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Clinical science

Minimum set of outcome measures for non-advanced age-related macular degeneration: a Delphi consensus statement by the TRACER (intermediate age-related macular degeneration) study group

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ABSTRACT

Background The purpose of this study was to define a minimum set of outcome measures for patients affected by non-advanced age-related macular degeneration (AMD).

Methods A structured Delphi consensus process was conducted by a panel of worldwide experts in treatment outcome registries, imaging, nutrition and other AMD aspects. The experts answered anonymously to a series of surveys, each followed by a face-to-face meeting to discuss the pooled results. Supporting literature was shared among the group members by a facilitator before each round. Finally, all the results were discussed and the consensus document was created based on the level of agreement between experts.

Results Six rounds were conducted until a formal consensus was achieved. Five main sections were identified: demographic characteristics, health factors, functional, imaging and clinical outcomes. A minimum set of 28 outcome measures was subsequently developed and approved by all members. Based on the priority of various items, 24 fields were designated as mandatory, while the remaining were deemed optional. Five items are required only at baseline, 12 are to be assessed annually for changes and the remaining 0 1must be collected at each clinical assessment.

Conclusion This newly defined minimum set of outcome measures for non-advanced AMD could be employed in future real-world data collection registries aimed at gathering comprehensive and longitudinally extensive clinical data on a global scale. This may help to elucidate the natural progression of non-advanced AMD and its response to new therapies.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Advanced forms of age-related macular degeneration (AMD) can still lead to irreversible vision loss, and there is limited evidence on the long-term clinical outcomes of earlier disease stages.

WHAT THIS STUDY ADDS

⇒ A consensus-derived minimum set of outcome measures for patients with non-advanced AMD was established by a panel of experts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This minimum set could support future real-world data registries by enabling consistent, comprehensive and long-term clinical data collection on non-advanced AMD at a global level.

INTRODUCTION

Age-related macular degeneration (AMD) is a chronic condition affecting the elderly population.[1] An interplay of retinal metabolism and nutrition with ageing and environmental and lifestyle factors, such as smoking,[2] alcohol consumption,[3] diet[4] and genetic susceptibility,[5] contributes to the pathogenesis of AMD. The prevalence of vision loss from AMD is predicted to increase and affect 288 million people by 2040, making it the most common cause for visual impairment in the elderly worldwide.[6]

The clinical definition of AMD includes an early/intermediate stage (non-advanced). Non-advanced AMD is clinically characterised by the presence of drusen and/or pigmentary changes in the macula lutea—with minimal impact on visual acuity. Late stages include neovascular and atrophic changes that can both lead to loss of central vision.[7]

Significant improvements have been made over the past two decades in the management of neovascular AMD with antibodies that inhibit vascular endothelial growth factors.[8 9] The US Food and Drug Administration has recently approved new treatments for atrophic AMD that are designed to slow progression of the disease.[10 11] Both neovascular and atrophic AMD can still cause significant and irreversible loss of vision despite these treatments. Since degenerative changes to the retina are currently irreversible, treatments that can be

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implemented at the earliest stage of the disease, when vision is still unaffected, are the most likely to prevent loss of vision from AMD.

Treatment options for non-advanced AMD are limited. Large multicentre randomised clinical trials have demonstrated the benefits of oral supplementation with a combination of antioxidants and minerals in reducing the risk of disease progression from intermediate to advanced forms.[12–14] Other approaches, such as multiwavelength photobiomodulation, have been recently cleared by regulators in the USA.[15 16]

We aimed to establish a formal consensus on a minimum set of standardised outcome measures to evaluate and track patients affected by early and intermediate forms of AMD. This standardised process may help to provide a better understanding of long-term disease progression. We have employed a Delphi approach for a working group consisting of fourteen experts from diverse fields related to AMD. A minimum essential standard outcome set will provide a foundation for gathering a large, representative database of longitudinal outcomes of non-advanced AMD worldwide.

