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Review Article

Current Trends and Challenges in Clinical Trials for Wet Age-Related Macular Degeneration: A Review

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Abstract

Background: Wet Age-Related Macular Degeneration (wAMD) is a major contributor to severe vision impairment among older adults. Although anti-VEGF therapies are available, the condition continues to pose a considerable public health issue because of challenges related to effectiveness, recurrence, and the burden of treatment.

Objectives: This review seeks to examine the latest trends, recent developments, and ongoing challenges in clinical trials for wAMD. Additionally, it assesses the impact of innovative therapeutic approaches and regulatory obstacles on the results of clinical trials.

Methodology: An extensive literature search was conducted using databases such as PubMed, Scopus, and ClinicalTrials.gov. Relevant clinical trials, systematic reviews, and regulatory guidelines from the last decade were analyzed to assess emerging trends, key barriers, and future directions in wAMD clinical research.

Results: The analysis revealed a trend towards personalized medicine, gene and cell therapies, and continuous drug delivery systems in wAMD clinical trials. Nevertheless, significant obstacles remain, such as difficulties in patient recruitment, elevated trial expenses, absence of predictive biomarkers, and the intricacies involved in assessing long-term efficacy. Additionally, variations in regulations and ethical issues hinder the seamless advancement of trials.

Conclusion: Despite advancements in clinical research for wAMD through innovative therapies and enhanced designs, it is vital to address current challenges to effectively translate promising treatments into successful real-world applications. Cooperative initiatives among researchers, clinicians, regulatory agencies, and the industry are critical for refining trial frameworks and improving patient outcomes.

Keywords: Clinical trials; management; degeneration; treatment; current status; macular.

1. INTRODUCTION

Age-Related Macular Degeneration (AMD) is a primary cause of irreversible vision loss in the elderly population globally, with the neovascular or 'wet' form being responsible for most severe cases of vision impairment. Wet AMD is marked by the development of abnormal blood vessels beneath the macula, resulting in leakage, bleeding, and scarring, which ultimately harms central vision. Although anti-VEGF therapies are available, there are still challenges related to treatment burden, limited efficacy in certain patients, and disease progression ¹⁻². Ongoing efforts to create more effective and durable therapies underscore the critical role of clinical trials in improving the management of wet AMD ³.

1.1. Overview of Age-Related Macular Degeneration (AMD)

Age-Related Macular Degeneration (AMD) is a progressive retinal condition that mainly impacts the macula—the central part of the retina that is crucial for

high-resolution vision needed for tasks like reading, driving, and recognizing faces. AMD is generally categorized into two main types: dry (non-neovascular) and wet (neovascular) AMD ⁴. The dry form, which is more common, is marked by the buildup of drusen (lipid-rich deposits) and a gradual thinning of the macula. Conversely, wet AMD, which represents only 10–15% of all AMD instances, is responsible for nearly 90% of severe vision loss associated with AMD due to the swift formation of abnormal blood vessels beneath the macula, resulting in leakage, bleeding, and subsequent scar tissue development ⁴⁻⁵. The development of AMD is influenced by a complex interaction of genetic factors, oxidative stress, chronic inflammation, and the dysregulation of angiogenic processes, particularly those involving vascular endothelial growth factor (VEGF) ⁵. As the condition progresses, patients often experience a marked reduction in central vision, while their peripheral vision usually remains unaffected. This loss of central vision can occur suddenly and significantly

hinder a patient's independence and overall quality of life, rendering AMD a significant public health issue ⁶.

1.2. Epidemiology and Disease Burden

Worldwide, AMD is a major contributor to visual impairment among the elderly, especially in developed countries. Recent epidemiological studies indicate that over 190 million people were affected by AMD in 2020, with projections suggesting this figure could rise to nearly 288 million by 2040 due to longer life expectancy and an aging population. Wet AMD impacts about 10% of those with AMD but is the leading cause of severe vision loss ⁷. The implications of AMD go beyond just vision loss, affecting psychological, social, and economic aspects of life. Individuals with advanced AMD frequently encounter challenges in their daily routines, decreased mobility, a heightened risk of depression, and increased reliance on caregivers ⁷⁻⁸. The financial repercussions are also considerable, including direct medical expenses for treatments (particularly with long-term anti-VEGF therapy) and indirect costs associated with lost productivity, vision rehabilitation, and social support ⁸. The rising incidence and impact of AMD, especially the vision-threatening neovascular type, highlight the critical need for ongoing research, early diagnosis, and the creation of more effective, accessible, and less burdensome treatment options ⁸⁻⁹.

