Age-related Macular Degeneration (AMD):
Clinical Trials and Therapeutic Developments

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Introduction

Age-related Macular Degeneration (AMD) is a prevalent condition affecting the central part of the retina, known as the macula, which is responsible for sharp, straight-ahead vision.

As a leading cause of vision impairment among the aging population, especially those over 50, Age-related Macular Degeneration significantly influences the quality of life by impairing the ability to perform daily tasks such as reading, driving, and recognizing faces. The disease is predominantly categorized into two types: dry (atrophic) AMD and wet (neovascular) AMD, each with distinct characteristics and progression patterns.

The understanding of Age-related Macular Degeneration has evolved significantly over the years. Initially, little was known about the disease's pathogenesis and treatment. However, advancements in medical research have led to better diagnostic techniques and therapeutic interventions. Historical perspectives show that the condition was once considered an unavoidable part of aging, but now, factors contributing to its development, such as genetics, environment, and lifestyle, are increasingly recognized.

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Local Trials, Global Approvals

Australian expertise combined with direct FDA submission capabilities, offering a streamlined path for global approval.

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Expertise From the Start

Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

Ready to discuss your Clinical Trial?
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

Diagnostic Criteria for Age-related Macular Degeneration

ICD-11 Codes for AMD

- **9B75.00 Early age-related macular degeneration:** Consists of a combination of multiple small drusen, few intermediate drusen (63 to 124 microns in diameter), or RPE abnormalities.
- **9B75.01 Intermediate age-related macular degeneration :** Consists of extensive intermediate drusen, at least one large druse (>=125 microns in diameter), or geographic atrophy not involving the centre of the fovea
- **9B75.03 Atrophic late-stage age-related macular degeneration**
- **9B75.04 Neovascular late-stage age-related macular degeneration**

Impact of ICD Codes on Clinical and Research Perspectives

Understanding and utilizing the correct ICD codes for AMD is crucial in the management and treatment of the disease. It aids in standardizing diagnoses, treatment protocols, and research efforts across the healthcare continuum.

Diagnostic Criteria for AMD

1. **Comprehensive Eye Exam** – Including visual acuity test, examination of the retina, and assessment for the presence of drusen and other retinal changes.
2. **The Amsler grid test** – Helps identify distortions or blind spots in your field of vision which could be signs of macular damage.
3. **Optical Coherence Tomography (OCT)** – A non-invasive imaging test providing detailed images of the retina.
4. **Fundus Photography** – Photographing the retina to monitor the progression of AMD over time and helps in identifying changes in the macula and surrounding areas.
5. **Fluorescein Angiography** – Involves injecting a fluorescent dye into the bloodstream to highlight blood flow in the retina and identify any abnormal vessels.
6. **Indocyanine Green Angiography (ICGA)** – Similar to fluorescein angiography but uses indocyanine green dye which provides better imaging of choroidal blood vessels.

Epidemiology of Age-related Macular Degeneration

Global Prevalence and Demographic Patterns:

Age-related Macular Degeneration (AMD) represents a significant global health concern, particularly in the aging population. It is the most common cause of irreversible blindness in individuals over the age of 60 in developed countries.

Age-related Trends:

The prevalence of AMD increases notably with age, affecting one in eight individuals aged 60 and above. Current estimates suggest that around 200 million people worldwide have AMD, and this figure is projected to increase to nearly 300 million by 2040 due to the aging global population. This age-related increase in prevalence underscores the growing concern of AMD as the global population continues to age.

Sex-specific Epidemiology:

Research suggests a slight sex disparity in AMD prevalence, with women being at a slightly higher risk than men. This difference may be attributed to the longer life expectancy of women, as AMD is more common in older age groups.

Racial and Ethnic Differences:

Epidemiological studies indicate significant racial and ethnic disparities in the prevalence of AMD. Caucasians are generally found to have a higher prevalence of AMD compared to African, Asian, and Hispanic populations. However, the reasons for these disparities are complex:

- **Genetic Differences:** Genetic makeup significantly influences susceptibility to AMD. Certain genetic markers associated with the disease may be more prevalent in one race or ethnicity compared to others.
- **Environmental Exposures:** Environmental factors, including exposure to sunlight (UV light) and pollution, can vary significantly between different regions and communities, influencing the risk of developing AMD.
- **Lifestyle Factors:** Lifestyle choices, such as diet and smoking habits, contribute to the risk of developing AMD. Diets high in certain fats and low in antioxidants can increase the risk, while smoking has been identified as a significant modifiable risk factor for AMD. The prevalence of these lifestyle factors can vary among different racial and ethnic groups due to cultural, socioeconomic, and educational differences.

