") OR ("activities PRE/1 daily living") OR ("sickness impact profile") OR ("patient PRE/1 satisfaction") OR ("patient PRE/1 repORted outcome\*")) OR (TITLE-ABS-KEY(depression) OR (anxiety) OR ("anxiety PRE/1 disORder\*") OR ("mental PRE/1 disORder\*") OR ("mental PRE/1 health") OR ("mental PRE/1 fatigue") OR ("coping PRE/1 strateg\*")))) (1,244)

## Database: Clinicaltrials.gov, Results <April 2011>

NCT Number	Title	Study Condition	Intervention	HRQL measure
NCT01131585	Safety and efficacy of ranibizumab in diabetic macular edema	Diabetic macular edema; proliferative diabetic retinopathy	Ranibizumab + laser; sham injections + laser	Unspecified QOL
NCT00701181	Prospective, randomized, multi-center, comparator study evaluating efficacy and safety of PF-04523655 versus laser in subjects with diabetic macular edema	Diabetic retinopathy; diabetes complications	Laser treatment; PF-04523655 (high dose); PF-04523655 (middle dose); PF-04523655 (low dose)	VFQ-25
NCT00090519	Reduction in the occurrence of center-involved diabetic macular edema	Diabetic retinopathy	Ruboxistaurin; placebo	VFQ-25
NCT00799227	Safety and efficacy of a new treatment in vitrectomized subjects with diabetic macular edema	Diabetic macular edema	Dexamethasone	VFQ-25
NCT00464685	Safety and efficacy of a new treatment in combination with laser for diabetic macular edema	Diabetic macular edema	Dexamethasone; sham injection	Unspecified QOL
NCT00168389	A study of the safety and efficacy of a new treatment for diabetic macular edema	Diabetic macular edema	Dexamethasone; sham dexamethasone	Unspecified QOL
NCT01171976	Efficacy and safety of Ranibizumab in two "treat and extend" treatment algorithms versus Ranibizumab as needed in patients with	Diabetic macular edema	Ranibizumab	VFQ-25

	macular edema and visual impairment secondary to diabetes mellitus (RETAIN)			
NCT00473382	A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RIDE)	Diabetes mellitus macular edema	Ranibizumab; sham	VFQ-25
NCT00473330	A study of ranibizumab injection in subjects with clinically significant macular edema with center involvement secondary to diabetes mellitus (RISE)	Diabetes mellitus macular edema	Ranibizumab; sham	VFQ-25
NCT00989989	Efficacy and Safety of Ranibizumab (Intravitreal Injections) in Patients With Visual Impairment Due to Diabetic Macular Edema	Diabetic macular edema	Ranibizumab; Laser photocoagulation	Unspecified PROs
NCT01292798	Treatment of Residual Diabetic Macular Edema With Ranibizumab	Diabetic macular edema	Ranibizumab	Participant scores on unspecified work productivity and activity impairment questionnaire
NCT01318941	Observe the effectiveness and safety of Ranibizumab in real life setting	Wet age-related macular degeneration, diabetic macular edema, retinal vein occlusion	Ranibizumab	VFQ-25
NCT01331681	VEGF Trap-Eye in vision impairment due to diabetic macular edema (DME)	Diabetes mellitus; macular edema	VEGF Trap-Eye (BAY86-5321); VEGF Trap-Eye (BAY86-5321); Laser treatment	Unspecified QOL

## Appendix B. Inclusion/Exclusion Form

Reviewer ID	Ref ID
<b>Criteria</b>	<b>Decision</b>
1. <b>Report of Primary Research</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
2. <b>Population:</b> Adults ( $\geq 18$ years)	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
3. <b>Population:</b> Diagnosed with diabetic retinopathy or diabetic macular edema or neovascular	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
4a. <b>Measurement:</b> Does the study report on the use of a patient-reported HRQL measure (physical, social, emotional, mental function)?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
4b. <b>Measurement:</b> Does the study report on the use of a patient-reported HRQL measure (physical, social, emotional, mental function) in the context of assessing an intervention (with or without a comparator) for DR?	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
<b>Reviewer Decision</b>	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unsure
<b>CONSENSUS DECISION</b>	<input type="checkbox"/> INCLUDE <input type="checkbox"/> EXCLUDE
*Flag studies that do not investigate an intervention for DR, but do provide the psychometric properties of a HRQL tool.	
<input type="checkbox"/> Abstract requiring full publication	
<input type="checkbox"/> Requires translation	Specify source language

## Appendix C. Excluded Studies

482 studies were excluded from the review. Reasons for exclusion include: publication type (n=78), age being less than 18 years (n=3), diagnosis without DR (n=117), intervention (n=99), outcomes (n=185).

### Publication type (n = 78)

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### Age <18 yr (n = 3)

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## Outcome (n = 185)

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## Appendix D. Characteristics of the health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy

Instrument	Administration	Domains Measured	Items/ Response Options	Scoring
<b>Generic HRQL assessment tools</b>				
<b>Short Form-36 (SF-36)<sup>56</sup></b>  <b>Primary author:</b> Ware, JE  <b>Date of 1<sup>st</sup> publication:</b> 1992  <b>Alternate versions:</b> SF-36v2 (2000)  <b>Related instruments:</b> SF-12; SF-18; SF-20;	<b>Target population:</b> general pt population, aged >14 yr  <b>Mode of administration:</b> self-complete questionnaire (paper or electronic), interview, etc.  <b>Time needed to complete:</b> 5–10 minutes	Physical functioning (10 items); Role limitations because of physical health problems (4 items); Bodily pain (2 items); Social functioning (2 items); General mental health (5 items); Role limitations because of emotional problems (3 items); Vitality (4 items); General health perceptions (5 items); Health transition (1 item)	<b>Items:</b> 8 items (excluding health transition); 8 scales that include 2–10 questions each; 2 summary measures, the Physical Composite Score, and the Mental Composite Score, aggregate the scales  <b>Response options:</b> Items 1–3, 6–11: answered on rating scales; Item 1/2: excellent/much better to poor/much worse (5 options); Item 3: limited a lot, to not limited at all (3 options); Items 4/5: answered with a yes/no Item 6/8: not at all to extremely (5 options); Item 7: none to very severe (6 options); Item 9: all of the time to none of the time (6 options); Item 10: all of the time to none of the time (5 options); Item 11: definitely true to definitely false (5 options)	<b>Scoring:</b> each item is assigned a score on the rating scale by the pt  <b>Final score algorithm:</b> items and scales were constructed for scoring using the Likert method of summated ratings  <b>Possible range:</b> all scales are linearly transformed to a score between 0 (least favorable) to 100 (most favorable)

DM = diabetes mellitus; DR = diabetic retinopathy; d/t = due to; max = maximum; pt = patient; QoL: Quality of Life; r/t = related to; tx = treatment; yr = year