1.3. Classification: Dry vs. Wet AMD

AMD is divided into two primary categories: dry (atrophic) and wet (neovascular or exudative) AMD, which are differentiated by their unique pathological characteristics and clinical development ⁹. Dry AMD is the more prevalent type, representing about 85-90% of all cases. It is characterized by the presence of drusen-yellowish deposits located beneath the retina-and a gradual degeneration of the retinal pigment epithelium (RPE), resulting in a slow yet progressive deterioration of central vision. Over time, dry AMD may advance to geographic atrophy, leading to considerable vision impairment ¹⁰⁻¹¹.

Conversely, wet AMD is less common but significantly more aggressive. It is defined by the abnormal proliferation of blood vessels from the choroid layer into the subretinal area, a phenomenon referred to as choroidal neovascularization (CNV) ¹². These vessels are delicate and susceptible to leakage, causing hemorrhaging, fluid buildup, and fibrotic scarring, which swiftly harms the macula and results in abrupt and severe loss of central vision. Understanding the difference between dry and wet AMD is essential, as wet AMD requires immediate and continuous treatment to avert permanent vision loss ¹³.

1.4. Importance of Clinical Trials in Wet AMD

Clinical trials serve as the cornerstone of evidence-based medicine, playing an essential role in converting scientific findings into effective therapeutic solutions, particularly for complex and vision-threatening conditions like wet AMD. As a rapidly advancing subtype of AMD, wet AMD necessitates prompt, ongoing, and targeted treatment to maintain vision. The advent of anti-

vascular endothelial growth factor (anti-VEGF) agents represented a major advancement in the management of wet AMD; however, these treatments come with their own set of challenges ¹⁴. The need for frequent intravitreal injections, variability in patient responses, potential long-term adverse effects, and the significant burden on both patients and healthcare systems highlight the necessity for ongoing therapeutic innovation ¹⁴⁻¹⁵.

Clinical trials offer a structured framework to assess the safety, efficacy, pharmacokinetics, and long-term effects of new agents and delivery methods. In addition to VEGF inhibition, recent clinical studies are investigating multi-targeted strategies, including the inhibition of angiopoietin-2, complement pathways, and inflammation modulators, along with gene therapies and sustained-release formulations, all aimed at enhancing treatment durability and minimizing injection frequency ¹⁶. Moreover, advanced imaging biomarkers and personalized treatment algorithms are being evaluated in trials to improve patient selection and optimize therapeutic results ¹⁷⁻¹⁸.

Crucially, clinical trials in wet AMD also aid in identifying and validating surrogate endpoints, such as alterations in central retinal thickness and visual acuity scores, which act as quantifiable measures of treatment efficacy ¹⁹. Additionally, these trials play a vital role in global regulatory approval processes and in establishing standardized clinical practice guidelines. In a time when real-world data and patient-centered outcomes are becoming increasingly significant, clinical trials also incorporate assessments of quality of life, patient adherence trends, and functional vision outcomes, offering a more comprehensive view of treatment impact ²⁰.

This in-depth review examines the changing landscape of clinical trials for wAMD, a major contributor to vision impairment in older adults. It starts by outlining the classification, epidemiology, and impact of AMD, differentiating between its dry and wet forms while highlighting the rapid progression and public health implications of wAMD. The article further investigates the disease's pathophysiology, focusing on mechanisms such as choroidal neovascularization (CNV), VEGF overexpression, and inflammatory pathways. It reviews current treatment strategies, primarily concentrating on anti-VEGF agents like ranibizumab and aflibercept, as well as new therapies including gene therapy, port delivery systems, and combination treatments. A specific section details the phases of clinical trials in wAMD, covering endpoints, inclusion criteria, and the necessity of modifying study designs to accommodate patient variability and treatment responses. The review also highlights recent and ongoing clinical trials, stressing advancements in drug delivery, biologics, and long-acting therapies. Additionally, it tackles significant challenges such as patient recruitment, high costs of trials, ethical issues, and the absence of predictive biomarkers. Lastly, it presents future perspectives, advocating for adaptive trial designs, personalized medicine, the integration of AI and advanced imaging,

and a stronger focus on real-world evidence and patient-reported outcomes. The review concludes by emphasizing the crucial role of clinical trials in connecting scientific progress with patient-centered care, urging collaborative efforts to address existing challenges and enhance therapeutic outcomes in wAMD.

2. PATHOPHYSIOLOGY OF WET AMD

Wet AMD, also referred to as neovascular AMD, is a progressive retinal condition marked by the abnormal growth of blood vessels beneath the macula, resulting in swift loss of central vision. This particular subtype of AMD arises from the pathological process known as choroidal neovascularization (CNV), where delicate and leaky blood vessels breach Bruch's membrane, leading to hemorrhaging, fluid buildup, and ultimately scarring of the retinal tissue²¹. A critical factor in this process is the overproduction of VEGF, which is instrumental in angiogenesis and heightened vascular permeability. Grasping the intricate molecular and cellular mechanisms that underlie wet AMD is vital for formulating effective treatment strategies and creating targeted clinical trials²¹⁻²².

