

# Quality of Life and Health Economic Assessments of Age-Related Macular Degeneration

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## **Running Header: QoL and HE Assessments of Age-Related Macular Degeneration**

### **Abstract**

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*Objective:* To review measures of patient reported outcomes (PROs) that can show whether a treatment for age-related macular degeneration also provides patient-perceived benefits. Additionally, to look at health economic measurements currently being used to develop cost-effectiveness models for age-related macular degeneration.

## Introduction

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Blindness has been recognized by WHO (World Health Organization) as one of the handicaps that most adversely affects individuals, the family and society. Visual impairment has a serious impact on older adults' ability to perform daily activities, measurably interfering with their ability to live independently<sup>1</sup>. It is a common reason for people to restrict their driving, a highly valued activity for most individuals. The loss of that ability can greatly reduce a person's sense of independence and well-being<sup>2</sup>. Visual impairment has also been associated with reduced survival in a population-based survey<sup>3</sup>. Foremost, the loss of vision has been and remains one of the most feared chronic disabilities. As early as 1973, WHO decreed that elimination of avoidable blindness was justified not only from a humanitarian point of view but also from a social and economic perspective.

Age-related macular degeneration (AMD) is the leading cause of blindness and severe vision loss in older persons within predominantly white populations of the industrial world<sup>4</sup>. AMD has a profound effect on patient's lives, and the disability and emotional impact associated with advanced AMD can be compared to other serious chronic diseases<sup>5</sup>. A study presented at the 2002 American Academy of Ophthalmology showed that one-third of patients with recently diagnosed AMD were clinically depressed and their depression severity was proportional to the level of visual function <sup>(Solomon, AAO 2002)</sup>. Two-thirds of AMD patients with uncorrected vision reported emotional distress compared to only 2% of those patients with corrected vision.

AMD falls within the overall category of macular disease (MD) that includes such disorders as age-related maculopathy, macular dystrophy and several acquired macular disorders. Symptoms are mainly due to a loss of central vision, which is required for activities such as reading, driving and recognizing faces. But since peripheral vision is not involved, people do not go completely blind from macular disease alone. AMD is the most common condition affecting the macula and is divided into two types. The dry (or nonexudative) form affects about 90% of those with the disease; its progression is relatively slow, it is usually symmetrical with a gradual loss of function of the visual cells in the macular region, and its cause is poorly understood. The wet (or exudative) form

makes up most of the remaining 10% of patients and although rarer, accounts for nearly 90% of all severe visual loss from AMD<sup>6,7</sup>.

Many new forms of treatment for AMD are on the horizon. Anecortave acetate currently under development by Alcon Research Ltd. for the predominantly classic form of wet AMD is just one example<sup>8</sup>. The efficacy and safety of new treatments such as anecortave acetate will need to be proven with traditional clinical endpoints. However, healthcare payers will also look for measures of patient reported outcomes (PROs) that can show whether the treatment also provides patient-perceived benefits. The addition of PRO measures to clinical trials has not been standard practice, but the trend is slowly moving in that direction. In addition, healthcare payers look for assessments of the impact of interventions on medical and non-medical future costs. The following sections describe quality of life and health economic measures that have been included in the anecortave acetate clinical trials to help decision-makers within the healthcare systems allocate resources more effectively

## **Quality of Life Measurements in MD**

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Questions that ask specifically about how eyesight affects aspects of life are included in vision function questionnaires (which are not, in our view, quality of life [QoL] measures) such as the NEI-VFQ51<sup>9</sup> and NEI-VFQ25<sup>10</sup>, the Activities of Daily Vision Scale (ADVS)<sup>11</sup> and the 14-item Visual Function Questionnaire (VF-14)<sup>12</sup>. The scores from these instruments are easier to interpret and more closely correlate with measures of vision than the scores from more generic health status instruments such as the SF-36<sup>13</sup> and the EuroQoL<sup>14</sup>. However, the correlation coefficient between NEI-VFQ distance or far vision sub-scale scores and distance visual acuity is 0.66 at best<sup>15</sup>. Other aspects of vision, such as contrast sensitivity and stereoacuity may also influence the scores<sup>16</sup> but do not give the complete picture. Professor Clare Bradley and Dr. Jan Mitchell, health psychologists at Royal Holloway in the UK, argue that these measures of functional status (e.g. how well a person judges he or she can read normal print) do not effectively capture the experience of living with MD or its impact on QoL. That is, to measure the impact of MD on quality of life, one needs to consider aspects of life of relevance to the individual concerned, and to measure both the impact of the condition on each aspect of life and the importance of each aspect of life to their QoL. For example, an individual