METHODS

We employed a Delphi consensus technique as a qualitative research approach based on experts' consensus to propose a standardised set of outcome measures for early/intermediate AMD. This strategy has a proven track record in establishing consensus across various medical and healthcare domains.[17–19]

Selection of the panel of experts

A panel of 14 experts from eight different countries (Italy, Spain, Switzerland, UK, Ireland, USA, Singapore, Australia) from four continents and one facilitator, from Italy, were identified to represent various fields of AMD (figure 1). Participants were identified based on their background, publication records (with at least 20 papers in their respective fields), academic profile and experience in different aspects of intermediate AMD and real-world outcome registries. Each panel member had a minimum of 10 years of experience in at least one of the following fields in AMD: outcome registries, nutrition, functional tests, macular imaging biomarkers and histopathology. Clinicians were required to have at least 10 years of experience in AMD management, active involvement in AMD clinical trials and participation in eye-related registry-based studies. Non-clinician experts were identified based on their research contributions in their respective fields as applied to AMD. Participants were provided with a literature review and a questionnaire to compile at each round. A quasi-anonymised approach was followed to reduce reciprocal influences, whereby the participants knew the identities of the other panel members but they did not know how they individually responded to any of the questions in any round.

Development and administration of questionnaires

A set of potential functional and anatomical outcome measures for patients affected by early/intermediate AMD was initially identified through a literature review using the following terms: ((“early Age-related macular degeneration” OR “early AMD” OR “intermediate Age-related macular degeneration” OR “intermediate AMD” OR “Macular Degeneration, Age-Related”[MeSH])) AND ((“outcome*” OR “Treatment Outcome”[MeSH])). The first preliminary questionnaire asked open-ended questions to identify the main outcome parameters to be included in the Delphi process (online supplemental table



Figure 1 Geographical distribution of the intermediate age-related macular degeneration) study group.

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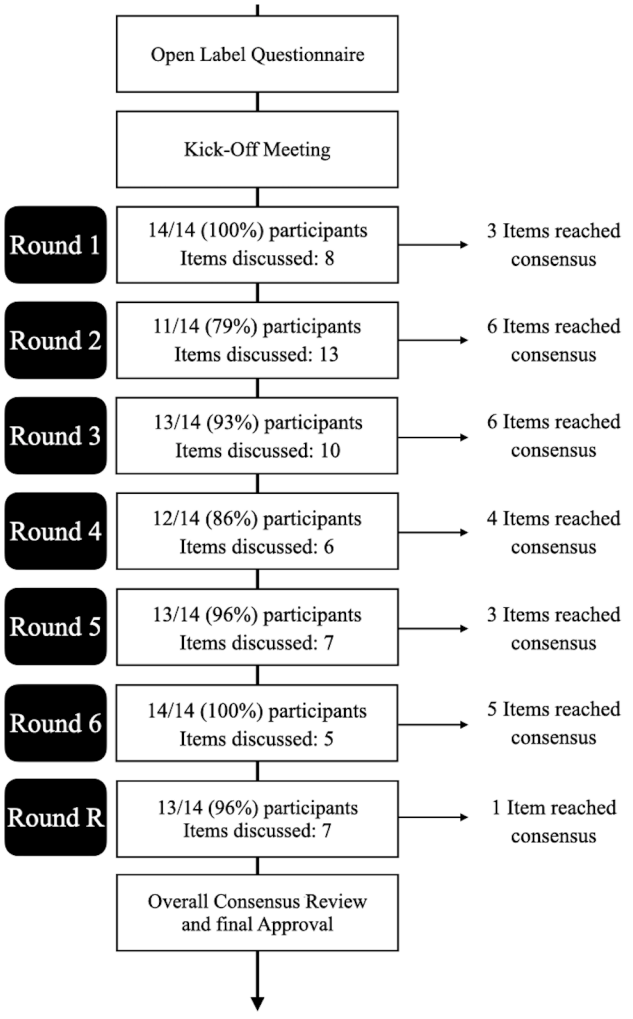


Figure 2 Flowchart illustrating the Delphi study design. For each round, the number of questionnaire participants is shown. Additionally, the figure displays the items included in the questionnaire and those that achieved a positive consensus for inclusion in the final statement. The final round (R) was conducted during the journal revision process.

