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Systematic Review

Do retinal implants provide long-term efficacy, safety and improve quality of life? A systematic review

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Abstract

Background: Retinal implants have emerged as interventions to partially restore functional vision such as light perception, motion detection or object localisation in patients with severe vision loss from degenerative retinal conditions, including retinitis pigmentosa (RP) and dry age-related macular degeneration (AMD).

Objectives: To evaluate the long-term efficacy, safety and quality of life (QoL) impact of retinal implants with ⩾1 year of follow-up.

Methods: Following PRISMA guidelines, a systematic search was conducted (31st July to 31st August 2024) in Web of Science, PubMed, Medline, Scopus, Cochrane Library and Embase, using the terms: ('retinal implant' OR 'retinal prosthesis') AND ('long-term' OR 'follow-up') AND ('efficacy' OR 'safety' OR 'quality of life'). No publication date restrictions were applied. Eligible studies were in English, involved human subjects with retinal degenerations, and reported ⩾1 year follow-up. Risk of bias was assessed using the Critical Appraisal Skills Programme (CASP) cohort study checklist for most studies, as they involved prospective follow-up without randomisation or control groups. The Joanna Briggs Institute (JBI) critical appraisal checklist for case series was applied to studies with a case series design. Narrative synthesis was applied.

Results: Thirteen studies met the inclusion criteria: 53.85% assessed epiretinal implants (Argus II), 30.77% subretinal (Alpha AMS and PRIMA), and 15.38% suprachoroidal (44 and 49-channel STS). Epiretinal implants improved visual function, with up to 89% better in SLT, 50%–56% in DOM, and 30%–40% reaching ⩾2.9 logMAR when activated. Subretinal implants enhanced light perception, localisation, and grating acuity (to 3.33 cycles/degree), with acuity of 20/460 and 20/550 in some cases. Suprachoroidal devices improved SLT, DOM and GVA. Adverse events were more frequent with epiretinal than other implant types. QoL outcomes improved, particularly in mobility, orientation, and daily tasks.

Conclusion: Retinal implants confer functional vision, but acuities remain below 20/200, and recipients continue to meet criteria for legal blindness. Given the high risk of bias, lack of controls and potential placebo effects, further high-quality evidence is needed to confirm their efficacy, safety and QoL impact.

Keywords: age-related macular degeneration (AMD), long-term efficacy and safety, quality of life (QoL), retinal implants, retinitis pigmentosa (RP)

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Introduction

Severe visual impairment and blindness are considered to be among the most feared disabilities worldwide.[1] According to the World Health Organization (WHO), more than two billion people globally experience some form of visual

impairment, including an estimated 217 million with moderate to severe impairment and approximately 36 million who are blind.[2,3] The International Statistical Classification of Diseases classifies individuals with visual acuity (VA) worse than 20/70 but equal to or better than 20/200 as having moderate visual impairment, and those with VA worse than 20/200 but equal to or better than 20/400 as having severe visual impairment. Individuals with VA worse than 20/400 in the better eye with best correction are classified as blind.[4,5] Common causes of blindness and visual impairment include macular degeneration, diabetic retinopathy, glaucoma, and cataract.[2] Approximately 50% of visual impairments globally result from retinal disorders.[6] Degenerative retinal conditions such as retinitis pigmentosa (RP), age-related macular degeneration (AMD), choroideremia, cone-rod dystrophy, and Stargardt disease result in severe vision loss and blindness due to a progressive loss of the retinal photoreceptors. In these conditions, damage gradually progresses in the outer retinal layers, whereas the inner retinal layers (including the bipolar and ganglion cells) remain primarily unaffected.[6–8] Unfortunately, the therapeutic possibilities and options for patients with advanced stages of these retinal degeneration conditions are limited and vision restoration is minimal.[1,7]