may report that, if they did not have MD, their physical appearance (including clothes and grooming) would be very much better, but that physical appearance is not at all important to them. Thus, although functional status in terms of self-care might be impaired, it has no impact on QoL. For another person, physical appearance may be very important and so the same impact score alone (as in a functional status questionnaire) may not fully reflect the distress experienced by that person. The Royal Holloway team has developed individualized QoL measures for a number of medical conditions including MD that allow relevance and importance of different aspects of life to be considered for each respondent as well as the impact of MD on relevant aspects of life

In 1999 the Royal Holloway team, supported by Alcon Research Ltd., initiated development work on a new PRO instrument named the Macular Disease Quality of Life (MacDQoL) instrument. The result of this work is an instrument that is an individualized measure of the impact of MD on QoL<sup>17</sup>. It is based on the individualized ADDQoL measure for people with diabetes<sup>18</sup>, which in turn was influenced by work on the SEIQoL generic interview measure of quality of life<sup>19</sup>. The MacDQoL, however, addresses aspects of life important to people with MD. Members of local Macular Disease Society groups in the UK contributed to the design work and participated in focus groups. A postal pilot test of the MacDQoL was carried out with a nationwide sample of members of the MD Society. Still other members helped to investigate whether MacDQoL scores were comparable when different methods of completing the questionnaire were used (pen and paper or telephone interview)<sup>(Mitchell, Qual Life Res 2004 Abstract)</sup>.

The MacDQoL has a single opening overview question about quality of life per se (7-point scale, range +3 [excellent], through 0 [neither good nor bad] to – 3 [extremely bad]), and a second overview item about the impact of MD on QoL (5-point scale, range –3 [very much better], through 0 [the same] to +1 [worse]). The remaining items cover different domains or aspects of life that may be 1) negatively impacted by MD and may be 2) important for an individual's QoL. Several items have a 'not applicable' option (e.g. work, holidays). Impact is scored on a 5-point scale (range –3 [very much better] through 0 [the same] to +1 [worse]). Importance is scored on a 4-point scale (range 3 [very important] to 0 [not at all important]). Impact and importance scores are multiplied to give a weighted impact score. A single, average weighted impact score is obtained by

calculating a mean of the weighted impact scores of all applicable items. Domains were selected with reference to the literature and after consultation with MD patients. The domain items in the MacDQoL currently in use are shown in Table 1. Negative wording was used in some items (e.g. *time taken*) in order to keep the grammatical structure as simple and clear as possible. Seventeen new language versions of the MacDQoL were produced by specialists in linguistic validation work at Mapi in Lyon, France in collaboration with the Royal Holloway team. The questionnaires are currently being used to collect QoL data from patients enrolled in the anecortave acetate phase III clinical trials.

**Table 1:** MacDQoL items (and response options) retained following psychometric evaluation

No.	Item Wording	Response Options
A	In general, my present quality of life is:	Excellent – extremely bad
B	If I did not have MD, my quality of life would be	Very much better - worse
Domain items Each item begins with the phrase: If I did not have MD .....		
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 working life and work-related opportunities would be:	Very much better – worse
5	My close personal relationship (e.g., marriage, living companion, steady relationship), now or in the future, would be:	Very much better – worse
6*	My family life would be:	Very much better – worse
7	My friendships and social life would be:	Very much better – worse
8	My physical appearance (including clothes and grooming) would be:	Very much better – worse
9	Physically, I could do:	Very much more - less
10	I could get out and about (e.g. on foot, or by car, bus or train)	Very much better – worse
11*	My holidays would be:	Very much better – worse
12	I could pursue or enjoy my leisure activities (e.g. reading, TV, radio, cinema):	Very much better – worse
13	I could pursue or enjoy my hobbies and interests (e.g. sport, crafts, pets, gardening):	Very much better – worse
14	My self-confidence would be:	Very much better – worse
15	If I did not have MD, my motivation to achieve things would be:	Very much better – worse
16	The way people in general react to me would be:	Very much better – worse
17	My feelings about the future (e.g. worries, hopes) would be:	Very much better – worse
18	My financial situation would be:	Very much better – worse
19	I would have to depend on others (when I do not want to):	Very much less - more
20	I could do things for others as I wish:	Very much better – worse
21	I would have mishaps or would lose things:	Very much less - more
22	I could enjoy meals:	Very much more - less
23	The time it takes me to do things would be:	Very much less - more
24	I could enjoy nature:	Very much more - less

\*indicates items for which an opening question allows the respondent to indicate that the item is not applicable to them, and move on to the next item.