**Appendix D. Characteristics of the health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

<b>Instrument</b>	<b>Administration</b>	<b>Domains Measured</b>	<b>Items/ Response Options</b>	<b>Scoring</b>
<b>Low vision-related HRQL assessment tools</b>				
<p><b>National Eye Institute Visual Function Questionnaire-25 (VFQ-25)</b><sup>63</sup></p> <p><b>Primary author:</b> RAND Corporation</p> <p><b>Date of 1<sup>st</sup> publication:</b> 2001</p> <p><b>Alternate versions:</b> NEI-VFQ-51</p>	<p><b>Target population:</b> pt with low vision</p> <p><b>Mode of administration:</b> pt interview; self administered</p> <p><b>Time needed to complete:</b> 5 minutes</p>	<p>Overall health (1 item); Overall vision (1 item); Difficulty with near vision (3 items); Difficulty with distance vision (3 items); Limitations in social functioning d/t vision (2 items); Role limitations d/t vision (2 items); Dependency on others d/t vision (3 items); Mental health symptoms d/t vision (4 items); Driving difficulties (2–3 items depending on version); Pain and discomfort around the eyes (2 items); Peripheral vision (1 item); Color vision (1 item)</p>	<p><b>Items:</b> 25 or 26 items (versions vary between 2 and 3 questions in the driving domain) answer questions r/t 12 areas of visual function</p> <p><b>Response options:</b>  <i>Items 1–4:</i> 5 or 6-point rating scale 1 (excellent) to 5/6 (severe);  <i>Items 5–14, 16:</i> 6-point rating scale 1 (no difficulty) to 5 (stopped d/t eyesight) or 6 (stopped for reason other than eyesight);  <i>Item 15:</i> Yes/No;  <i>Item 15a and 15b:</i> multiple choice responses;  <i>Items 17–25:</i> 5-point rating scale 1 (most difficulty) to 5 (no difficulty)</p>	<p><b>Scoring:</b> each item assigned a score by the pt out of 4/5/6, according to the scale used on the specific item</p> <p><b>Final score algorithm:</b> <i>Subscales Scores:</i> an average of the items on each subscale transformed to a score on a 0 to 100 scale; <i>Composite Score:</i> an unweighted average of the responses to all items except for the general health rating question, which is treated as a stand-alone item</p> <p><b>Possible range:</b> 0 (most severe impairment) to 100 (no impairment)</p>
<p><b>Visual Function-14 (VF-14)</b><sup>66</sup></p> <p><b>Primary author:</b> Steinberg, EP</p> <p><b>Date of 1<sup>st</sup> publication:</b> 1994</p> <p><b>Alternate versions:</b> None</p>	<p><b>Target population:</b> pt treated with cataract surgery</p> <p><b>Mode of administration:</b> NR</p> <p><b>Time needed to complete:</b> NR</p>	<p>Vision dependent functional activities: e.g. reading; recognizing people; seeing steps, stairs or curbs; doing fine handwork; writing checks or filling out forms; playing games, taking part in sports, cooking, watching television; and driving</p>	<p><b>Items:</b> 18 questions cover 14 items</p> <p><b>Response options:</b> items 1–12, 2-part questions;  <i>Items 1-12:</i> Yes/No/Not Applicable; If yes, 4-point rating scale: 1 (a little difficulty)–4 (unable to do activity);  <i>Items 13/16:</i> Yes/No;  <i>Items 14/15:</i> 4 point rating scale: 1(no difficulty)–4 (unable to do activity);  <i>Items 17/18:</i> Multiple choice responses</p>	<p><b>Scoring:</b> each item is assigned a score out of 4; Score of 0 assigned when pt unable to do activity d/t visual impairment; If pt did not do activity for a reason other than vision, item not included in scoring; No min number of applicable activities required</p> <p><b>Final score algorithm:</b> scores from all items pt performed or did not perform d/t their vision were averaged, resulting in a score between 0 and 4; Average score multiplied by 25</p> <p><b>Possible range:</b> 0 (most severe impairment) to 100 (no impairment)</p>

**Appendix D. Characteristics of the health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

<b>Instrument</b>	<b>Administration</b>	<b>Domains Measured</b>	<b>Items/ Response Options</b>	<b>Scoring</b>
<i>Diabetes-related HRQL assessment tools</i>				
<b>Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs)<sup>75</sup></b>  <b>Primary author:</b> Lewis, K  <b>Date of 1<sup>st</sup> publication:</b> 1988  <b>Alternate versions:</b> DTSQc (change version)	<b>Target population:</b> pt with DM  <b>Mode of administration:</b> self-completed questionnaire  <b>Time needed to complete:</b> NR	Treatment Satisfaction (items 1, 4–8); Perceived frequency of hyperglycemia (item 2); Perceived frequency of hypoglycemia (item 3)	<b>Items:</b> 8 items  <b>Response options:</b> <i>All items:</i> 7 point rating scale: 0 (very dissatisfied/none of the time) to 6 (very satisfied/most of the time);	<b>Scoring:</b> each item assigned a score by the pt out of 6  <b>Final score algorithm:</b> items, 1, 4–8 are summed to produce an overall score; Items 2 and 3 are treated individually  <b>Possible range:</b> <i>Treatment Satisfaction:</i> 0 (most dissatisfied) to 36 (most satisfied); <i>Perceived frequency of hyperglycemia/hypoglycemia:</i> 0 (least frequent) to 6 (most frequent)

**Appendix D. Characteristics of the health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

<b>Instrument</b>	<b>Administration</b>	<b>Domains Measured</b>	<b>Items/ Response Options</b>	<b>Scoring</b>
<b>Diabetic retinopathy-related HRQL assessment tools</b>				
<p><b>Retinopathy Dependent Quality of Life (RetDQoL)</b><sup>18,70</sup></p> <p><b>Primary author:</b> Woodcock, A</p> <p><b>Copyright holder:</b> Bradley, C</p> <p><b>Date of 1<sup>st</sup> publication:</b> 2004</p> <p><b>Alternate versions:</b> None</p>	<p><b>Target population:</b> pt with DR</p> <p><b>Mode of administration:</b> paper based questionnaire, written in a large font with a layout designed to facilitate reading by those with visual impairments</p> <p><b>Time needed to complete:</b> NR</p>	<p>Retinopathy-dependent quality of life: e.g. household tasks; personal affairs; shopping; feelings about the future/past; working life; close personal relationship; family life; social life; do things for others; get out and about; journeys; holidays; finances; peoples reaction to me; physical appearance, physical ability; leisure; hobbies/interests; self-confidence; motivation; dependence; mishaps/losses; time; care of diabetes; enjoy nature</p>	<p><b>Items:</b> overview questions: 1) present QoL; and 2) overall retinopathy-dependent QoL initiates questionnaire; Remaining 24 items r/t specific activities, which may be hindered by poor vision and affect QoL; Items 1-24 contained a part b, which assesses the importance of each item to the pt</p> <p><b>Response options:</b> <i>Overall QoL:</i> 7-point rating scale: -3 (extremely bad) to 3 (excellent) <i>Overall DR QoL:</i> 5-point rating scale: -3 (very much better) to 1 (worse) <i>Specific domain Items 1–24:</i> 5-point rating scale: -3 (best/easiest) to 1 (worse/more difficult) ; <i>Importance ratings:</i> very important (3), important (2), somewhat important (1), not at all important (0) <i>Open-ended question:</i> asks whether diabetic eye problems affect QoL in any way not covered by the questionnaire</p>	<p><b>Scoring:</b> <i>Weighted Impact score:</i> each specific domain is assigned an impact rating by the pt of -3 to 1 and is multiplied by the importance rating of 0 to 3, for a possible range of -9 (max negative impact) to 3 (max positive impact); Non-applicable domains are not scored</p> <p><b>Final score algorithm:</b> <i>Average Weighted Impact score:</i> calculated from a max of 23 specific domain items; Sum of weighted ratings of applicable domains divided by the number of applicable domains <i>Note:</i> the ‘work’ items has not undergone psychometric analysis and should therefore be excluded from the average weighted impact score</p> <p><b>Possible range:</b> -9 (max negative impact of DR on QoL) to 3 (max positive impact of DR on QoL)</p>

**Appendix D. Characteristics of the health-related quality of life assessment tools used in studies of the treatment of diabetic retinopathy (continued)**