2.1. Role of VEGF and Neovascularization

The primary molecular factor driving the pathogenesis of wet AMD is vascular endothelial growth factor (VEGF), especially VEGF-A. In normal physiological conditions, VEGF plays a crucial role in maintaining the homeostasis of retinal and choroidal blood vessels. However, in wet AMD, retinal ischemia and oxidative stress result in an overproduction of VEGF by retinal pigment epithelial (RPE) cells, Müller glia, and choroidal fibroblasts²³. VEGF interacts with VEGFR-2 on endothelial cells, initiating processes such as endothelial proliferation, migration, and survival, along with an increase in vascular permeability. This sequence of events leads to the

development of new capillaries that emerge from the choroidal vasculature, penetrating Bruch's membrane into the sub-retinal space. These immature, fenestrated vessels allow plasma and red blood cells to leak into the retinal layers, compromising the structural integrity of the macula²⁴. Over time, persistent leakage results in fibrotic remodeling, photoreceptor cell death, and irreversible vision impairment. The critical involvement of VEGF in choroidal neovascularization (CNV) underpins the creation of existing anti-VEGF treatments (such as ranibizumab, aflibercept, and brolucizumab)²⁵.

2.2. Inflammatory and Genetic Mechanisms

Inflammation plays a crucial role in the onset and advancement of choroidal neovascularization (CNV) in wet age-related macular degeneration (AMD). Dysregulation of the complement system, which includes elements like C3, C5, and the membrane attack complex (MAC), fosters persistent inflammation within the retina²⁶. Genetic variations in the complement factor H (CFH) and complement component 3 (C3) genes are closely linked to the risk and severity of AMD, primarily due to the compromised regulation of complement activation. Activated microglia, macrophages, and mast cells invade the subretinal area, releasing pro-inflammatory cytokines and chemokines such as IL-6, IL-8, MCP-1, and TNF- α , which further stimulate VEGF expression and the progression of CNV²⁴⁻²⁶.

Moreover, oxidative stress resulting from aging mitochondria in the retinal pigment epithelium (RPE) and external factors like smoking contribute to the buildup of lipofuscin and the formation of drusen, which act as inflammatory triggers²⁷. This inflammatory microenvironment intensifies angiogenic signaling and compromises the integrity of the blood-retinal barrier, perpetuating the neovascular cycle²⁷⁻²⁸.