Retinal implants, also called 'retinal prostheses', have been developed and have emerged as promising interventions to partially restore functional vision in patients with severe vision loss due to degenerative disorders affecting the outer retinal layers.[6] Although research on retinal implants has increased recently, their development began several decades ago. Early research in visual prosthetics began in the 18th century, when Charles Le Roy reported that a blind patient experienced transient flashes of light (phosphenes) following electrical stimulation of the head.[7,9,10] In the 20th century researchers like Foester, Brindley, Lewin and Dobelle demonstrating that electrical stimulation of the visual cortex could produce visual sensation in blind individuals.[7,9,11–13] The first documented retinal prosthesis was reported by Tassicker in 1956, who implanted a photovoltaic array in the suprachoroidal space.[7,14] Since the 1990s, pioneers including Humayun, Greenberg, De Juan, Weiland, Liu, Eckmiller, Alan, Chow, Rizzo, Wyatt, and Zrenner have contributed significantly to the development of retinal implants, including epiretinal and subretinal designs. Their work has led to major advancements and the evolution of the field.[7,9]

Electronic retinal implants attempt to restore partial vision by replacing the function of damaged photoreceptors and electrically stimulating the remaining viable inner retinal layers.[15] These implants are typically classified according to their anatomical position: epi-retinal (on the retinal surface), sub-retinal (beneath the retina), suprachoroidal (in the suprachoroidal space) and intrascleral (within a scleral pocket).[7]

Key to the evaluation of retinal prostheses is the assessment of the efficacy, safety profile and impact of retinal implants on patients' quality of life (QoL). A multi-centre clinical trial by Stingl et al.[16] studied Alpha IMS subretinal implants in 29 participants with severe vision loss caused by retinal photoreceptor degeneration. The study found that visual function, mobility and activities of daily living were significantly improved post-implantation. Moreover, two ocular complications (retinal detachment and raised intra-ocular pressure) were reported but successfully treated. Interestingly, the study noted a reduction in the effectiveness of the implants over time in many participants. This decline in function underscores the importance of studying the long-term efficacy, safety profile and sustained improvements in patients' QoL related to various types of retinal implant.

A narrative review conducted by Rachitskaya and Yuan[17] focused exclusively on the Argus II retinal implants, describing their components, studies, challenges and future directions. The review concluded that this type of retinal implant has been effectively and safely used to restore partial, useful vision in patients with RP. However, the long-term reliability and durability of these implants remains unknown and their impact on the function and structure of the retina has yet to be fully understood.

A systematic literature review by Hallum and Dakin[15] evaluated the effectiveness of various types of retinal implant by assessing the visual outcomes post-implantation in patients with RP. This review found that retinal implants may be effective in terms of partially restoring vision in these patients. However, the review reported variable results in the included studies; some showed reasonable grating acuity, whereas others indicated

poor performance in the implanted participants. Furthermore, whilst retinal prostheses may improve light perception, the evidence regarding their efficacy in restoring motion perception and spatial vision remains unclear. Additionally, this review highlighted that, despite the encouraging results, there is a demand for high-quality evidence regarding the effectiveness of these implants. This aligns with more recent work by Ramirez et al.,[18] which reported that the long-term effectiveness and safety of these devices remain uncertain. Although Hallum and Dakin[15] systematically reviewed the efficacy of retinal implantations, they did not consistently focus on the long-term outcomes because they included studies with varying follow-up durations ranging from a few months to several years. Moreover, the included studies were limited to those published between 2015 and 2019. There was also a lack of safety profile data and direct QoL assessments. To the best of our knowledge, no systematic review in the previous literature has focused on long-term studies of retinal implants.

Consequently, there is a need to perform a comprehensive systematic literature review which evaluates and synthesises the available evidence regarding the efficacy of various types of retinal implant in terms of improving visual function, their safety profile, and their impact on the QoL of patients with severe vision loss over the long-term.

This systematic review aims to evaluate the long-term efficacy, safety and impact of various retinal implants on patients' QoL. Previous reviews have not fully addressed recent evidence or long-term follow-up outcomes. Therefore, this review seeks to fill that gap by including more recent studies and focusing on long-term outcomes. The findings may contribute valuable information to the field by supporting clinical practice and patient care, especially in selecting and managing different types of retinal prostheses for patients with significant visual loss. Furthermore, understanding the long-term benefits and limitations of these implants may help clinicians better manage patients' expectations and post-operative care. In addition, the outcomes of this review may influence policymakers' decisions with regards to financing and approving these prostheses. Finally, further research directions will be discussed based on the findings and limitations identified.