<b>Instrument</b>	<b>Administration</b>	<b>Domains Measured</b>	<b>Items/ Response Options</b>	<b>Scoring</b>
<p><b>Retinopathy Treatment Satisfaction Questionnaire (RetTSQ)</b><sup>71,81</sup></p> <p><b>Primary author:</b> Woodcock, A</p> <p><b>Copyright holder:</b> Bradley, C</p> <p><b>Date of 1<sup>st</sup> publication:</b> 2005</p> <p><b>Alternate versions:</b> None</p>	<p><b>Target population</b> pt with DR</p> <p><b>Mode of administration:</b> paper based questionnaire, written in a large font with a layout designed to facilitate reading by those with visual impairments</p> <p><b>Time needed to complete:</b> NR</p>	<p>Satisfaction of treatment for diabetic retinopathy: e.g. tx satisfaction, perceived effectiveness of tx; tx side effects; discomfort or pain; unpleasantness of tx; difficulty of tx; feelings of apprehension r/t tx; feelings of satisfaction regarding influence over tx; safety of tx; time-consumed by tx; information about tx; recommend tx to someone else; willingness to continue/repeat tx</p>	<p><b>Items:</b> 13 items asking pt to rate different aspects of treatment; Items 1, 2, 8, 9, 11–13 compile the positive aspects subscale; Items 3–7 &amp; 10 compile the negative aspects subscale</p> <p><b>Response options:</b> 7-point rating scale: 0 (very dissatisfied/bothered/unpleasant/difficult/apprehensive/time-consuming) to 6 (very satisfied, not at all bothered/apprehensive/unpleasant/time consuming); <i>Open-ended question:</i> asks respondents for any further aspects of treatment which cause satisfaction or dissatisfaction</p>	<p><b>Scoring:</b> each item is assigned a score by the pt out of 6</p> <p><b>Final score algorithm:</b> <i>Positive aspects subscale:</i> calculated by summing the scores from the 7 items that make up the subscale; <i>Negative aspects subscale:</i> calculated by summing the scores from 6 items that make up the subscale <i>Total score:</i> sum of all of the 13 items that make up the RetTSQ</p> <p><b>Possible range:</b> <i>Positive aspects subscale:</i> 0 (worst) to 42 (best); <i>Negative aspects subscale:</i> 0 (worst) to 36 (best); <i>Total score:</i> 0 (worst) to 78 (best)</p>

## **Appendix E. Sample HRQL assessment tools**

### **Generic HRQL assessment tools:**

SF-36

### **Low vision-related HRQL assessment tools:**

NEI-VFQ-25

VF-14

### **Diabetes-related HRQL assessment tools:**

DTSQ

### **Diabetic retinopathy-related HRQL assessment tools:**

RetDQoL

RetTSQ

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# Your Health and Well-Being

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This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an  in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>



3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	▼	▼	▼
a <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
b <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
c Lifting or carrying groceries .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
d Climbing <u>several</u> flights of stairs .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
e Climbing <u>one</u> flight of stairs .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
f Bending, kneeling, or stooping .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
g Walking <u>more than a kilometre</u> .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
h Walking <u>several hundred metres</u> .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
i Walking <u>one hundred metres</u> .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
j Bathing or dressing yourself .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Cut down on the <u>amount of time</u> you spent on work or other activities .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b <u>Accomplished less</u> than you would like .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Were limited in the <u>kind</u> of work or other activities .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort) .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

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5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a					
Cut down on the <u>amount of time</u> you spent on work or other activities.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b					
<u>Accomplished less</u> than you would like.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c					
Did work or other activities <u>less carefully</u> than usual.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	▼	▼	▼	▼	▼
a Did you feel full of life? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b Have you been very nervous? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c Have you felt so down in the dumps that nothing could cheer you up? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d Have you felt calm and peaceful? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
e Did you have a lot of energy? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
f Have you felt downhearted and depressed? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
g Did you feel worn out? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
h Have you been happy? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
i Did you feel tired? .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
	▼	▼	▼	▼	▼	
a	I seem to get sick a little easier than other people.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
b	I am as healthy as anybody I know .....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
c	I expect my health to get worse.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5
d	My health is excellent.....	<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5

Thank you for completing these questions!

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National Eye Institute  
Visual Functioning Questionnaire - 25  
(VFQ-25)

version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

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The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

#### INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.
2. Please answer every question (unless you are asked to skip questions because they don't apply to you).
3. Answer the questions by circling the appropriate number.
4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.
5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.
6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

#### STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

# Visual Functioning Questionnaire - 25

## PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

(Circle One)

- Excellent ..... 1
- Very Good ..... 2
- Good..... 3
- Fair ..... 4
- Poor..... 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

(Circle One)

- Excellent ..... 1
- Good..... 2
- Fair ..... 3
- Poor..... 4
- Very Poor ..... 5
- Completely Blind ..... 6

3. How much of the time do you worry about your eyesight?

(Circle One)

- None of the time ..... 1
- A little of the time ..... 2
- Some of the time ..... 3
- Most of the time ..... 4
- All of the time? ..... 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

- None ..... 1
- Mild ..... 2
- Moderate ..... 3
- Severe, or ..... 4
- Very severe? ..... 5

**PART 2 - DIFFICULTY WITH ACTIVITIES**

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6



6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not  
interested in doing this ..... 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not  
interested in doing this ..... 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not  
interested in doing this ..... 6

12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants ?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

15. Are you currently driving, at least once in a while?

(Circle One)

Yes ..... 1 Skip To Q 15c

No ..... 2

15a. IF NO: Have you never driven a car or have you given up driving?

(Circle One)

Never drove ..... 1 Skip To Part 3, Q 17

Gave up..... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?

(Circle One)

Mainly eyesight ..... 1 Skip To Part 3, Q 17

Mainly other reasons ..... 2 Skip To Part 3, Q 17

Both eyesight and other reasons .... 3 Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:

(Circle One)

No difficulty at all..... 1

A little difficulty..... 2

Moderate difficulty..... 3

Extreme difficulty ..... 4

16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Have you stopped doing this because of your eyesight ..... 5
- Have you stopped doing this for other reasons or are you not interested in doing this ..... 6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Have you stopped doing this because of your eyesight ..... 5
- Have you stopped doing this for other reasons or are you not interested in doing this ..... 6

PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

READ CATEGORIES:	All of the time	Most of the time	Some of the time	A little of the time	None of the time
------------------	-----------------------	------------------------	------------------------	----------------------------	------------------------

17. <u>Do you accomplish less</u> than you would like because of your vision?	1	2	3	4	5
---	---	---	---	---	---

18. <u>Are you limited</u> in how long you can work or do other activities because of your vision? .....	1	2	3	4	5
---	---	---	---	---	---

19. How much does pain or discomfort <u>in or around</u> <u>your eyes</u> , for example, burning, itching, or aching, keep you from doing what you'd like to be doing? Would you say:	1	2	3	4	5
---	---	---	---	---	---

For each of the following statements, please circle the number to indicate whether for you the statement is definitely true, mostly true, mostly false, or definitely false for you or you are not sure.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
20. I <u>stay home most of the time</u> because of my eyesight .....	1	2	3	4	5
21. I feel <u>frustrated</u> a lot of the time because of my eyesight.....	1	2	3	4	5
22. I have <u>much less control</u> over what I do, because of my eyesight.....	1	2	3	4	5
23. Because of my eyesight, I have to <u>rely too much on</u> <u>what other people tell me</u> ...	1	2	3	4	5
24. I <u>need a lot of help</u> from others because of my eyesight.....	1	2	3	4	5
25. I worry about <u>doing things</u> <u>that will embarrass myself</u> <u>or others</u> , because of my eyesight.....	1	2	3	4	5

## Appendix of Optional Additional Questions

### SUBSCALE: GENERAL HEALTH

A1. How would you rate your overall health, on a scale where zero is as bad as death and 10 is best possible health?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

### SUBSCALE: GENERAL VISION

A2. How would you rate your eyesight now (with glasses or contact lens on, if you wear them), on a scale of from 0 to 10, where zero means the worst possible eyesight, as bad or worse than being blind, and 10 means the best possible eyesight?