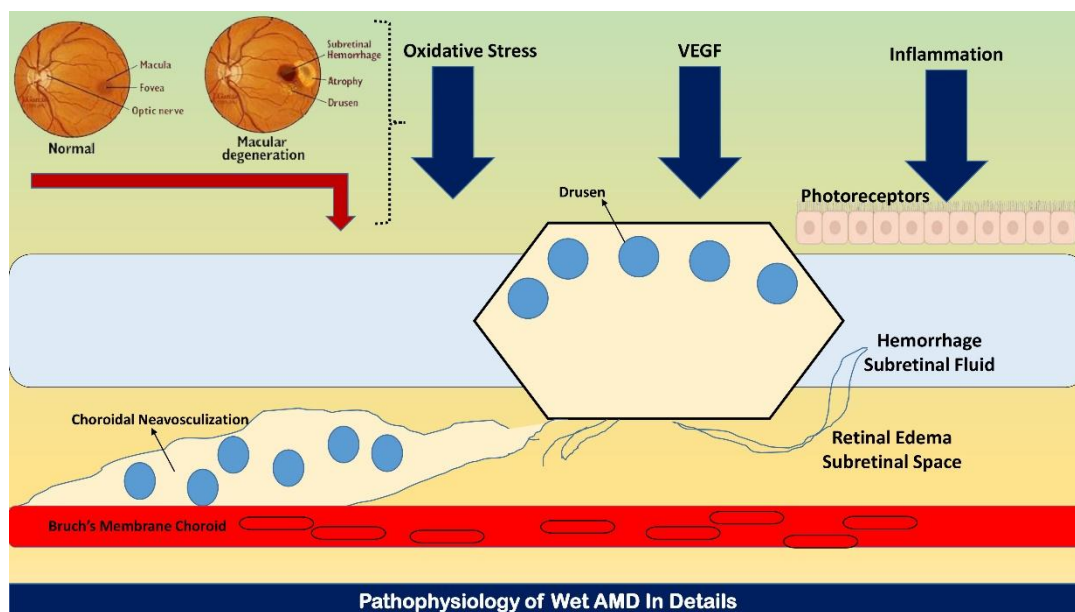


Figure 1: Schematic representation of Pathophysiology of wet AMD with details

2.3. Disease Progression and Vision Loss

The progression of wet AMD is marked by sudden or intermittent flare-ups caused by active CNV. At first, patients might notice metamorphopsia (distorted vision), blurred central vision, or scotomas. If not addressed promptly, CNV lesions can grow, resulting in repeated accumulation of subretinal and intraretinal fluid, bleeding, and exudates, all of which contribute to the deterioration of the outer retina and the photoreceptor-RPE interface²⁹. If neovascularization is chronic and left untreated, it leads to disciform scars made up of fibrovascular tissue that replaces the normal structure of the retina. This scarring results in permanent loss of central vision, leaving patients with considerable visual impairment. In contrast to dry AMD, which progresses slowly, wet AMD can cause rapid and severe loss of vision within a matter of days or weeks²⁹⁻³⁰. While peripheral vision may remain unaffected, the loss of central vision has a profound impact on a patient's quality of life, independence, and functional capabilities, highlighting the importance of early diagnosis and ongoing monitoring³⁰. In summary, the pathophysiology of wet AMD is characterized by a complex interaction of angiogenic signaling, persistent inflammation, and genetic predisposition, with VEGF-driven neovascularization being central to the process—emphasizing the urgent requirement for targeted treatments and prompt intervention to avert irreversible vision impairment.

3. CURRENT THERAPEUTIC STRATEGIES IN WET AMD

wAMD, which is marked by choroidal neovascularization, is a primary cause of irreversible vision loss among older adults globally. In the last twenty years, there have been considerable improvements in the treatment of wAMD, primarily due to the introduction of anti-vascular endothelial growth factor (anti-VEGF) therapies³¹. These medications, such as ranibizumab, aflibercept, and brolocizumab, have transformed clinical practice by effectively inhibiting neovascularization and either stabilizing or enhancing visual outcomes for numerous patients. However, despite their effectiveness, these treatments necessitate frequent intravitreal injections, which create challenges related to patient compliance, treatment burden, and real-world effectiveness³²⁻³³.

New strategies are being developed to overcome these challenges, including long-acting formulations, gene therapies, port delivery systems, and biosimilars. Additionally, researchers are investigating combination therapies and new molecular targets to improve therapeutic effectiveness and lower recurrence rates³⁵. This dynamic therapeutic environment supports ongoing clinical trial initiatives aimed at refining treatment protocols and assessing innovative interventions to achieve lasting, vision-preserving results in the management of wAMD³⁴.

3.1. Anti-VEGF Agents (Ranibizumab, Aflibercept, Brolocizumab)

Anti-VEGF therapy is considered the gold standard for treating wet Age-related Macular Degeneration (wet

AMD), a condition marked by abnormal choroidal neovascularization (CNV) and the accumulation of retinal fluid primarily caused by the overproduction of VEGF-A. These therapies function by blocking VEGF-A, which in turn decreases vascular permeability, neovascular growth, and macular edema³⁵.

Key agents include:

- **Ranibizumab (Lucentis®):** This is a recombinant, humanized monoclonal antibody fragment (Fab) that specifically binds to VEGF-A, inhibiting its interaction with VEGFR-1 and VEGFR-2 receptors found on endothelial cells. It is typically given as a monthly intravitreal injection, although treat-and-extend protocols are frequently utilized to lessen the burden on patients. Clinical studies such as ANCHOR and MARINA have shown significant improvements in vision for patients³⁶.
- **Aflibercept (Eylea®):** This is a fusion protein that acts as a VEGF trap, binding to VEGF-A, VEGF-B, and placental growth factor (PlGF). It provides longer intravitreal durability compared to ranibizumab, allowing for bi-monthly or even extended dosing schedules following an initial loading phase. Aflibercept has demonstrated non-inferiority in the VIEW 1 and VIEW 2 trials and is often favored for patients who need less frequent dosing³⁵⁻³⁷.
- **Brolocizumab (Beovu®):** This is a single-chain antibody fragment that is smaller in molecular size than ranibizumab and aflibercept, enabling higher molar concentration delivery and deeper penetration into the retina. It was approved based on the HAWK and HARRIER trials, where Brolocizumab showed non-inferior efficacy with the benefit of 12-week dosing intervals. However, post-marketing surveillance has identified rare but serious cases of intraocular inflammation and retinal vasculitis, necessitating careful selection and monitoring of patients³⁸.

These agents have significantly altered the prognosis for wet AMD, yet challenges such as the frequency of injections, incomplete responders, and resistance issues remain to be addressed.