In 2004, data from this trial have been used to investigate the reliability and validity of the MacDQoL in the new language versions. Some refinement of items has been made shortening the questionnaire without losing important information and it is apparent that items 12 and 13, concerning leisure activities and hobbies and interests, can be merged to form a single item. Changes made were supported by data from a parallel validation study in Nottingham, UK to evaluate the MacDQoL measures outside of a clinical trial<sup>20</sup> This study includes an investigation of the MacDQoL's responsiveness to change in severity of MD over a period of one year. People with both wet and dry MD participating in the study have a wide range of severity and years of disease experience. Baseline data from the Nottingham study already demonstrate the MacDQoL's suitability for use with all kinds of MD and not just those with wet MD who are being included in the clinical trial.

Questionnaires based on the principles of judgement analysis, including the MacDQoL, tend to be longer than other questionnaires because there are two aspects to each domain (impact and importance). However, for most purposes this is justified by the value of the information gained. For some purposes it may be sufficient to use the MD-specific overview item (which correlates 0.58 with the average weighted impact score<sup>20</sup>) where brevity is of prime importance. Participants need to have been aware of having the condition for long enough to have a view of the impact of MD on their QoL before they can reasonably be expected to complete the questionnaire. This would also be true of many if not all components of visual function measures. Whereas it is currently fashionable to use Rasch analysis in the development of questionnaires and scales, the method is not appropriate for the MacDQoL. Rasch analysis requires a simple scoring scale and it does not lend itself to the more complex scoring system of the MacDQoL. The Rasch method may lead to the elimination of a number of items and this would damage the face and content validity of the measure, which the designers consider to be of primary importance.

In addition to a disease-specific PRO measure, a generic measure of psychological well-being, the 12-item Well-being Questionnaire (W-BQ12), has been included in the phase III trial. The original, generic 28-item W-BQ was designed in 1982 for use in a World Health Organization study of new treatments for the management of diabetes and was developed to provide a 22-item measure of depressed mood, anxiety, energy and

positive well-being<sup>21</sup>. Considerable data have since been reported on the instrument's validity, sensitivity to change and reliability in diabetes<sup>22</sup>, healthy relatives of people with diabetes<sup>(Hendrieckx, PhD thesis, Royal Holloway 2001)</sup>, and in other conditions such as growth hormone deficiency<sup>23</sup>. Additionally, the instrument has been successfully translated and validated in many European languages<sup>22, 24</sup>. Research to create a Japanese version of the W-BQ has resulted in a shorter version (12 items; 5 minutes to administer) of the instrument which has been supported by detailed work on the Dutch version<sup>25, 26</sup> and confirmed in many other languages<sup>22, 27</sup>.

This W-BQ12 generic tool improves on many previous generic tools including the Psychological General Well-being Index<sup>23</sup> and the well-being subscale of the Medical Outcomes Short-Form 36, SF-36<sup>19, 28</sup> by its well-balanced selection of items (equal numbers of positive and negative items), clear factor structure and brevity. In improving the balance of the positively and negatively worded items, the factor structure was improved. Three 4-item sub-scales make up the W-BQ12 (i.e., negative well-being, energy, positive well-being) and a total general well-being score can also be computed. The negative well-being subscale includes two items each from the previous depression and anxiety subscales, all four of which are negatively worded. These balance the positive well-being subscale which includes 4 of the previous 6 positive well-being items all of which are positively worded. The energy subscale remains unchanged from the W-BQ22 with 2 positively worded and 2 negatively worded items. The W-BQ12 was incorporated into the UK Macular Disease Society Questionnaire to provide psychometric data in this patient population. The survey data were published in 2001<sup>29, 30</sup>.