(Circle One)

0	1	2	3	4	5	6	7	8	9	10
Worst										Best

### SUBSCALE: NEAR VISION

A3. Wearing glasses, how much difficulty do you have reading the small print in a telephone book, on a medicine bottle, or on legal forms?  
Would you say:

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6



A4. Because of your eyesight, how much difficulty do you have figuring out whether bills you receive are accurate?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

A5. Because of your eyesight, how much difficulty do you have doing things like shaving, styling your hair, or putting on makeup?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

SUBSCALE: DISTANCE VISION

A6. Because of your eyesight, how much difficulty do you have recognizing people you know from across a room?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

A7. Because of your eyesight, how much difficulty do you have taking part in active sports or other outdoor activities that you enjoy (like golf, bowling, jogging, or walking)?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

A8. Because of your eyesight, how much difficulty do you have seeing and enjoying programs on TV?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

**SUBSCALE: SOCIAL FUNCTION**

A9. Because of your eyesight, how much difficulty do you have entertaining friends and family in your home?

(Circle One)

- No difficulty at all ..... 1
- A little difficulty ..... 2
- Moderate difficulty ..... 3
- Extreme difficulty ..... 4
- Stopped doing this because of your eyesight ..... 5
- Stopped doing this for other reasons or not interested in doing this ..... 6

SUBSCALE: DRIVING

A10. [This item, “driving in difficult conditions”, has been included as part of the base set of 25 items as item 16a.]

SUBSCALE: ROLE LIMITATIONS

A11. The next questions are about things you may do because of your vision. For each item, please circle the number to indicate whether for you this is true for you all, most, some, a little, or none of the time.

(Circle One On Each Line)

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. <u>Do you have more help</u> from others because of your vision?.....	1	2	3	4	5
b. <u>Are you limited in the</u> kinds of things you can do because of your vision?.	1	2	3	4	5

SUBSCALES: WELL-BEING/DISTRESS (#A12) and DEPENDENCY (#A13)

The next questions are about how you deal with your vision. For each statement, please circle the number to indicate whether for you it is definitely true, mostly true, mostly false, or definitely false for you or you don't know.

(Circle One On Each Line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
A12. I am often <u>irritable</u> because of my eyesight .....	1	2	3	4	5
A13. I <u>don't go out of my home alone</u> , because of my eyesight.....	1	2	3	4	5

## Visual Function—14 Questionnaire

1. Do you have any difficulty, even with glasses, reading small print, such as labels on medicine bottles, a telephone book, food labels?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

2. Do you have any difficulty, even with glasses, reading a newspaper or a book?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

3. Do you have any difficulty, even with glasses, reading a large-print book or large-print newspaper or numbers on a telephone?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

4. Do you have difficulty, even with glasses, recognizing people when they are close to you?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

5. Do you have difficulty, even with glasses, seeing steps, stairs or curbs?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

6. Do you have any difficulty, even with glasses, reading traffic signs, street signs, or store signs?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

7. Do you have any difficulty, even with glasses, doing fine handwork like sewing, knitting, crocheting, carpentry?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

8. Do you have any difficulty, even with glasses, writing checks or filling out forms?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

9. Do you have any difficulty, even with glasses, playing games such as bingo, dominos, card games, mahjong?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

10. Do you have any difficulty, even with glasses, taking part in sports like bowling, handball, tennis, golf?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

11. Do you have any difficulty, even with glasses, cooking?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

12. Do you have any difficulty, even with glasses, watching television?

Yes  No  Not applicable

If yes, how much difficulty do you currently have?

1. A little
2. A moderate amount
3. A great deal
4. Are you unable to do the activity?

13. Do you currently drive a car?

Yes (go to 14)  No (go to 16)

14. How much difficulty do you have driving during the day because of your vision? Do you have:

1. No difficulty
2. A little difficulty
3. A moderate amount of difficulty
4. A great deal of difficulty?

15. How much difficulty do you have driving at night because of your vision? Do you have:

1. No difficulty
2. A little difficulty
3. A moderate amount of difficulty
4. A great deal of difficulty?

16. Have you ever driven a car?

Yes (go to 17)  No (stop)

17. When did you stop driving?

- Less than 6 months ago
- 6–12 months ago
- More than 12 months ago

18. Why did you stop driving?

- Vision
- Other illness
- Other reason

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## Items included in the Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The following questions are concerned with the treatment of your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks.

1	How satisfied are you with your current treatment?	very satisfied — very dissatisfied
2	How often have you felt that your blood sugars have been unacceptably high recently?	most of the time — none of the time
3	How often have you felt that your blood sugars have been unacceptably low recently?	most of the time — none of the time
4	How convenient have you been finding your treatment to be recently?	very convenient — very inconvenient
5	How flexible have you been finding your treatment to be recently?	very flexible — very inflexible
6	How satisfied are you with your understanding of your diabetes?	very satisfied — very dissatisfied
7	Would you recommend this form of treatment to someone else with your kind of diabetes?	yes, I would definitely recommend the treatment — no, I would definitely not recommend the treatment
8	How satisfied would you be to continue with your present form of treatment?	very satisfied — very dissatisfied

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## Items included in the Retinopathy Dependent Quality of Life (RetDQoL) Questionnaire

This questionnaire asks about your quality of life—in other words, how good or bad you feel your life is.	
I	In general, my present quality of life is: excellent — extremely bad
II	If I did not have diabetic eye problems, my quality of life would be: very much better — worse
NOTE: All items 1–24 begin with the phrase: If I did not have diabetic eye problems:	
1	I could handle my household tasks: very much better — worse
2	I could handle my personal affairs (letters, bills, etc): very much better — worse
3	My experience of shopping would be: very much better — worse
4	My feelings about the future (e.g. worries, hopes) would be: very much better — worse
5	My feelings about past medical care and/or self-care (e.g. anger or regret) would be: very much better — worse
6	*My work life would be: very much better — worse
7	*My closest personal relationship would be: very much better — worse
8	*If I did not have diabetic eye problems, my family life would be: very much better — worse
9	My friendships and social life would be: very much better — worse
10	I could do things for others as I wish: very much better — worse
11	I could get out and about (e.g. on foot, or by car, bus or train): very much better — worse
12	*My vacations would be: very much better — worse
13	My financial situation would be: very much better — worse
14	The way people in general react to me would be: very much better — worse
15	My physical appearance (including clothes and grooming) would be: very much better — worse
16	Physically I could do: very much more — less
17	I could enjoy my leisure activities and interests (e.g. reading, TV, radio, hobbies): very much more — less
18	My self-confidence would be: very much better — worse
19	My motivation would be: very much better — worse
20	*I could do things independently: very much better — worse
21	I would have mishaps or would lose things: very much less — more
22	The time it takes me to do things would be: very much less — more
23	I would find taking care of my diabetes (e.g. self-testing, medication, food, exercise): very much easier — more difficult
24	I could enjoy nature: very much more — less
25	Do your diabetic eye problems affect your quality of life in any ways that have not been covered by the questionnaire? If 'yes', please describe.

\*Denotes a 'not applicable' option

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**Content of the 2 overview items (showing the scores assigned)**

I) In general, my present quality of life is:	
Excellent	3
Very good	2
Good	1
Neither good nor bad	0
Bad	-1
Very bad	-2
Extremely bad	-3

II) If I did not have diabetic eye problems, my quality of life would be:	
Very much better	-3
Much better	-2
A little better	-1
The same	0
Worse	1

**Content of a condition-specific domain (showing the scores assigned)**

9a) If I did not have diabetic eye problems, my friendships and social life would be:	
Very much better	-3
Much better	-2
A little better	-1
The same	0
Worse	1

9b) My friendships and social life are:	
Very important	3
Important	2
Somewhat important	1
Not at all important	0

## Items included in the Retinopathy Treatment Satisfaction Questionnaire (RetTSQ)

The following questions are about your experience of treatment for your diabetic eye problems—the eye problems often caused by diabetes

1	How satisfied are you with the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
2	How well do you feel the treatment for your diabetic eye problems is working?	very well — very badly
3	How bothered are you by any side effects both during and after treatment for your diabetic eye problems?	not at all bothered — very bothered
4	How bothered are you by any discomfort or pain from the treatment for your diabetic eye problems?	not at all bothered — very bothered
5	How unpleasant do you find the treatment for your diabetic eye problems?	not at all unpleasant — very unpleasant
6	How difficult for you is the treatment for your diabetic eye problems?	very easy — very difficult
7	How apprehensive do you feel about the treatment for your diabetic eye problems?	not at all apprehensive — very apprehensive
8	How satisfied are you with the influence you have over the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
9	How satisfied are you with the safety of the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
10	How satisfied are you with the time taken by the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
11	How satisfied are you with the information provided about the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
12	Would you encourage someone else with diabetic eye problems like yours to have a treatment similar to yours?	yes, I would definitely encourage them — no, I would definitely not encourage them
13	How satisfied would you be to continue or repeat the treatment for your diabetic eye problems?	very satisfied — very dissatisfied
14	Are there any other features of the treatment for your diabetic eye problems, causing you either satisfaction or dissatisfaction, that have not been covered by the questionnaire?	If 'yes', please describe.