3.2. Steroids and Combination Therapies

While anti-VEGF therapy remains the primary treatment for wet AMD, there is ongoing research into corticosteroids and combination strategies due to their potential complementary effects and ability to lessen the treatment burden. Intravitreal corticosteroids, like triamcinolone acetonide, work by reducing inflammation, decreasing VEGF expression, and reinforcing the blood-retinal barrier. However, their application is often restricted because of side effects such as elevated intraocular pressure (IOP), glaucoma, and cataract development³⁹. Nevertheless, they may prove advantageous for patients who do not respond to anti-VEGF monotherapy or those with inflammatory aspects⁴⁰. Combination therapies are designed to address multiple pathogenic pathways at once. Some examples include:

- **Anti-VEGF + Steroids:** This combination may yield a synergistic effect by managing both angiogenesis and inflammation.
- **Anti-VEGF + Photodynamic Therapy (PDT):** PDT using verteporfin selectively damages neovascular tissue. When paired with anti-VEGF agents (as seen in the MONT BLANC and DENALI trials), there have been reports of enhanced lesion control and decreased injection frequency in specific patient groups³⁹.
- **Triple therapy (Anti-VEGF + PDT + Steroid):** This approach has been studied in cases of refractory wet AMD where standard dual therapies have not succeeded in controlling the disease.

Although combination regimens exhibit promise, the evaluation of their benefit-risk ratio, cost-effectiveness, and the necessity for tailored treatment protocols is ongoing in clinical practice⁴¹.

3.3. Emerging and Investigational Therapies

Given the constraints of existing treatments—such as the requirement for frequent intravitreal injections, inadequate responses in some patients, and the progressive nature of wet age-related macular degeneration (AMD)—extensive research is being directed towards the development of next-generation therapeutics. A particularly promising strategy involves long-acting delivery systems, exemplified by the Port Delivery System (PDS) with ranibizumab, which is a surgically implanted, refillable device designed to provide sustained intraocular drug release. The ARCHWAY trial revealed that a PDS refilled every 24 weeks was non-inferior to monthly intravitreal injections, significantly alleviating the treatment burden⁴¹⁻⁴².

Concurrently, gene therapy methods are gaining momentum, utilizing adeno-associated viral (AAV) vectors to introduce genes that encode anti-VEGF proteins directly into retinal cells. Agents such as RGX-314 and ADVM-022, which are currently in advanced clinical trials, aim to achieve long-term VEGF suppression with a single treatment, potentially offering a functional cure. Another innovative approach involves bispecific antibodies like faricimab, which simultaneously target VEGF-A and Angiopoietin-2 (Ang-2), both of which are crucial regulators of vascular instability. Clinical trials like TENAYA and LUCERNE have demonstrated that faricimab can extend dosing intervals up to 16 weeks without compromising efficacy⁴³. Furthermore, new agents under investigation include KSI-301, a high-durability antibody-biopolymer conjugate, integrin inhibitors such as ALG-1001 that disrupt pathological angiogenesis, complement pathway inhibitors aimed at addressing inflammation-mediated retinal damage, and siRNAs or small molecules like bevasiranib that inhibit VEGF production at the genetic level⁴³⁻⁴⁴. Together, these emerging therapies strive to enhance outcomes by improving efficacy, reducing injection frequency, and accommodating biological variability, thus progressing towards a more personalized and sustainable treatment approach for wet AMD⁴⁴.

In summary, the existing therapeutic approaches for wet AMD have greatly progressed, with anti-VEGF agents such as ranibizumab, aflibercept, and brolucizumab serving as the foundation of treatment. Additional methods that include corticosteroids, combination therapies, and exciting developments in long-acting delivery systems, gene therapies, and innovative biologics are broadening the treatment options. Collectively, these strategies seek to enhance visual outcomes, lessen the treatment burden, and provide more tailored and effective care for individuals with wet AMD.

4. OVERVIEW OF CLINICAL TRIAL PHASES FOR WET AMD

Clinical trials for Wet AMD are conducted in a systematic and regulated manner, progressing through four main phases—each aimed at assessing specific elements of a drug or therapy's effectiveness. Phase I is dedicated to evaluating safety, tolerability, and pharmacokinetics among a small cohort of healthy volunteers or affected patients. Following this, Phase II investigates initial efficacy, optimal dosing, and side effects within a slightly larger group of patients⁴⁵. Phase III trials are crucial, involving a significantly larger population to validate efficacy, track adverse reactions, and compare the experimental treatment against existing standards of care. Once regulatory approval is obtained, Phase IV, or post-marketing surveillance, continues to assess long-term safety and effectiveness in real-world clinical environments⁴⁵⁻⁴⁶. Each phase is essential in the drug development process, especially for Wet AMD, where visual outcomes, response durability, and injection frequency greatly impact clinical success. Additionally, the intricacies of ocular drug delivery and patient variability present unique challenges in trial design and phase transitions, requiring adaptive strategies and innovative endpoints⁴⁷.