Methods

Systematic literature review protocol

The review was designed to answer the following question: Do various types of retinal implants provide long-term efficacy, safety and improvements in QoL for patients with severe vision loss? The review followed the PICO framework. The population (P) included patients with severe vision loss. The intervention (I) focused on various types of retinal implants, including epi-retinal, sub-retinal and suprachoroidal implants. The comparison (C) involved outcomes pre and post implantation or with and without the implant. The outcomes (O) examined long-term efficacy, safety and improvements in QoL.

The components of the review question were grouped into three main domains: efficacy, safety profile and impact on QoL. Each domain included several questions that helped focus the data extraction and synthesis (Supplemental Appendix 1).

The primary objectives of this review were to determine the effectiveness of various retinal implant technologies in improving vision over a long-term period (1 year or more) and to assess their safety profile by evaluating the types and incidence of adverse events and complications. The secondary objective was to evaluate the impact of these implants on the QoL of patients with severe vision loss.

Inclusion criteria. The review included a broad range of study designs: randomised controlled trials (RCTs), clinical trials, prospective or retrospective cohort studies, case-control studies, longitudinal observational studies, and case series or reports. Eligible studies involved human subjects aged 18 years or older who experienced severe vision loss due to retinal diseases such as RP, AMD or similar disorders. The studies evaluated various types of retinal implants, including, epiretinal, subretinal and suprachoroidal devices.

To be included, studies needed to report on the following outcomes: long-term efficacy measured by visual function assessments such as visual acuity; safety, as indicated by the types and incidence rates of adverse events or complications; and impact on QoL as assessed by patient-reported outcomes, functional assessments, or vision-related activities. Studies were only included if

they reported outcomes with a minimum follow-up duration of 1 year. Only English-language studies published within the field of ophthalmology were considered.

Exclusion criteria. Studies were excluded if they were review articles or systematic reviews, grey literature such as conference abstracts, non-English language publications, animal studies, or if they reported only short-term outcomes with less than 1 year of follow-up.

Search methods

From 31st July 2024 to 31st August 2024, a search was conducted using the following electronic databases: Web of Science, PubMed, Medline, Scopus, Cochrane Library and Embase. The search terms were identified through preliminary searches and aligned with the PICO framework to address the stated review objectives.[19]

The search terms included were:

S1: Retinal implants
S2: ('S1' OR 'retinal prosthesis')
S3: ('S2') AND ('long-term 'OR follow-up')
S4: ('S3') AND ('efficacy' OR 'safety')
S5: ('S4 OR 'quality of life')

These keywords were combined using Boolean operators to broaden or narrow the search, ensuring a comprehensive and precise result.[20] The final keywords used were: ('retinal implant' OR 'retinal prosthesis') AND ('long-term' OR 'follow-up') AND ('efficacy' OR 'safety' OR 'quality of life'). Minor modifications to the search syntax were made to suit the advanced search options of each database.

Additionally, a manual search of the reference lists of eligible studies was undertaken to identify any additional relevant papers. The results from these six databases are presented in Supplemental Appendix 2.

Study selection

Filters were applied in the databases to refine the search results, limiting the language to English and restricting the participants to human subjects. Duplicate records were removed using Mendeley Reference Manager (Version 2.122.0) and manually by the reviewer. The screening process was conducted in two stages: title and abstract screening, followed by full-text screening to determine inclusion and progression to the critical appraisal process.