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## Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL

Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<b>Laser photocoagulation</b>				
<i>Tranos, 2004</i> <sup>44</sup>	<p><b>Study design:</b> prospective cohort</p> <p><b>Inclusion criteria:</b> 1) age <math>\geq 17</math> yr; 2) English speaking; 3) evidence of DME by slit lamp biomicroscopy; 4) pass on an abbreviated version of the Folstein Mini-Mental State examination</p> <p><b>Exclusion criteria:</b> 1) previous laser photocoagulation for PDR or DME 2) vitreous hemorrhage present at recruitment or after enrollment; 3) clinically significant coexisting ocular pathology such as glaucoma and ARMD</p> <p><b>Intervention (n):</b> <i>G1 (all pt)</i>—laser tx; focal laser tx (38), grid laser tx (17)</p>	<p><b>Total population (n):</b> 64  <b>Total eyes in study (n):</b> NR  <b>Withdrew (n):</b> developed vitreous hemorrhage (2), proliferative diabetic changes requiring panretinal photocoagulation (4), moved and had ongoing follow-up by a non study ophthalmologist (3)  <b>Analyzed n (%):</b> 55 (85.9)</p> <p><b>Age, mean<math>\pm</math>SD(range):</b> 65.1<math>\pm</math>9.7 (NR)  <b>Males n (%):</b> 17 (30.9)  <b>Type of DM n (%):</b> NR</p> <p><b>Visual acuity:</b> NR  <b>DR n (%):</b> 55 (100)  <b>DME n (%):</b> 55 (100)  <b>Type of DR n (%):</b>  <i>mild NPDR</i>—13 (23.6);  <i>moderate NPDR</i>—32 (58.2);  <i>severe NPDR</i>—10 (18.2)</p>	<p><b>Instrument/technique:</b> NEI-VFQ-51</p> <p><b>Method of administration:</b> pt self-completed with verbal instructions and assistance from research staff</p> <p><b>Respondent:</b> Pt</p> <p><b>Time points of administration:</b> before and 3–4 mo after tx</p> <p><b>Baseline score mean<math>\pm</math>SD(range):</b>  <i>NEI-VFQ-51</i>  <i>G1</i>—77.9 (17.6)</p>	<p><i>VFQ-51 composite score</i>—82.8 <math>\pm</math>15.1  improvement: 4.9<math>\pm</math>8.9 (<math>p &lt; 0.001</math>)</p> <p><i>Subscales</i>—statistically significant improvement on 8 of 11 vision-related domains</p> <p><i>Distance vision</i>—baseline: 42.7<math>\pm</math>8.4 letters; improvement: 2.2<math>\pm</math>6.2</p> <p><i>Near vision</i>—baseline: 56.4<math>\pm</math>9.1 letters; improvement: 2.1<math>\pm</math>5.0</p>

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

<b>Study</b>	<b>Study Characteristics</b>	<b>Study Population</b>	<b>HRQL Instrument(s)</b>	<b>Results</b>
<i>Mozaffarieh, 2005b</i> <sup>50</sup>	<p><b>Study design:</b> prospective cohort</p> <p><b>Inclusion criteria:</b> 1) undergoing 1<sup>st</sup> laser tx for DME or PDR</p> <p><b>Exclusion criteria:</b> NR</p> <p><b>Intervention (n):</b>                      G1—pt with PDR: panretinal photocoagulation tx for neovascularization on the disk, or elsewhere in accordance to ETDRS guidelines (56);                      G2—pt with DME: macular laser tx, as defined by ETDRS guidelines for retinal edema threatening the fovea (49)</p>	<p><b>Total population (n):</b> 123  <b>Total eyes in study (n):</b>  <b>Withdrew (n):</b> died (2), LTF (3), did not complete/return questionnaire (13)  <b>Analyzed n (%):</b> 105 (85.4)</p> <p><b>Age, mean±SD(range):</b> NR  <b>Males n (%):</b> NR  <b>Type of DM n (%):</b> NR</p> <p><b>Visual acuity:</b> NR  <b>DR n (%):</b> 56 (53.3)  <b>Type of DR n (%):</b> PDR—56 (53.3)  <b>DME n (%):</b> 49 (46.7)</p>	<p><b>Instrument/technique:</b>                      DTSQ;                      Degree of satisfaction (questionnaire developed for study)</p> <p><b>Respondent:</b> Pt</p> <p><b>Time points of administration:</b> DTSQ—after initial tx (baseline) and final (9 mo.) tx;                      Degree of satisfaction—after final (9 mo.) tx</p> <p><b>Baseline score mean±SD(range):</b> DTSQ—29.6±5.6; 45.7% of all pt scored ≥31 (max 36); for 5 of 6 subscales, 59.1% of pt scores ≥25</p>	<p><i>DTSQ (mean±SD)—27.9±5.2</i></p> <p><i>Degree of satisfaction—69.5% of pt completely satisfied, 20.9% partially satisfied, 9.6% dissatisfied</i></p> <p><i>Patient reported VA—24.7% of all pt reported improvement in VA; 71.4% of pt reported no change in VA; 3.8% of pt reported deterioration in VA</i></p>

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<b>Vitrectomy</b> <i>Emi, 2008<sup>42</sup></i>	<b>Study design:</b> cohort	<b>Total population (n):</b> 87 <b>Total eyes in study (n):</b> 87 <b>Withdrew (n):</b> 0 (0) <b>Analyzed n (%):</b> 87 (100%)	<b>Instrument/technique:</b> VFQ-25	VFQ-25 6 mo scores per item (mean):
<b>Country:</b> Japan	<b>Inclusion criteria:</b> 1) Pt dx with DR; 2) Pt who underwent vitrectomy	<b>Age, mean±SD(range):</b> G1—60.4 (7.1) G2—63.6 (5.0) G3—55.3 (9.0)	<b>Respondent:</b> Pt	G1—Item 1: 39; Item 2: 68; Item 3: 91; Item 4: 70; Item 5: 77; Item 6: 87; Item 7: 74; Item 8: 78; Item 9: 79; Item 10: 68; Item 11: 95; Item 12: 80
<b>Date of study:</b> NR	<b>Exclusion criteria:</b> NR	<b>Males n (%):</b> G1—23 (56.1) G2—18 (64.3) G3—9 (50)	<b>Time points of administration:</b> VFQ-25—baseline; 6 mo after tx	G2—Item 1: 42; Item 2: 53; Item 3: 94; Item 4: 58; Item 5: 72; Item 6: 79; Item 7: 65; Item 8: 73; Item 9: 80; Item 10: 58; Item 11: 91; Item 12: 79
<b>Study setting:</b> NR	<b>Intervention (n):</b> <i>All groups</i> —pars plana vitrectomy (87)	<b>Type of DM n (%):</b> NR	<b>Baseline score mean±SD(range):</b> VFQ-25, scores per item:	G3—Item 1: 45; Item 2: 63; Item 3: 80; Item 4: 66; Item 5: 75; Item 6: 87; Item 7: 66; Item 8: 72; Item 9: 75; Item 10: 52; Item 11: 95; Item 12: 80
	<b>Patient groups n (%)</b> G1—vitreous hemorrhage: 41 (47.1); G2—DME: 28 (32.2); G3—fibrovascular membrane: 18 (20.7)	<b>Visual acuity:</b> NR	G1—Item 1: 37; Item 2: 42; Item 3: 94; Item 4: 47; Item 5: 58; Item 6: 75; Item 7: 54; Item 8: 62; Item 9: 69; Item 10: 35; Item 11: 89; Item 12: 65;	
		<b>DR n (%):</b> 87 (100%) <b>Type of DR n (%):</b> NR	G2—Item 1: 42; Item 2: 45; Item 3: 93; Item 4: 57; Item 5: 71; Item 6: 86; Item 7: 64; Item 8: 78; Item 9: 81; Item 10: 54; Item 11: 96; Item 12: 77;	
			G3—Item 1: 45; Item 2: 47; Item 3: 93; Item 4: 74; Item 5: 83; Item 6: 93; Item 7: 72; Item 8: 79; Item 9: 89; Item 10: 51; Item 11: 87; Item 12: 85	