4.1. Phase I–IV Trial Design

Clinical trials for wet Age-Related Macular Degeneration (AMD) are structured in a progressive and scientifically regulated manner, encompassing four distinct phases (Phase I to Phase IV), each targeting specific research goals. Phase I represents the initial stage and typically involves a small group of healthy volunteers or patients (usually between 20 and 80 individuals). In the case of ophthalmic disorders like wet AMD, patients are often recruited instead of healthy individuals due to ethical considerations⁴⁸. The main objective is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of the investigational drug, such as anti-VEGF (vascular endothelial growth factor) agents or gene therapies. Dose escalation is employed to determine the maximum tolerated dose (MTD) while minimizing adverse effects. Phase II trials aim to further explore the drug's efficacy, generally enrolling several hundred patients diagnosed with wet AMD. This phase assists in defining the optimal therapeutic dosage and treatment protocol. Researchers also begin assessing initial biological activity, such as the reduction of retinal fluid or enhancements in central macular thickness through Optical Coherence Tomography (OCT). While safety

monitoring persists, the emphasis shifts to determining whether the treatment shows sufficient promise to advance to larger-scale trials⁴⁹.

Phase III trials are crucial, large-scale, randomized controlled studies that involve hundreds to thousands of patients. These trials seek to validate the therapeutic efficacy, further assess adverse effects, and compare the new treatment against existing standards like ranibizumab, aflibercept, or brolucizumab⁵⁰. Achieving success in Phase III often results in regulatory approval from authorities such as the FDA (U.S.) or EMA (Europe). These trials usually encompass diverse populations and multiple clinical centers to improve the generalizability of the data. Phase IV trials, which take place after a drug has received market authorization, are referred to as post-marketing surveillance studies. They are designed to monitor long-term safety, effectiveness, and overall performance of the drug in the general population⁵¹.

4.2. Key Endpoints and Outcome Measures

In clinical trials for wet AMD, endpoints are meticulously chosen to represent significant clinical advancements and inform regulatory choices. The primary endpoint in the majority of trials is the alteration in Best-Corrected Visual Acuity (BCVA), typically assessed using the ETDRS (Early Treatment Diabetic Retinopathy Study) chart. A gain of ≥ 15 letters from the baseline over a defined duration (usually 6 or 12 months) is deemed a clinically meaningful improvement⁵². Visual acuity serves as a functional indicator, demonstrating how effectively a patient can see post-treatment and is directly linked to their quality of life. Secondary endpoints encompass anatomical results, especially the change in Central Retinal Thickness (CRT) evaluated through Spectral-Domain OCT, which delivers high-resolution cross-sectional images of the retina. A reduction in CRT signifies a decrease in retinal edema, fluid leakage, or the resolution of hemorrhage⁵³. Additional frequently utilized endpoints include the number and frequency of intravitreal injections, as newer treatments strive to alleviate the treatment burden by prolonging dosing intervals. Moreover, angiographic endpoints such as variations in choroidal neovascularization (CNV) size or leakage assessed through fluorescein or indocyanine green angiography are also employed. Trials may additionally integrate patient-reported outcome measures (PROMs) like the National Eye Institute Visual Function Questionnaire (NEI-VFQ-25), which evaluates the impact on daily life. Upcoming trials might incorporate exploratory biomarkers such as VEGF levels, inflammation indicators, or genetic variants to predict treatment responses⁵³⁻⁵⁴.

4.3. Patient Selection and Inclusion Criteria

Proper selection of patients is crucial for the validity, safety, and success of clinical trials focused on wet AMD. Inclusion and exclusion criteria are set to form a uniform patient group, reduce confounding factors, and safeguard vulnerable individuals⁵⁵. Common inclusion criteria for wet AMD studies typically require participants to be 50 years or older, with active, treatment-naïve subfoveal or

juxtafoveal CNV due to AMD, as confirmed by OCT and fluorescein angiography. A baseline BCVA ranging from 20/40 to 20/320 (or its equivalent) is often necessary to allow for detectable visual improvement or deterioration. Patients must be capable of providing informed consent and adhering to follow-up appointments⁵⁶.

Exclusion criteria generally eliminate individuals with other eye conditions that might affect the evaluation of efficacy—such as diabetic retinopathy, retinal vein occlusion, or significant cataracts. Those who have undergone previous intraocular surgery, have recently used investigational drugs, or suffer from systemic conditions like uncontrolled hypertension or coagulopathies may also be excluded⁵⁷. While stringent criteria are essential for maintaining internal validity, they can restrict external generalizability, a concern sometimes tackled in Phase IV trials or real-world observational studies⁵⁶⁻⁵⁸. Particular emphasis is placed on ensuring ocular stability, the absence of previous anti-VEGF treatment, and clear media for imaging purposes. Inclusion criteria also specify the type of lesion (classic, occult, or mixed CNV) and its size, which can influence drug effectiveness. Therefore, thorough patient screening is vital for achieving meaningful, reliable, and reproducible clinical outcomes in the development of therapies for wet AMD⁵⁹.