Risk of bias assessment

Each of the studies that progressed to this stage was critically appraised using the CASP checklists or the JBI critical appraisal checklists, depending on the study design. The CASP cohort study checklist was used for most of the studies because they involved observing and following up with a single group of participants (without randomisation or a control group) prospectively after the retinal prosthesis implantation to assess outcomes (see Tables 1 and 2). Although the study designs were not typically cohort studies, which usually investigate the association between exposure to a risk factor and the incidence of an outcome, the lack of a control group or randomisation in these interventional clinical trials makes the CASP cohort study checklist an appropriate means of appraisal.[21,22]

The study of Arevalo et al.[23] was critically appraised using the JBI critical appraisal checklist for case series (see Table 3) because its study design was interventional case series.[24] All of the included papers were assessed against the most common risks of bias, including selection bias, performance bias, attrition bias, detection bias and reporting bias.[25]

Data extraction

The data collection form in the current study was adapted from another similar systematic review by Hallum and Dakin[15] and modified to suit all of the papers included in this review. In addition, to ensure the collection of all critical data, the reviewer referred to Chapter Five of the Cochrane Handbook for Systematic Reviews.[26]

The following data were extracted from each included study: title, authors, publication year and journal, DOI, study design, study aim, inclusion and exclusion criteria, recruitment dates, sample size, participants' demographic data, follow-up duration, outcomes, intervention type, implanted eye, statistical tests and key findings.

All the processes of this systematic review were conducted by a single reviewer, as it was not possible to have two or more reviewers given that this work was part of a master's degree dissertation.

Table 1. The CASP cohort study checklist.

Assessment questions	Ho et al.[37]	da Cruz et al.[38]	Fujikado et al.[29]	Stingl et al.[40]	Duncan et al. [39]
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes
Have the authors identified all of the important confounding factors?	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell
Have they taken the confounding factors into account in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes
Was the follow-up of subjects sufficiently complete?	Yes	No	Yes	No	Yes
Was the follow-up of subjects sufficiently long?	Yes	Yes	Yes	Yes	Yes
What are the results of this study?	See the data extraction forms in the Appendices				
How precise are the results?	Moderate	Moderate	Moderate	Moderate	Moderate
Do you believe the results?	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Cannot tell	Yes	Yes
Do the results of this study fit with the other available evidence?	Yes	Yes	Yes	Yes	Yes
What are the implications of this study in practice?	Limited: Small sample size	Limited: Small sample size	Very limited: Small sample size; Pilot study	Limited: Small sample size Interim study	Limited: Small sample size
Decision	Include	Include	Include	Include	Include

Registration

This systematic review was not registered in a review registry such as PROSPERO.

Results

The search yielded a total of 222 papers from various databases: Web of Science ($n=27$), PubMed ($n=9$), Medline ($n=23$), Scopus ($n=76$), Cochrane Library ($n=6$) and Embase ($n=81$). After removing 105 duplicate papers, 117 unique papers remained for eligibility screening. After screening the titles and abstracts, 96 papers were excluded because they were irrelevant to the review aim or did not satisfy the inclusion criteria. Among these, the EPI-RET3 study by Menzel-Severing et al.[27] was excluded because the implanted prostheses were explanted 4 weeks after implantation, and the participants were followed up 2 years later after device removal. In addition, a clinical study investigating the IMIE 256 retinal implant was excluded due to a short follow-up duration of only 3 months.[28] Of the remaining 21 papers, 7 were excluded after reading the full text because they were irrelevant to the outcomes of interest or contained insufficient detail. Therefore, 14 papers were included and progressed to the critical appraisal process. The PRISMA flow diagram illustrates the search process, detailing the number of studies

Table 2. The CASP cohort study checklist for the remaining studies.

Assessment questions	Edwards et al.[41]	Schaffrath et al.[35]	Palanker et al.[59]	Stanga et al.[33]	Delyfer et al.[42]	Petoe et al.[30]	Muqit et al.[34]
Did the study address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the cohort recruited in an acceptable way?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the exposure accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the outcome accurately measured to minimise bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Have the authors identified all of the important confounding factors?	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell	Cannot tell
Have they taken the confounding factors into account in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the follow-up of subjects sufficiently complete?	No	No	Yes	No	Yes	Yes	No
Was the follow-up of subjects sufficiently long?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
What are the results of this study?	See the data extraction forms in the Appendices						
How precise are the results?	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Do you believe the results?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do the results of this study fit with the other available evidence?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
What are the implications of this study in practice?	Very limited: Small sample size	Limited: Small sample size	Very limited: Small sample size; First in human	Very limited: Small sample size	Limited: Small sample size	Very limited Small sample size; Interim study	Very limited: Small sample size
Decision	Include	Include	Include	Include	Include	Include	Include

identified, screened, excluded and included at each stage (see Figure 1).