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

<b>Study</b>	<b>Study Characteristics</b>	<b>Study Population</b>	<b>HRQL Instrument(s)</b>	<b>Results</b>
<i>Okamoto, 2010</i> <sup>40</sup>	<p><b>Study design:</b> prospective cohort</p> <p><b>Inclusion criteria:</b> indications for vitrectomy in:  <i>G1</i>—PDR: recurrent or persistent nonclearing vitreous hemorrhage, traction, or combined traction-rhegmatogenous RD and adherent posterior hyaloid causing excessive macular traction;  <i>G2</i>—DME: clinically significant according to ETDRS guidelines and when <math>\geq 3</math> mo had passed after <math>\geq 1</math> session of laser tx and when logMAR BCVA in the affected eye was 0.2 or worse</p> <p><b>Exclusion criteria:</b> 1) pt with hx of vitreoretinal surgery and ocular disorders except for mild refractive errors and mild cataract; 2) pt who had undergone bilateral vitrectomy within 3 mo</p> <p><b>Intervention (n):</b>  <i>G1</i> &amp; <i>G2</i>—received pars plana vitrectomy  <i>G3</i>—normal controls (100)</p>	<p><b>Total population (n):</b> 399  <b>Total eyes in study (n):</b> 399  <b>Withdrew (n):</b> 0  <b>Analyzed n (%):</b> 399 (100)</p> <p><b>Age, mean<math>\pm</math>SD(range):</b>  <i>G1</i>—57.7<math>\pm</math>12.9;  <i>G2</i>—62.7<math>\pm</math>9.0</p> <p><b>Males n (%):</b>  <i>G1</i>—53 (13.3);  <i>G2</i>—23 (5.8)</p> <p><b>Type of DM n (%):</b> NR</p> <p><b>Visual acuity:</b>  <i>G1</i>—BCVA: 1.37<math>\pm</math>0.75; CS: 5.4<math>\pm</math>7.2  <i>G2</i>—BCVA: 0.76<math>\pm</math>0.49; CS: 9.2<math>\pm</math>6.5</p> <p><b>DR n (%):</b> 99 (24.8)  <b>Type of DR n (%):</b> PDR—99 (100)</p> <p><b>Other included retinal diseases n (%):</b>  DME—38 (9.5);  BRVO—20 (5.0);  CRVO—12 (3.0);  MH—42 (10.5);  ERM—33 (8.3);  RD—55 (13.8)</p>	<p><b>Instrument/technique:</b> VFQ—25</p> <p><b>Method of administration:</b> VFQ—25—self-completed with instructions and assistance from research staff</p> <p><b>Respondent:</b> Pt</p> <p><b>Time points of administration:</b> before and 3 mo after tx</p> <p><b>Baseline score mean<math>\pm</math>SD(range):</b>  <i>G1</i>—52.8<math>\pm</math>19.0;  <i>G2</i>—53.0<math>\pm</math>20.5</p>	<p><i>VFQ-25 (mean<math>\pm</math>SD)</i>  <i>G1</i>—63.6<math>\pm</math>17.5;  <i>G2</i>—59.0<math>\pm</math>21.0</p> <p><i>VA (mean<math>\pm</math>SD)</i>  <i>G1</i>—BCVA: 0.53<math>\pm</math>0.62; p&lt;0.0001; CS: 14.0<math>\pm</math>7.9; p&lt;0.0001  <i>G2</i>—BCVA: 0.55<math>\pm</math>0.51; p&lt;0.001; CS: 12.7<math>\pm</math>7.1; p&lt;0.0001</p>

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<b>Vitrectomy and panretinal photocoagulation</b>				
<i>Emi, 2009</i> <sup>43</sup>	<b>Study design:</b> cohort	<b>Total population (n):</b> 327 <b>Total eyes in study (n):</b> NR <b>Withdrew (n):</b> 0 (0) <b>Analyzed n (%):</b> 327 (100%)	<b>Instrument/technique:</b> VFQ-25  <b>Time points of administration:</b> VFQ-25—baseline; 1 yr after tx	VFQ-25 1 yr scores per item (mean):  G1—Item 1: 49; Item 2: 75; Item 3: 94; Item 4: 86; Item 5: 93; Item 6: 98; Item 7: 92; Item 8: 93; Item 9: 99; Item 10: 90; Item 11: 100; Item 12: 90
<b>Country:</b> Japan	<b>Inclusion criteria:</b> NR	<b>Age, mean±SD(range):</b> G1—62.7 (10.0) G2—60.6 (10.1) G3—59.6 (9.6)	<b>Baseline score mean±SD(range):</b> VFQ-25 scores, per item:  G1—Item 1: 43; Item 2: 73; Item 3: 95; Item 4: 85; Item 5: 93; Item 6: 97; Item 7: 92; Item 8: 93; Item 9: 98; Item 10: 90; Item 11: 98; Item 12: 91	G2—Item 1: 41; Item 2: 60; Item 3: 89; Item 4: 66; Item 5: 80; Item 6: 88; Item 7: 70; Item 8: 70; Item 9: 83; Item 10: 76; Item 11: 92; Item 12: 84
<b>Date of study:</b> NR	<b>Exclusion criteria:</b> NR	<b>Males n (%):</b> G1—89 (67.9) G2—39 (65.0) G3—80 (58.8)	G2—Item 1: 39; Item 2: 58; Item 3: 90; Item 4: 68; Item 5: 84; Item 6: 90; Item 7: 76; Item 8: 78; Item 9: 87; Item 10: 78; Item 11: 92; Item 12: 89	G3—Item 1: 42; Item 2: 61; Item 3: 88; Item 4: 61; Item 5: 77; Item 6: 82; Item 7: 70; Item 8: 73; Item 9: 81; Item 10: 60; Item 11: 92; Item 12: 78
<b>Study setting:</b> outpatient clinic	<b>Intervention (n):</b> G1—no DR: no treatment (131) G2—simple DR: photocoagulation, laser surgery (60) G3—PDR: par plana vitrectomy (136)	<b>Type of DM n (%):</b> NR  <b>Visual acuity: logMAR (mean):</b> G1—right eye: 1.09; left eye: 1.1; G2—right eye: 0.64; left eye: 0.61; G3—right eye: 0.21; left eye: 0.19	G3—Item 1: 40; Item 2: 43; Item 3: 92; Item 4: 51; Item 5: 64; Item 6: 78; Item 7: 58; Item 8: 71; Item 9: 75; Item 10: 46; Item 11: 89; Item 12: 73	
		<b>DR n (%):</b> 196 (60) <b>Type of DR n (%):</b> simple DR: 60 (18.3); PDR: 136 (41.6)		
		<b>Other included retinal diseases n (%):</b> NR		