A look at commonly prescribed FDA-Approved Drugs for AMD

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Byooviz	2021	Samsung Bioepis Co., Ltd. and Biogen Inc.	Biosimilar to Lucentis (ranibizumab injection)	Treats wet AMD, macular edema, and myopic choroidal neovascularization.
Izervay	2023	Astellas	Blocks protein (complement C5)	Reduces progression of late-stage dry AMD (geographic atrophy).
Syfovre	2023	Apellis Pharmaceuticals	Complement C3 (C3 And PZP Like Alpha 2 Macroglobulin Domain Containing Protein 1 or C3) Inhibitor	Slows progression of dry AMD, administered via eye injection every 25 to 60 days.
Eylea HD	2023	Regeneron Pharmaceuticals	Higher dose formulation for wet AMD	Requires fewer eye injections compared to the standard dose.
Vabysmo	2022	F. Hoffmann-La Roche Ltd	Angiopoietin 2 (Ang 2 or ANGPT2) Inhibitor; Vascular Endothelial Growth Factor A (Vascular Permeability Factor or VEGFA) Inhibitor	Used for treatment of neovascular (wet) AMD.

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Pivotal Endpoints for AMD Clinical Trials

In Age-related Macular Degeneration clinical trials, the choice of endpoints is crucial for evaluating the effectiveness of new treatments. Pivotal endpoints are specific objectives used to measure the outcome of intervention studies. In the realm of Age-related Macular Degeneration, these endpoints have evolved significantly, focusing on functional, structural, and patient-reported outcomes.

1. Best-Corrected Visual Acuity (BCVA):

Measures the smallest letters a patient can read on an eye chart.

2. Anatomical Changes via OCT:

Assesses structural changes in the retina.

3. Functional Measures (Sensitivity, Reading Speed):

Evaluates real-world vision capabilities.

4. Quality of Life Assessments (NEI-VFQ):

Assesses the impact on daily living.

5. Low-Luminance Visual Acuity (LLVA):

Vision under dim light.

6. Microperimetry:

Maps central and paracentral visual field.

7. Area and Progression of Geographic Atrophy:

Measures area of retinal thinning.

8. Dark Adaptation:

Time to adjust from bright to dark.

An analysis of failed clinical trials in the AMD arena

Name of Drug	Clinical Trial Identifier	Reason for Termination/Failure
Fovista	NCT01940900	Did not meet primary endpoint in phase 3 trials. **Primary Efficacy Endpoint:** • The primary efficacy endpoint is the mean change in visual acuity (ETDRS letters) from baseline at the month 12 visit. **Safety Endpoints:** • Safety endpoints include adverse events, vital signs, ophthalmic variables [ophthalmic examination, intraocular pressure (IOP), fluorescein angiogram (FA), optical coherence tomography (OCT)], ECG, and laboratory variables.
Lampalizumab	NCT02247479	Failed to demonstrate efficacy in reducing disease progression.
Abicipar	NCT02462928	High incidence of intraocular inflammation outweighing benefit-risk ratio.

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Navigating Challenges in Age-related Macular Degeneration Clinical Trials

In the realm of ophthalmology, Age-related Macular Degeneration stands as a formidable adversary, challenging researchers and clinicians alike in their quest for effective treatments. As we venture into the intricacies of Age-related Macular Degeneration clinical trials, we confront a labyrinth of challenges, from patient recruitment to the subtle nuances of disease progression.

1. Diagnostic Misclassification:

Incorrectly diagnosing the stage of AMD.

2. Variable Disease Progression:

Diverse rates of AMD progression among participants.

3. Statistical and Methodological Flaws:

Inadequate sample size or incorrect data analysis methods.

4. Adherence to Treatment:

Participants not adhering to the treatment regimen.

5. Outcome Measurement:

Challenges in consistently measuring complex outcomes.

6. Placebo Response:

Participants showing improvement due to placebo effect.

7. Patient Recruitment and Retention:

Difficulty in recruiting and retaining enough participants.

8. Data Handling Errors:

Mismanagement or loss of critical data.

Addressing Safety and Care in AMD Management

Ensuring Well-being

For individuals living with AMD, managing the condition involves more than just addressing physical symptoms. It's about ensuring overall well-being through comprehensive care that prioritizes safety, psychological support, and adherence to standard treatment protocols.

1. **Infection Risks:** Injections into the eye can introduce bacteria, leading to serious infections like endophthalmitis.
2. **Retinal Detachment:** Procedures or the disease itself can cause the retina to detach, requiring urgent surgical repair.
3. **Adverse Reactions to Medications:** Anti-VEGF therapies can cause eye inflammation, increased intraocular pressure, or arterial thromboembolic events.
4. **Systemic Effects:** Oral supplements, especially in high doses, might interact with other conditions or medications.
5. **Visual Acuity Changes:** Treatment might not improve vision or could inadvertently worsen it, necessitating close monitoring.

Ensuring Safety and Efficacy

Current AMD treatments, particularly anti-VEGF injections, carry risks like potential eye infections, inflammation, and increased eye pressure. There's also a small risk of arterial thromboembolic events.

Treatments require close monitoring and sterile procedures to minimize complications. Therapies like laser treatments or supplements, have their own set of potential side effects, emphasizing the importance of personalized care plans and regular patient evaluations to ensure safety and efficacy.