In summary, the phases of clinical trials for wet AMD are carefully organized to guarantee the safety, effectiveness, and long-term dependability of new therapies. Each phase—from the preliminary safety evaluations in Phase I to extensive efficacy assessments in Phase III and post-marketing monitoring in Phase IV—serves a crucial function in enhancing treatment protocols. With well-defined endpoints, rigorous patient selection criteria, and comprehensive outcome measures, these trials not only aid in obtaining regulatory approvals but also inform clinical decision-making and enhance patient care in the treatment of wet AMD⁵⁸⁻⁶⁰.

5. RECENT AND ONGOING CLINICAL TRIALS

Recent and ongoing clinical trials focused on wAMD demonstrate an increasing emphasis on creating therapies that offer enhanced efficacy, durability, and patient adherence. These studies investigate a variety of innovative approaches, such as longer-lasting anti-VEGF agents, gene therapies, sustained drug delivery systems, and combination treatments that target multiple pathological pathways⁶¹. Numerous current investigations seek to overcome the shortcomings of existing therapies—like the need for frequent intravitreal injections and less than optimal visual outcomes—by introducing new biologics, bispecific antibodies, and implantable devices⁶². Furthermore, adaptive trial designs and the integration of real-world data are being utilized more frequently to expedite regulatory approval and more accurately reflect patient responses⁶³. This section outlines significant investigational therapies and presents an overview of selected clinical trials that could transform the future treatment landscape for wAMD.

Table 1. List of clinical trials on Wet AMD with their details

Title	NCT Number	Phase	Study Type	Sponsor / Collaborator	Condition	Intervention	Start Date
ADVM-022 Gene Therapy (OPTIC)	NCT03748784	I	Open-label	Adverum Biotechnologies	Wet AMD	Intravitreal ADVM-022	Apr 2019
RGX-314 Suprachoroidal (AAVIATE)	NCT04514653	II	Randomized Seq.	Regenxbio		Suprachoroidal RGX-314	Sep 2020
RGX-314 Subretinal (ASCENT)	NCT05407636	III	Randomized				Jul 2022
RGX-314 Subretinal (ATMOSPHERE)	NCT04704921	II/III					Feb 2021
CMAB818 vs. Lucentis	NCT04884399	I	Comparative	(China biotech)		CMAB818 injection	Sep 2021
EYP-1901 vs. Aflibercept	NCT05381948	II	Randomized dbl-mask	EyePoint Pharma		Intravitreal EYP-1901	May 2022
OPT-302 + Ranibizumab (ShORe)	NCT04757610	III	RCT dbl-masked	Opthea		OPT-302 + ranibizumab	Feb 2021
OPT-302 + Aflibercept (COAST)	NCT04757636	III				Feb 2021	
KSI-301 vs Aflibercept (DAYLIGHT)	NCT04964089	II/III	RCT	Kodiak Sciences		Intravitreal KSI-301	Jul 2021
rAAV.sFlt-1 Gene Therapy	NCT01494805	I/II		(academic sponsor)		Subretinal rAAV.sFlt-1	Nov 2011
4D-150 Gene Therapy	NCT05197270	I/II		4D Molecular		Intravitreal 4D-150	Jan 2022
AIV007 Multi-TK Inhibitor	NCT04422899	I	Open-label	AiViva BioPharma		Intravitreal AIV007	Jul 2020
UBX1325 Bcl-xL Inhibitor	NCT05275205	II	RCT	Unity Biotechnology		Intravitreal UBX1325	Jul 2022
IBI302 Anti-VEGF/C3bispecific	NCT05403749	II		Innovent Biologics		Intravitreal IBI302	Jun 2022
Strontium-90 Brachytherapy + PRN	NCT02988895	II	Single-arm	Salutaris Medical		Episcleral Sr-90 + aflibercept	Nov 2016
D-4517.2 Subcutaneous TK-inhibitor	NCT05387837	I	Safety/PK	Ashvattha	Subcutaneous D-4517.2	Jun 2022	

This collection showcases the variety of therapeutic approaches currently in development from gene therapies designed for lasting, one-time effects, to bispecific proteins, small molecules, and even radiation-enhanced combination therapies. Collectively, they represent continuous efforts to lessen treatment burdens, enhance efficacy among different patient subgroups, and meet the unmet needs in the care of wet AMD ⁶⁴.