1). These responses were collected and discussed in the first face-to-face online meeting.

Subsequently, every 4 to eight weeks, a dedicated questionnaire was developed by the facilitator and shared with the whole group. Before each round, supporting literature was shared between the group members. Between each questionnaire, a web-based meeting was conducted to present aggregated agreement scores for each item and discuss the feedback from group members. There was no pre-determined number of rounds; each item was discussed until an agreement was reached. Consequently, each questionnaire was also tailored based on the previously aggregated results. Each round involved the following procedures: administering a tailored questionnaire, sharing the aggregated results and facilitating a subsequent discussion among panel participants.

To validate each round, at least 11 out of 14 (~80%) of the group members had to answer the proposed questionnaire. A schematic representation of the conducted Delphi approach is presented in figure 2.

The European Commission's official online survey-management system (EUSurvey platform, software V.1.5.3) built for creation and publication of globally accessible forms and questionnaires was identified as a customised tool to gather the opinion from experts. In particular, the online Delphi module was used to design each round of questions. The software enables the inclusion of different types of questions including free text, single choice, multiple choice, ranking, number-slider, date, time, matrix, table, regular expression and rating. We mainly adopted multiple choice and single choice (YES/NO) questions.

The survey was conducted anonymously. Answers were not connected to any specific participant, and the system provided gathered results and anonymised responses only.

Establishing Agreement

Since we could not find consistent definitions of percentages of agreement among participants in the Delphi method, we adopted predetermined agreement rates as follows:

- No agreement: < 50%
- Low agreement: 51–70%.
- Moderate agreement: 71–80%.
- Strong agreement: 81–100%.

Results are presented with descriptive statistics computed as percentages for categorical questions. The analyses were automatically provided by the EUSurvey system. Items that reached a positive agreement higher than 70% (moderate or strong agreement) were included in the minimum set of outcome measures.

RESULTS

The study was conducted between October 2022 and October 2023. A total of 14 experts from eight different countries agreed to participate (M.C.; S.A.Z.; K.B.; C.A.C.; F.V.; H.M.; J.Z-V.; K.T.; L.O.; J.A.; G.S.; M.G.; D.B.; A.I.). A single moderator (M.C.) presided over each session, provided literature resources and presented aggregated results at each meeting. Six rounds were necessary to define the overall consensus, divided as follows: four rounds to define demographic characteristics and health factors, three rounds to gain consensus about functional outcomes and three rounds to reach an agreement on imaging and clinical outcomes. Some rounds may have overlapped between two case-mix categories (table 1). An additional round was conducted to assess the level of agreement on items suggested by journal reviewers.

The minimum set of outcome measures was developed to include clinical aspects and characteristics of patients with AMD before they had developed advanced disease. Consequently, the target population for the non-advanced AMD minimum set of outcomes measures was defined as follows: patients aged 55 years and older with drusen (> 63 µm) and/or subretinal drusenoid deposits (at least five defined lesions in a single B-scan confirmed by at least one en-face modality) in the 6 mm diameter Early Treatment Diabetic Retinopathy Study (ETDRS) grid with or without pigment abnormalities. Exclusion criteria include the presence of geographic atrophy or macular neovascularisation in the tracked eye. All items, along with their final corresponding percentage of votes, are listed in table 1.

Demographic characteristics

The working group decided to include and track the patient's year of birth, biological sex at birth and ethnicity. Ethnicity was defined as the self-reported cultural identity to which a person most strongly felt they belonged. These categorical variables are summarised in online supplemental table 2. The postcode, defined as the numerical or alphanumeric code assigned to a specific geographical area or address by a postal authority where

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Table 1 Summary of outcomes recommended by the intermediate age-related macular degeneration) study group