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<b>Phacoemulsification cataract surgery</b>				
<i>Mozaffarieh, 2005a</i> <sup>49</sup>	<p><b>Study design:</b> prospective cohort</p> <p><b>Country:</b> Austria</p> <p><b>Date of study:</b> May 2001 to May 2003</p> <p><b>Study setting:</b> outpatient clinic</p> <p><b>Inclusion criteria:</b> 1) undergoing standardized first-eye phacoemulsification cataract surgery</p> <p><b>Exclusion criteria:</b> 1) pt dx with glaucoma, uveitis, hx of ocular trauma or any other co-existing, visually limiting condition other than those associated with DR; 2) pt with a progression of DR in the non-operated fellow eye</p> <p><b>Intervention (n):</b>  <i>G1</i>—pt with no apparent retinopathy (17)  <i>G2</i>—pt with mild NPDR (19)  <i>G3</i>—pt with severe NPDR (16)  <i>G4</i>—pt with PDR (15)                      All groups—received phacoemulsification cataract surgery</p>	<p><b>Total population (n):</b> 74  <b>Total eyes in study (n):</b> 74  <b>Withdrew (n):</b> died (1), did not complete/return questionnaire (6)  <b>Analyzed n (%):</b> 67 (90.5)</p> <p><b>Age, mean±SD(range):</b> 57.8 (42–68) (all); <i>G1</i>—57.9 (48–67); <i>G2</i>—55.5 (42–66); <i>G3</i>—59.1 (49–67); <i>G4</i>—59.1 (44–71)</p> <p><b>Males n (%):</b> NR  <b>Type of DM n (%):</b> T2D—65 (97)</p> <p><b>Visual acuity: mean (range)</b>  <i>G1</i>—Snellen: 0.29 (0.05–0.50); logMAR VA: 0.62 (0.30–1.30);  <i>G2</i>—Snellen: 0.29 (0.05–0.50); logMAR VA: 0.60 (0.30–1.30);  <i>G3</i>—Snellen: 0.28 (0.05–0.50); logMAR VA: 0.67 (0.30–1.30);  <i>G4</i>—Snellen: 0.24 (0.05–0.40); logMAR VA: 0.71 (0.40–1.30)</p> <p><b>DR n (%):</b> 50 (74.6)  <b>Type of DR n (%):</b> mild NPDR 19 (28.3); severe NPDR 16 (23.9); PDR 15 (22.4)</p> <p><b>Other included retinal diseases n (%):</b> 3 patients with severe NPDR had DME</p>	<p><b>Instrument/technique:</b> VF–14; patient satisfaction questionnaire</p> <p><b>Time points of administration:</b> <i>VF–14</i>—before and 3 mo after tx; <i>Snellen chart</i>—before and 3 mo after tx; <i>Patient satisfaction questionnaire</i>—3 mo after tx</p> <p><b>Baseline score mean±SD(range):</b>  <i>VF–14:</i>  <i>G1</i>—52.21 (32.14–78.57);  <i>G2</i>—55.92 (30.36–85.71);  <i>G3</i>—46.65 (30.36–64.29);  <i>G4</i>—40.12 (25.00–67.86)</p>	<p><i>VF–14 (mean [range])</i>  <i>G1</i>—94.54 (85.71–100)  <i>G2</i>—91.92 (62.50–100)  <i>G3</i>—55.92 (41.07–69.64)  <i>G4</i>—45.12 (0–78.57)</p> <p><i>Patient satisfaction</i>—65.7% of pt completely satisfied  <i>G1</i>—82.4%  <i>G2</i>—79.0%  <i>G3</i>—56.3%  <i>G4</i>—40%;                      surgery met expectations—  <i>G1</i>—70.6%  <i>G2</i>—73.6%  <i>G3</i>—31.2%  <i>G4</i>—26.6%</p> <p><i>Visual Acuity (mean [range])</i>  <i>G1</i>—Snellen: 0.85 (0.60–1.00); logMAR VA: 0.07 (0–0.22);  <i>G2</i>—0.80 (0.50–1.00); logMAR VA: 0.10 (0–0.30);  <i>G3</i>—Snellen: 0.49 (0.10–0.70); logMAR VA: 0.40 (0.15–1.00)  <i>G3</i>—Snellen: 0.37 (0.01–0.60); logMAR VA: 0.56 (0.22–2.00)</p>

ARMD = age-related macular degeneration; BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; Diabetes Treatment Satisfaction Questionnaire = DTSQ; ERM = epiretinal membrane; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup; MH = macular hole; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; RD = rhegmatogenous retinal detachment; RBX = Ruboxistaurin; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ–25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)



**Appendix F. Extended study characteristics and outcomes for studies reporting the impact of interventions for diabetic retinopathy on HRQL (continued)**

<b>Study</b>	<b>Study Characteristics</b>	<b>Study Population</b>	<b>HRQL Instrument(s)</b>	<b>Results</b>
<i>Mozaffarieh, 2009<sup>41</sup></i>	<p><b>Study design:</b> prospective cohort</p> <p><b>Country:</b> Austria</p> <p><b>Date of study:</b> NR</p> <p><b>Study setting:</b> outpatient clinic</p> <p><b>Inclusion criteria:</b> 1) presence of bilateral cataract</p> <p><b>Exclusion criteria:</b> 2) pt in whom lenticular opacity did not allow accurate diagnosis of preoperative level of DR; 2) pt with glaucoma, uveitis, hx of ocular trauma or any other coexisting, visually limiting condition; 3) level of DR in the fellow eye was different from first eye at the 6 mo followup</p> <p><b>Intervention (n):</b>                      G1—pt treated with a single surgery (41)                      G2—pt treated with a second surgery (48)  <i>Both groups:</i>                      phacoemulsification cataract surgery</p>	<p><b>Total population (n):</b> 102</p> <p><b>Total eyes in study (n):</b></p> <p><b>Withdrew (n):</b> died (2), lost to followup (7), excluded at 6 mo (4)</p> <p><b>Analyzed n (%):</b> 89 (87.3)</p> <p><b>Age, mean±SD(range):</b> 63.5 (49–78) (total)                      G1—56.9                      G2—58.9</p> <p><b>Males n (%):</b> 49 (55.1) (total)                      G1—24 (58.6)                      G2—25 (52)</p> <p><b>Type of DM n (%):</b> NR</p> <p><b>Visual acuity:</b> NR</p> <p><b>DR n (%):</b> 66 (74.2)</p> <p><b>Type of DR n (%):</b> mild DR—23 (25.8); moderate DR—22 (24.7); PDR—21 (23.6)</p> <p><b>Other included retinal diseases n (%):</b> 1 patient with moderate DR had DME</p>	<p><b>Instrument/technique:</b> VF—14</p> <p><b>Time points of administration:</b>                      VF—14—before tx, 1, 3, 6, 8, 12 mo after tx</p> <p><b>Baseline score mean±SD(range):</b>                      G1—No DR: 69.3±12.4; mild NPDR: 39.3±5.2; severe NPDR: 40.9±8.6; PDR: 35.3±4.4                      G2—No DR: 46.8±8.7; mild NPDR: 63.4±16.3; severe NPDR: 54.6±8.8; PDR: 50.6±11.4</p>	<p><i>VF-14 (mean±SD)—</i>                      G1                      1 mo—no DR: 97.1±2.6; mild NPDR: 86.7±14.2; severe NPDR: 40.9±8.6; PDR: 36.3±3.9                      3 mo—no DR: 97.1±2.6; mild NPDR: 86.7±14.2; severe NPDR: 50.2±6.4; PDR: 38.1±14.9                      6 mo—no DR: 96.8±2.0; mild NPDR: 86.5±13.6; severe NPDR: 48.8±6.7; PDR: 37.9±14.0                      8 mo—no DR: 79.5±5.5; mild NPDR: 73.2±8.1; severe NPDR: 47.7±10.4; PDR: 41.5±9.8                      12 mo—no DR: 79.5±5.5; mild NPDR: 72.2±8.3; severe NPDR: 46.1±10.7; PDR: 39.9±9.0                      G2                      1 mo—no DR: 93.3±4.2; mild NPDR: 96.4±2.3; severe NPDR: 54.6±8.7; PDR: 49.2±10.9                      3 mo—no DR: 93.4±4.3; mild NPDR: 96.4±2.3; severe NPDR: 61.2±6.4; PDR: 57.1±11.6                      6 mo—no DR: 93.0±4.3; mild NPDR: 94.6±2.5; severe NPDR: 60.9 6.6; PDR: 53.0±10.9                      8 mo—no DR: 93.5±3.1; mild NPDR: 95.9±3.5; severe NPDR: 50.9±16.3; PDR: 53.8±17.6                      12 mo—no DR: 95.3±1.9; mild NPDR: 95.3±2.2; severe NPDR: 47.8±16.0; PDR: 47.6±15.0</p>