Standards of care for AMD patient well-being include:

- Regular eye examinations
- Personalized treatment plans
- Lifestyle modifications
- Patient education
- Psychological support

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Enhancing Clinical Trial Protocols: Towards FDA Approval

Improving clinical trial protocols for Age-related Macular Degeneration is pivotal for enhancing the probability of FDA approval and ultimately providing better healthcare outcomes. This entails:

Innovative Trial Designs

Adaptive trial designs can offer significant benefits, allowing for modifications based on interim results without compromising the study's integrity. Incorporating biomarkers as surrogate endpoints can provide early indicators of treatment efficacy.

Patient Selection & Stratification

Accurate patient selection can increase the homogeneity of trial participants, reducing variability and improving the statistical power of the study. Stratification ensures that the treatment effects are not confounded by patient-related factors.

Enhanced Outcome Measures

Implementing more sensitive and specific outcome measures, such as advanced imaging techniques, can help in detecting subtle changes in disease progression, providing more robust data on the drug's efficacy.

Regulatory Compliance & Documentation

Thorough understanding and adherence to regulatory guidelines are crucial. Detailed documentation and clear communication with regulatory bodies can streamline the review process and potential issues early on.

Safety Monitoring

Robust safety monitoring mechanisms are essential for identifying and mitigating risks promptly, safeguarding participant well-being, and ensuring regulatory compliance.

By focusing on these areas, researchers can design more efficient, effective, and patient-centered clinical trials for Age-related Macular Degeneration treatments. Ultimately, these efforts aim to accelerate the development of safe and effective therapies, addressing the unmet needs of patients and advancing the field of Age-related Macular Degeneration research and treatment.

Notable Key Opinion Leaders in Age-related Macular Degeneration

Name	Specialty	Designation	Location	Brief Bio
Dr. Michael Jamieson MBB FRANZCO	Ophthalmology; Surgery	Specialist, Bendigo Health and Castlemaine Health	Victoria, Australia	Dr. Michael Jamieson is an ophthalmologist with a focus on glaucoma and additional expertise in cataract, macular degeneration, diabetes, and other eye diseases. Dr. Jamieson also consults as a staff specialist in the glaucoma unit at the Royal Victorian Eye and Ear Hospital. He completed his medical degree with honors from Monash University and also received honors for his Medical Science degree, which concentrated on new treatments for macular degeneration.
Dr. Brad Johnson FRANZCO MBBS (Hons)	Ophthalmology	Founder, Northern Eye Surgeons	Western Australia	Dr. Brad Johnson is a consultant ophthalmic surgeon specializing in retinal and cataract conditions. Dr. Johnson is not only recognized for his expertise in treating age-related macular degeneration, retinal vascular diseases, and diabetic retinopathy but is also known for his significant contributions as a cataract surgeon. He opened Northern Eye Surgeons in late 2011, which has grown into one of the largest ophthalmology practices in the northern suburbs of Perth, Australia.
Dr. Hemal Mehta MBBS MD(Cantab.) FRCOphth FRANZCO	Ophthalmology; Surgery	Ophthalmic Surgeon, Strathfield Retina Clinic	New South Wales, Australia	Dr. Hemal Mehta is a distinguished ophthalmic surgeon specializing in macula disease and cataract surgery. Dr. Mehta has gained significant experience through fellowships at renowned institutions including the Sydney Eye Hospital and Moorfields Eye Hospital in London. His expertise encompasses a wide range of ophthalmological areas, with a particular focus on the diagnosis and management of retinal conditions such as age-related macular degeneration, diabetic retinopathy, and retinal vein occlusions.
Dr. Guy W Bylsma MBB FRANZCO	Ophthalmology	Consultant Ophthalmologist, Hobart Eye Surgeons	Tasmania, Australia	Dr. Guy Bylsma plays an integral role in ophthalmic emergencies in Hobart, provides supervision to ophthalmology surgical trainees at the Royal Hobart Hospital, and is involved in ongoing clinical trials. His commitment to the field is also evident in his role on the Continual Professional Development Committee for the Royal Australian College of Ophthalmology. In 2005, he was involved as a medical retina research fellow at the Centre for Eye Research, where he was part of the pioneering international trials of injectable anti-VEGF agents for Macular Degeneration.
Dr. Anthony S L Kwan MBChB (UK) MD(London) FRCOphth(UK) FRANZCO	Ophthalmology	Director of Vitreoretinal Service, Queensland Eye Institute	Queensland, Australia	Dr. Anthony Kwan has specialized expertise in treating retinal and macular diseases, including AMD, epiretinal membrane, macular hole, diabetic retinopathy, and retinal detachment. Dr. Kwan has held several prestigious positions including Director of Ophthalmology at Mater Health Services in Brisbane and Director of the Queensland Electro-Diagnostic and Imaging Centre. Dr. Kwan provides specialist services across Mt Gravatt, the Gold Coast, Northern NSW, Southport, and Coolangatta.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

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