Case-mix category	ITEM	Definition	Agreement	Rounds needed	Optional fields	Timing
	PatientID	Indicate the patient's medical record number	100%	1		Baseline only
Demographic information	Year of birth	Year of birth	100%	1		Baseline only
	Biological sex	The patient's sex at birth	100%	1		Baseline only
	Ethnicity	The cultural ethnicity of the person that they most closely identify with, self-reported by the patient	75%	4		Baseline only
	Postcode	Numerical or alphanumeric code assigned to a specific geographical area or address by a postal authority	73%	2	Optional	Baseline only
Health factors	Smoking status	A person's current and past smoking behaviour	85%	3		Annual Check
	AMD family history	Reporting any relative with any AMD diagnosis	82%	2		Annual Check
	Diabetes	Any diagnosis of diabetes	100%	1		Annual Check
	Diabetes	Year of diabetes diagnosis	91%	1		Annual Check
	Diabetes	Diabetes medications	77%	2		Annual Check
	Alcohol use	Number of alcohol drinks per week	100%	2		Annual Check
	Hypercholesterolaemia	Any diagnosis of Hypercholesterolaemia	100%	1		Annual Check
	Hypercholesterolaemia	Statin medications	77%	2		Annual Check
	Hypercholesterolaemia	Name of statin medication	75%	3	Optional	Annual Check
	Diet	Lutein/Zeaxanthin Screener Questionnaire+Omega-3 fatty acid screener	85%	1		Annual Check
	Supplementation	Please indicate whether the patient is using nutritional supplements	100%	1		Annual Check
	Supplementation	name of nutritional supplementation	92%	2	Optional	Annual Check
Functional outcomes	Visual acuity (logMAR score)	Indicate the person's distance visual acuity, corrected or uncorrected.	92%	1		Every assessment
	Low luminance visual acuity	Visual acuity measured by adding a neutral density (ND) filter to the refraction so that luminance is reduced by 2.0 log units	58%	2	Optional (100%)	Every assessment
Imaging outcomes	Drusen	Indicate the presence of Drusen in the 6 mm ETDRS grid	100%	1		Every assessment
	Reticular pseudodrusen	Indicate the presence of RPD anywhere in the macular area	85%	2		Every assessment
	Pigmentary abnormality	Any definite hyper- or hypopigmentary abnormalities associated with medium or large drusen but not associated with known disease entities	77%	2		Every assessment
	iRORA	OCT feature characterised by (1) photoreceptor degeneration, (2) attenuation or disruption of the RPE and (3) hypertransmission into the choroid <250 microns	77%	R		Every assessment
	Macular abnormality other than	Indicate the presence of any other macular abnormality rather than drusen or RPD	71%	3		Every assessment
Clinical outcomes	Advanced AMD conversion	Indicate if there is a progression to advanced AMD form, either GA or MNV	100%	2		Every assessment
	Audit discontinued	Select to discontinue this eye from the audit	79%	2		Every assessment
	Fellow eye not included in the audit	Specify the current ocular condition of the fellow eye	93%	1		Every assessment
	Fellow eye visual acuity	Indicate the person's distance visual acuity, corrected or uncorrected	86%	1		Every assessment

AMD, age-related macular degeneration; ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; iRORA, incomplete retinal pigment epithelial and outer retinal atrophy; LLVA, low luminance visual acuity; MNV, macular neovascularisation; R, Delphi round conducted during the journal revision process; RPD, reticular pseudodrusen; RPE, retinal pigment epithelium; VA, visual acuity.

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Table 2 Minimum set of outcome measures for health factor characteristics