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Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<b>Anti-VEGF</b> <i>Mitchell 2011</i>	<b>Study design:</b> RCT  <b>Inclusion criteria:</b> ≥18 years with either type 1 or type 2 diabetes mellitus; HbA1c ≤ 10%; stable medication for management of DM; visual impairment due to DME in ≥1 eye that was eligible for laser tx; BCVA between 78–39 (20/32–20/160 Snellen); decreased vision not due to other causes than DME  <b>Exclusion criteria:</b> concomitant conditions preventing vision improvement; active inflammation in other eye; uncontrolled glaucoma; panretinal laser photocoagulation (w/ in 6 mo) or focal/grid laser photocoagulation (w/ in 3 mo); antiangiogenic drugs w/in 3 mo; hx of stroke, hypertension or change in hypertensive tx (w/ in 3 mo)  <b>Intervention (n):</b> G1—ranibizumab 0.5 mg + sham laser (116) G2—ranibizumab 0.5 mg + laser (118) G3—laser + sham injection (111)	<b>Total population (n):</b> 345 <b>Total eyes in study (n):</b> 345 <b>Randomized:</b> 345 <b>Withdrew (n):</b> 42 <b>Analyzed [HRQL at 12 mo] (n; %)</b> 303 (88)  <b>Age, mean±SD:</b> G1—62.9±9.29 G2—64.0±8.15 G3—63.5±8.81  <b>Males n (%):</b> G1—73 (63) G2—70 (59) G3—58 (52)  <b>Type of DM n (%):</b> T1D—41 (12); T2D—302 (88); unknown—2 (<1)  <b>VA (letter score), mean±SD:</b> G1—64.8±10.11 G2—63.4±9.99 G3—62.4±11.11  <b>Type of DME n (%):</b> <i>Focal</i> —185 (54) <i>Diffuse</i> —143 (41) <i>Unknown</i> —17 (5)	<b>Instrument:</b> NEI-VFQ-25  <b>Method of administration:</b> NR  <b>Respondent:</b> Pt  <b>Time points of administration:</b> baseline, 3 mo, 12 mo  <b>Baseline score, mean±SD:</b> <i>NEI-VFQ-25</i> G1—NR G2—NR G3—NR	<i>VFQ-25, composite score at 12 mo</i> G1—baseline: NR; improvement: 5.0 G2—baseline: NR; improvement: 5.4 G3—baseline: NR; improvement: 0.6  <i>VFQ-25, subscales at 12 mo</i>  General vision G1—baseline: NR; improvement: 8.9 G2—baseline: NR; improvement: 8.0 G3—baseline: NR; improvement: 1.1  Distance activities G1—baseline: NR; improvement: 5.3 G2—baseline: NR; improvement: 5.6 G3—baseline: NR; improvement: 0.4  Near activities G1—baseline: NR; improvement: 9.0 G2—baseline: NR; improvement: 9.1 G3—baseline: NR; improvement: 1.1  Remaining vision related subscales—NR

BCVA = best corrected visual acuity; BRVO = branch retinal vein occlusion; CRVO = central retinal vein occlusion; CS = contrast sensitivity; CSMO = Clinically Significant Macular oedema; DM = diabetes mellitus; DME = diabetic macular edema; DR = diabetic retinopathy; ETDRS = Early Treatment Diabetic Retinopathy Research Group; hx = history; LTF = lost to followup;; mo = month; NPDR = non proliferative diabetic retinopathy; NR = not reported; OCT = optical coherence tomography; PDR = proliferative diabetic retinopathy; pt = patient; QOL = quality of life; T1D = type 1 diabetes mellitus; T2D = type 2 diabetes mellitus; tx = treatment; VA = visual acuity; VF = visual function; VFQ-25 = National Eye Institute Visual Function Questionnaire-25; yr = year(s)

Study	Study Characteristics	Study Population	HRQL Instrument(s)	Results
<i>Sultan 2011</i>	<p><b>Study design:</b> RCT</p> <p><b>Inclusion criteria:</b> ≥18 yr; DME involving center of the macula not assoc with ischemia; foveal thickness ≥250µm; BCVA 65–35 (20/50–20/200 Snellen); intraocular pressure ≤21mmHg; clear ocular media; adequate papillary dilation, hematologic, liver &amp; renal function</p> <p><b>Exclusion criteria:</b> any abnormality likely to confound assessment of VA; atrophy/scarring/fibrosis of center of macula; subfoveal hard exudates or retinal pigment epithelial atrophy; YAG laser, peripheral retinal cryoablation, laser retinopexy, focal or grid photocoagulation within prior 16 wk; panretinal photocoagulation within prior 6 mo or needed within in 9 mo; intraocular surgery within in 6 prior mo; hx of vitrectomy; previous filtering surgery or placement of drainage device; significant media opacities; pathologic high myopia; prior radiation in region of study eye; uncontrolled DM</p> <p><b>Intervention (n):</b> G1—pegaptanib 0.3 mg (133) G2—sham injection (127)</p>	<p><b>Total population (n):</b> 288 <b>Total eyes in study (n):</b> 288 <b>Withdrew (n):</b> 28 (at wk 54); 95 (at wk 102) <b>Analyzed [HRQL, 54 wk] n (%):</b>260 (90)</p> <p><b>Age, mean±SD:</b> G1—62.3±9.3 G2—62.5±10.2</p> <p><b>Males n (%):</b> G1—81 (61) G2—68 (54)</p> <p><b>Type of DM n (%):</b>T1D—18 (7); T2D—242 (93)</p> <p><b>VA (letter score), mean±SD:</b> G1—57.0±8.9 G2—57.5±8.1</p> <p><b>Type of DME n (%):</b> 100 (100%)</p>	<p><b>Instrument/technique:</b> NEI-VFQ-25</p> <p><b>Method of administration:</b> in person in India; via telephone for all other centers</p> <p><b>Respondent:</b> Pt</p> <p><b>Time points of administration:</b> baseline, 18, 54 &amp; 102 wk</p> <p><b>Baseline score mean±SD(range):</b> <i>NEI-VFQ-25</i> G1—65.9 G2—67.9</p>	<p><i>VFQ-25, composite score at 54 wk:</i> G1—70.4; improvement 4.5 G2—69.2; improvement 1.3 <i>Between group differences—</i>2.92; range -0.32 to 6.16 (p = 0.077)</p> <p><i>VFQ-25 subscales at 54 wk:</i> Near vision activities— between group differences: 5.70; 0.48-10.91 (p = 0.033)</p> <p>Distance vision functioning— between group differences: 8.50; 2.74-14.25 (p = 0.044)</p> <p>Social functioning—between group differences: 7.99; 2.90-13.09 (p = 0.002)</p> <p>Between group differences were not statistically significant for the 8 remaining vision related subscales</p> <p><i>VFQ-25, composite score at 102 wk (n = 207):</i> G1—69.8; improvement 4.6 G2—66.2; improvement 0.1 <i>Between group differences—</i>4.47; range -0.26 to 8.68 (p = 0.038)</p>

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