## Health Economic Measurements in AMD

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Health economic measures have also been included in the phase III trials that focus on the economic impact of the disease. It has been estimated that the annual worldwide productivity cost of blindness was \$168 billion based on 1993 data for prevalence rates, gross domestic products and populations<sup>31</sup>. More recent studies have also documented the large burden of blindness and visual impairment on the social systems of developed countries around the world<sup>32, 33</sup>. These costs will increase dramatically in the future as populations age.

Decreased vision can lead to changes in occupation, missed time from work, increased need for patient caregivers (e.g., family, friends, hired help), and changes in patients' functional abilities affecting activities of daily living. Moreover, different treatments can have different outcomes that may impact on the direct and indirect treatment costs over time. Economic questions have been included in the phase III clinical trials that will collect data to help decision-makers evaluate the economic impact of treating this disease with the various therapies studied.

In addition to collecting economic data from clinical trials, a survey of individuals in the US with AMD was initiated via a questionnaire sent to individuals on the mailing list of the Macular Degeneration Partnership, a support organization for AMD patients. Over 800 individuals completed the survey providing data on the use of assistive services and supports. This study also explored how the level of visual impairment impacted on the use and cost of these services and supports. Non-medical direct costs for services and devices ranged from \$506 to \$1,619 depending on the visual acuity level. However, more significantly, indirect costs associated with the care provider ranged from \$225 to \$47,086 depending on the visual acuity level. A paper describing these results has been submitted for publication and they will be used in future economic models <sup>(Schmier, Submitted to Retina 2005)</sup>

Additional studies have been completed in Europe to look at the consequences of blindness and the results have been published or submitted for publication<sup>34, 35, 36</sup>. In 1998 and 1999, the French National Institute for Statistics and Economic Studies conducted two national surveys, the first in institutions and the second at home, in order to assess the prevalence of various handicaps and their consequences in terms of disability and dependence. A questionnaire dedicated to vision was inserted and the individuals could declare themselves as blind (light perception at best) or visually impaired (shape perception at least). The basic finding was that blind and visually impaired individuals meet difficulties when performing most of their daily activities regardless of their age, the number of people available to assist them, or the presence of other handicaps (motor, cerebral, etc.). Based on these and other results, non-medical costs were calculated at the national level and compared to medical costs which showed that most of the cost of blindness is outside the healthcare system.

Currently, photodynamic therapy (PDT), intravitreal injection with pegaptanib and laser photocoagulation are the only FDA approved treatments available for individuals with choroidal neovascularization (CNV) secondary to AMD. Economic models examining the cost-effectiveness of many of these treatments already exist in the literature<sup>37, 38, 39</sup>. These economic models support the cost-effectiveness of laser photocoagulation and question the cost-effectiveness of PDT at least for individuals with poor vision or whose macular lesions were not purely classic. The quality of life and health economic measures we have included in the anecortave acetate clinical trials will help healthcare payers more effectively compare this new intervention for AMD with currently used treatments.

In the field of AMD, researchers increasingly come up against the physio-pathology of aging. The next innovations are expected to be more costly but to have improved efficacy. By postponing the onset of visual impairment, savings will be realized within the healthcare system but mainly outside of it. The resources required to bring the next generation of AMD therapeutic successes to market will be considerable and the global economics of visual impairment will need to be considered. Recently completed studies will provide data to cover many dimensions of AMD economics. By showing the complete cost of advancing AMD, healthcare payers will have the opportunity to make true comparisons between new treatments with current therapy. In the end they will be able to make better reimbursement decisions based on the overall costs including the psychosocial and financial costs to patients.

### **Method of Literature Search**

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Our literature search included the following databases: Pubmed, Science Direct, Psychinfo, Medline, PDR, USP, Agricola, Applied Science & Technology, Biosis, Chembank, Drug Info FullText, eFacts, Embase, IPA, Life Sciences, NERAC, PharmaProjects, and Stedman's Medical Dictionary. References have been included spanning the years 1991-2005. The search terms included 'visual impairment', 'low vision', 'macular degeneration', 'visual function', 'functional status', 'quality of life', 'cost of blindness' and 'cost-effectiveness'. In addition, we obtained articles cited in the

reference lists of other papers. Articles published in languages other than English were not considered.

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