Smoking status	
Heavy smoker	A person who smokes ≥10 cigarettes daily
Smoker:	A person who smokes <10 cigarettes daily but >10 cigarettes per week
Light smoker	A person who smokes <10 cigarettes weekly
Ex-smoker	A person who does not smoke at all now, but has smoked at least 100 cigarettes within the last 15 years
Never-smoker	A person who does not smoke now and has not smoked in the last 15 years.
AMD family history	
Parent/s	Any parent with a diagnosis of any form of AMD
Brothers/sisters	Any brother or sister with a diagnosis of any form of AMD
Diabetes	
Yes/no	Any diagnosis of diabetes
YYYY	Year of diabetes diagnosis
Diabetes medication	
1	Metformin
2	Insulin
3	Other
Alcohol use	
1	Not at all
2	<14 alcohol drinks per week (eight for females)
3	≥14 alcohol drinks per week (eight for females)
Hypercholesterolaemia	
Yes/no	Any diagnosis of Hypercholesterolaemia
Yes/no	Statin medication
Statin name (optional)	Name of statin medication patient is taking
Diet	
FFQ 1*	Lutein and Zeaxanthin screener
FFQ 2†	Omega-3 fatty acid screener
Supplementation	
Yes/no	Nutritional supplements
Supplements name (optional)	Name of supplementation patient is taking

*online supplemental table 3
†online supplemental table 4
AMD, age-related macular degeneration; FFQ, food frequency questionnaire.

the subject lived, was considered optional data. All these fields are recommended to be included only in the baseline examination.

Health Factors

The group agreed to include several health factors known to play a crucial role in the development of AMD (table 2). Most of the experts (85%) concurred on the inclusion and monitoring of diet, which encompasses the pattern of food consumption and nutrient intake by an individual over a specific timeframe. To achieve this, the experts opted to use a previously validated food frequency questionnaire (FFQ) screener for lutein and zeaxanthin (online supplemental table 3).[20] A second FFQ screener for Omega-3 fatty acid was adapted from Sublette *et al* (online supplemental table 4).[21]

All these fields are recommended to be included during the baseline examination and checked annually for any changes.

Functional outcomes

The participating experts recommended (agreement 92%) that visual acuity should be the primary and standardised functional outcome measure for AMD. The recommendation entails recording distance visual acuity (best of uncorrected, corrected using glasses or contact lenses, or pinhole if required) in the affected eye during each clinical visit. Visual acuity should be reported in logarithm of the minimal angle of resolution (LogMAR) letters score. The use of LogMAR charts is strongly recommended, although other measurement systems may be used and subsequently converted to LogMAR letters score.

In addition to distance visual acuity, the group discussed the possible use of several alternative functional outcome measures, including contrast sensitivity, low-luminance visual acuity (LLVA) and rod-mediated dark adaptation. The panel of experts concluded that LLVA could serve as a complementary method for measuring visual function and thus recommended its inclusion as an optional approach for real-world data collection. LLVA is assessed by adding a neutral density filter to the refraction so that luminance is reduced by 2.0 log units.[22] Consensus was not reached for the other functional tests.

Imaging Outcomes

Several clinical anatomical outcomes are recognised to have a predictive role in AMD progression, spanning from its early to late stages. However, the panel selectively considered only those clinically relevant and commonly adopted by clinicians for inclusion in the minimum standard measures (online supplemental table 5, figure 3).

Drusen, defined as small yellow or white deposits that accumulate between the retinal pigment epithelium (RPE) basal lamina and the inner collagenous layer of Bruch's membrane, are considered the hallmark of AMD. In accordance with previous classification systems and adopted in a clinical classification of AMD, medium drusen are defined as >63 micrometres and ≤125 micrometres, while large drusen are classified as greater than 125 micrometres.[7 23] The subfoveal area is considered the central subfield of the ETDRS grid (1 mm diameter).

Reticular pseudodrusen (RPD), also known as subretinal drusenoid deposits (SDD), are defined as small deposits located between the RPE and photoreceptor outer and inner segments.[24] These lesions have recently been identified as a third independent risk factor for the progression from non-advanced to late AMD, alongside the well-known features of drusen and pigmentary abnormalities.[25] As such, experts have endorsed and agreed to track this outcome.

Pigmentary abnormalities, which are strongly associated with hyperreflective foci on OCT, will be tracked as present or absent since they are also considered late-stage risk factors for AMD.[26 27] Consensus was reached (77%) to include the OCT feature known as incomplete RPE and outer retinal atrophy (iRORA) as a mandatory outcome measure. Additionally, the presence of any macular abnormalities other than those described above will be documented and reported.