6. CURRENT CHALLENGES, FUTURE PERSPECTIVES AND RESEARCH DIRECTIONS

Despite notable progress in comprehending the pathophysiology of wet age-related macular degeneration (wAMD) and the advancement of anti-VEGF therapies, several significant challenges still impede the design, implementation, and outcomes of clinical trials in this area. A primary concern is patient heterogeneity, which results in variability in treatment responses and complicates the generalization of trial

findings ⁶⁵. Moreover, while visual acuity is commonly used as a primary endpoint, it may not adequately reflect improvements in a patient's functional vision or quality of life. The recruitment and retention of participants, particularly elderly patients with comorbidities, pose challenges due to strict inclusion criteria, frequent monitoring visits, and extended study durations ⁶⁴⁻⁶⁵. In addition, there is an absence of standardized imaging protocols and biomarkers that could offer more predictive or objective assessments of disease progression and therapeutic response. Regulatory and ethical issues also emerge concerning sham injections and placebo-controlled designs, especially when effective treatments are already available ⁶⁶. Finally, the substantial costs and lengthy timelines associated with wAMD trials restrict broader drug development and innovation, highlighting the necessity for adaptive trial designs, integration of real-world data, and patient-centered strategies to address these ongoing challenges ⁶⁷.

The changing landscape of clinical research in wAMD offers numerous opportunities to enhance current treatment approaches and address the shortcomings of existing clinical trial methods. The future of wAMD research is rooted in the integration of technological advancements, personalized medicine, and a comprehensive understanding of disease progression⁶⁸. Given that standard anti-VEGF therapies, while effective, necessitate frequent intravitreal injections and exhibit varied responses among patients, there is an urgent need to investigate long-acting formulations, sustained-release systems, and alternative delivery methods such as gene therapy, ocular implants, and port delivery systems. These innovations can significantly alleviate the treatment burden on both patients and caregivers, while also improving long-term adherence and visual outcomes⁶⁹.

A primary focus for future research is the creation and validation of new biomarkers capable of accurately predicting disease onset, tracking therapeutic responses, and distinguishing between responders and non-responders. Cutting-edge multimodal imaging techniques, such as optical coherence tomography angiography (OCTA), hyperspectral imaging, and adaptive optics, have the potential to provide non-invasive, real-time insights into retinal structure and vascular alterations. The integration of artificial intelligence (AI) and machine learning algorithms in the analysis of imaging data and electronic health records (EHRs) can further enhance diagnosis, improve patient selection, and customize treatment strategies based on individual disease characteristics⁶⁵⁻⁶⁹.

Moreover, future clinical trials should transition towards more adaptive, flexible, and patient-focused designs. Adaptive trial methodologies—such as Bayesian frameworks, seamless phase transitions, and dose-finding algorithms—enable real-time adjustments based on interim data, thereby enhancing trial efficiency and ethical standards. Decentralized clinical trials (DCTs), telemedicine integration, and remote monitoring are also essential components of this evolution⁶⁸⁻⁷⁰.

CONCLUSION

Wet age-related macular degeneration (wAMD) continues to be a major cause of visual impairment and blindness in older adults, posing an ongoing public health challenge globally. Over the last twenty years, the treatment landscape for wAMD has significantly evolved, especially with the introduction and widespread use of intravitreal anti-VEGF therapies. Although these treatments have enhanced visual outcomes for numerous patients, they have also exposed limitations such as the need for frequent dosing, treatment fatigue, varying patient responses, and concerns regarding cost and accessibility. Clinical trials have been crucial in enhancing our understanding of the disease and informing therapeutic choices; however, traditional trial designs often fail to capture the complete range of patient experiences, particularly in diverse and real-world settings. This review has underscored the current trends in wAMD trials, including the investigation of extended-release therapies, combination treatments, and

innovative biologics, as well as the increasing focus on integrating advanced imaging techniques, real-world data, and patient-reported outcomes into trial endpoints. It has also tackled significant challenges, such as the recruitment and retention of elderly patients, ethical dilemmas surrounding sham controls, the absence of predictive biomarkers, and the shortcomings of conventional endpoints like best-corrected visual acuity (BCVA), which may not sufficiently represent patients' quality of life or functional vision. To navigate these complexities, the future of wAMD clinical research must be rooted in innovation, personalization, and inclusivity. Adaptive trial designs, digital health technologies, AI-driven analytics, and collaborative engagement among multiple stakeholders are vital for modernizing clinical trial methodologies and enhancing the application of research findings in clinical practice.

LIST OF ABBREVIATIONS

wAMD: Wet age-related macular degeneration; **BCVA:** Best-corrected visual acuity; **VEGF:** Vascular endothelial growth factor; **RPE:** Retinal pigment epithelium; **CNV:** Choroidal neovascularization; **MAC:** membrane attack complex; **CFH:** Complement factor H; **PIGF:** Placental growth factor; **IOP:** Intraocular pressure; **PDT:** Photodynamic therapy; **AAV:** Adeno-associated viral; **OCT:** Optical coherence tomography; **CRT:** Central retinal thickness; **OCTA:** Optical coherence tomography angiography.

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