Clinical outcomes

The primary objective of establishing this minimum standard set was to monitor the progression of AMD and subsequently assess the time to conversion to advanced disease for individual patients with non-advanced AMD. Delaying or preventing the development of advanced AMD is critically important for both patients and clinicians, so the expert panel unanimously agreed on the necessity of documenting progression to advanced AMD. Additionally, the condition of the fellow eye will be categorised and reasons for discontinued follow-up will be collected. The

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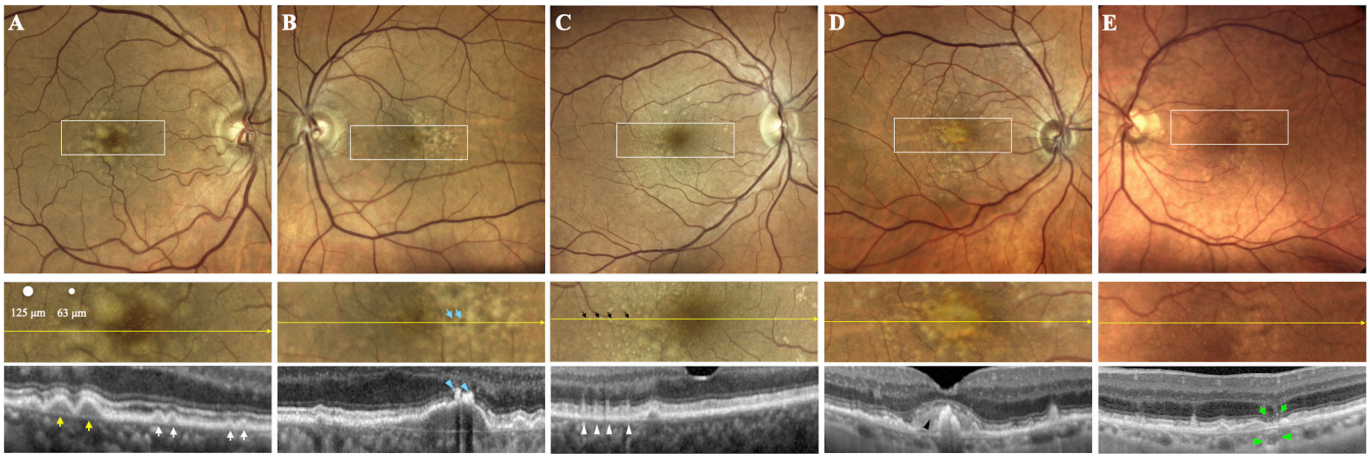


Figure 3 Examples of imaging outcomes recommended for inclusion in the minimum set of outcome measures for non-advanced age-related macular degeneration (AMD). White slit light emitting diode confocal colour fundus photography (CFP) and magnified structural optical coherence tomography (OCT) B-scans are presented. In (A), subfoveal large drusen (>125 micrometres, yellow arrows) and extrafoveal medium drusen (>63 micrometres and ≤125 micrometres, white arrows) are shown as key clinical features to distinguish between early and intermediate AMD. (B) Large soft drusen with associated pigmentary abnormalities (turquoise arrows), corresponding to hyperreflective foci (turquoise arrowheads) on the OCT scan. Reticular pseudodrusen (also known as subretinal drusenoid deposits, SDD) are shown in (C) on CFP (black arrows) and are confirmed by OCT, revealing multiple dot-like SDDs temporal to the fovea (white arrowheads). (D) A clinically relevant yellowish deposit corresponding to an acquired vitelliform lesion in the macula lutea, visualised on OCT as an accumulation of hyper-reflective material (black arrowhead) beneath the neuroretina. Notably, multiple drusen are visible across the macular area. Finally, (E) an example of incomplete retinal pigment epithelial and outer retinal atrophy (iRORA). The OCT scan demonstrates all defining features of iRORA: photoreceptor degeneration evidenced by outer nuclear layer thinning and loss of the external limiting membrane and ellipsoid zone (green arrows). Additionally, a region of retinal pigment epithelium disruption is observed, accompanied by a zone of hypertransmission into the choroid measuring less than 250 µm (green arrowheads).

summary of clinical outcomes is presented in online supplemental table 6.

The final standard set underwent refinement and received unanimous approval from all members of the working group.

DISCUSSION

We have developed a minimum set of outcome measures for non-advanced AMD through a modified Delphi approach to be collected over time for patients affected by early or intermediate stages of AMD. This outcome set is designed to provide the foundation for a global disease-based registry. Establishing a dedicated registry for the non-advanced phases of AMD will facilitate the acquisition of real-world data, the collection of useful information on the natural history and variable progression of the disease and the testing of potential treatments targeting this stage of the disease. These outcome measures should be considered a fundamental framework for epidemiological studies and non-trial research; while they can be adopted for randomised controlled trials (RCTs), additional measures may be required to meet specific RCT objectives.

Outcome registries also require a number of patient characteristics to be documented from the outset so that comparisons of the outcomes between different cohorts can be adjusted. One of these is ethnicity, a well-described risk factor for AMD. Several epidemiological studies have reported a higher prevalence of the disease in the white/Caucasian population.[28–31]

Environmental factors appear to potentially influence epigenetic modifications, thereby affecting disease prevalence and progression. For this reason, collecting postal codes would be relevant, even though the group agreed to keep this as a non-mandatory field, given the restrictions applied in some countries for privacy reasons.

The most significant modifiable environmental risk factor for AMD is smoking, which is associated with a two- to fourfold increased risk for any form of AMD.[32–35] Most studies also confirmed that smoking has a dose-response effect on AMD.[36 37] Due to these considerations, the experts decided to include smoking not only as a dichotomous variable, but also to categorise the smoking group into different (quantitative) classes while maintaining the data's ease of collection.

Physical activity is increasingly recognised as a modifiable risk factor for AMD, with several studies suggesting a protective effect through its role in cardiovascular and metabolic health.[38 39] However, the expert panel did not reach consensus on its inclusion in the core dataset despite its clinical relevance.

The association between diabetes and AMD is not clear due to the underlying confounders. Some reports propose diabetes as a risk factor, while others suggest it has no effect.[32 36 40–42] Similarly, the impact of diabetic treatments like metformin on AMD remains uncertain.[43 44] An agreement was reached to collect data on both diabetes diagnosis and treatments to address these points in the future.

There is growing evidence that statin-based therapy has a therapeutic effect on drusen and helps reduce macular drusen volume.[45] On the other hand, there is discordant evidence on the role of hypercholesterolaemia in the progression of AMD. Similarly, the potential effect of high-density lipoproteins in AMD remains unclear despite their recognised role in complement components, regulation and delivery of xanthophyll carotenoids to the retina (see also below).[46 47] The panel agreed to track both hypercholesterolaemia diagnosis and statin treatment.

A possible dose-response causal effect of alcohol consumption on different forms of AMD has been recently reported.[3 48] Similar evidence has been provided in the past, although the impact of smoking, a significant confounding factor, could not be entirely ruled out.[49 50] Given the potential causal association and the need for further evidence to support this possible

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association, alcohol consumption has been included as a binary outcome.

Emerging evidence suggests diet is also an additional modifiable risk factor for AMD progression.[51 52] In particular, it is widely accepted that higher intake of Omega-3 fatty acids and the carotenoids lutein and zeaxanthin is associated with a lower risk of developing AMD.[51 53–55] Despite this evidence, collecting dietary information in a web-based international registry remains challenging. The group agreed to adopt a dedicated FFQ to collect dietary intake data for lutein, zeaxanthin and Omega-3 fatty acids. This validated tool collects a broad range of dietary information while remaining quick and easy enough to be administered in the everyday clinical practice.[20] Consideration is also being given to the future development and validation of a simplified FFQ that could incorporate additional dietary risk factors, such as high fat intake and high glycaemic load, which have also been implicated in AMD pathogenesis.[56 57]

The most extensively studied intervention proven to delay the progression from intermediate to advanced AMD forms is the supplementation of antioxidant micronutrients.[58] These primarily include vitamin C, vitamin E, xanthophyll carotenoids, selenium and zinc.[59–62] The main evidence comes from the two large, randomised studies, Age-Related Eye Disease Studies (AREDS) and AREDS2, conducted by the National Eye Institute.[12 13] Thus, details on supplementation will be collected as part of the minimum set of outcome measures for non-advanced AMD (table 2). Other potential treatment strategies are currently under investigation and may be integrated in the near future.[16 63 64]

The working group acknowledged that measuring distance visual function might not be the most suitable functional outcome for patients with non-advanced AMD. Nonetheless, this remains the only globally recognised and standardised functional outcome routinely assessed in clinical settings.[65] Visual acuity is also important to guarantee the consistency with the neovascular AMD standard set of treatment outcomes.[17] Patients with early and intermediate AMD often experience a slowing in the recovery of light sensitivity after exposure to bright light.[66] A dedicated test of rod-mediated dark adaptation has proven to be a powerful functional biomarker for non-advanced AMD.[67] However, the test is time-consuming and remains primarily limited to research settings at this time.[68] Consequently, the group identified the LLVA as a complementary functional marker. This psychophysical test records visual acuity after luminance is reduced by 100-fold. The test is straightforward, cheap and relatively quick, making it a recognised alternative functional endpoint.[69 70]

Since drusen are widely considered the anatomical hallmark of AMD, their location and size will be tracked. We acknowledge that drusen size is not typically recorded in routine clinical practice. However, the current clinical AMD classification is based on drusen diameter, forcing its inclusion.[7] This information will enable further differentiation between early and intermediate AMD. Additionally, the presence of RPD will be reported. Currently, there is no standardised approach to quantify macular RPD load; thus, the only additional information will be based on localisation.[71 72] Similarly, pigmentary abnormalities and hyperreflective foci, known to be strongly associated with the progress of AMD, will be tracked accordingly. The authors recognise the existence of various anatomical classifications of drusen, RPD and pigmentary abnormalities, which are graded differently in the AREDS and Beckman classifications.[73] However, these recommendations aim to facilitate consistency in data collection globally, with simplicity being the primary goal of our consensus.

Several emerging OCT-based biomarkers have shown promise in predicting AMD progression. While many of these features were considered through the Delphi process, the panel agreed to include only the presence of iRORA, which is already well-established in the literature and adopted in clinical practice.[74] In contrast, other potential biomarkers, such as hyperreflective crystalline deposits, calcified drusen, hypertransmission defects and ellipsoid zone loss, did not reach consensus for inclusion at this time. This is likely attributed to the limited integration into routine clinical workflow, though they may be considered in future updates.

We recognise limitations to this study. First, the proposed minimum set of outcome measures did not consider the patient's perspective. In fact, the group included researchers and clinicians specialised in AMD, but no patient community or organisation representatives. Second, the dataset has not been tested in routine clinical practice. Prior to implementation, it will be necessary to conduct a feasibility study on clinical data collection. Third, we have intentionally excluded any imaging-based measurements. Future integration of upcoming artificial intelligence in OCT, with automatic quantification of disease-specific biomarkers, could be considered. Finally, large genome-wide association studies have identified two large genetic variants involved in AMD progression: complement factor H (and the age-related maculopathy susceptibility 2 variants.[75] Although genetic factors are known to play an important role in the AMD progression, it is not currently possible to include genotypes in the minimum set of outcome measures for non-advanced AMD, because genotyping is not widely available.

These recommendations establish a minimum standard set of outcome measures for non-advanced AMD. Our purpose is to standardise data collection in routine clinical practice. The globally shared long-term data will facilitate the identification of optimal treatment strategies. The goal is to intervene before visual function becomes irreversibly compromised. Given the growing interest of the scientific community in this field, advancing technology and forthcoming results from multicentre clinical trials, these recommendations will likely be adjusted in the future to ensure their continued relevance and effectiveness.

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