Following the quality assessment and critical analysis, one study was excluded due to its high risk of bias and poor overall quality (Supplemental Appendix 2). The final decision was made to include 13 of the studies, and these progressed to the data extraction stage. The completed data extraction forms for all 13 studies are presented in Supplemental Appendix 3.

Characteristics of included studies

The characteristics of the included studies are summarised in Table 4. Most of the included

studies were conducted in the US and Europe. The exceptions were the studies of Fujikado et al.,[29] Arevalo et al.,[23] and Petoe et al.,[30] which were conducted in Japan, Saudi Arabia, and Australia, respectively. It was unclear whether that was because the eligible studies were limited to the English language or because the companies that developed these retinal implants were based in Germany, France, Japan or the United States.[7] Moreover, it was unclear if this was due to the target population of RP patients, where this condition has the highest prevalence among European countries, especially in Germany.[31] All of the included studies are prospective clinical trials except for one study by Arevalo et al[23] which is a retrospective interventional case study. All of the included studies investigated retinal implants in participants with RP except for three studies (Palanker et al.,[32] Stanga et al.,[33] and Muqit et al.[34]) in which their enrolled subjects had advanced dry AMD with geographic atrophy (GA). All of the studies had small sample sizes, ranging from three in Fujikado et al.[29] to 47 in Schaffrath et al.[35] In addition, the mean age of the subjects in all of the studies was approximately the same, except for two studies (Stanga et al.,[33] and Muqit et al.[34]), which had the highest average age of 75 years. This can be explained by their study population with AMD, which usually affects the older population.[36] Conversely, the study by Arevalo et al.[23] had the youngest average age of 41.3 years. The baseline vision shows that all of the included studies enrolled participants with profound visual loss or blindness. Furthermore, four studies (Ho et al.,[37] da Cruz et al.,[38] Duncan et al.,[39] and Petoe et al.[30]) had a higher percentage of male than female participants.

The included studies can be categorised based on the type of intervention or the site of the implantation: seven studies investigating epiretinal implants; four studies investigating subretinal implants and two studies investigating suprachoroidal implants (see Table 5). This variation in the type of intervention played a role in the heterogeneity of the studies. The comparison in most of the studies was post-implantation within-participant controls between the implanted eye and fellow eye and the implant turned on versus off, except for two studies (Duncan et al.,[39] and Stanga et al.[33]) which compared the visual function pre- and post-implantation.

The protocol of the current systematic review pre-defined the follow-up period for at least 1 year (12 months) to address the long-term aim. The included studies' follow-up durations ranged from 12 months to 60 months.

Table 3. The JBI critical appraisal checklist for case series.

Assessment questions	Arevalo et al.[23]
Were there clear criteria for inclusion in the case series?	Yes
Was the condition measured in a standard, reliable way for all of the participants included in the case series?	Yes
Were valid methods used to identify the condition for all of the participants included in the case series?	Yes
Did the case series have consecutive inclusion of the participants?	Yes
Did the case series have complete inclusion of the participants?	Yes
Was there clear reporting of the demographics of the participants in the study?	Yes
Was there clear reporting of the participants' clinical information?	Yes
Were the outcomes or follow-up results of the cases clearly reported?	Yes
Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?	Yes
Was the statistical analysis appropriate?	Unclear
Decision	Include

The included studies measured at least two of the pre-defined outcomes, except for that of Duncan et al.,[39] which only included a QoL assessment, as shown in Table 6. The current review included Duncan et al.'s[39] study because it had the same trial registration number as Ho et al.,[37] which measured the other outcomes.

Risk of bias assessment

The included papers were assessed against the most common risks of bias, including selection bias, performance bias, attrition bias, detection bias and reporting bias.[25]

Source of bias in the included clinical trials. The trials of Ho et al.,[37] da Cruz et al.,[38] Fujikado et al.,[29] Stingl et al.,[40] Duncan et al.,[39] Edwards et al.,[41] Schaffrath et al.,[35] Palanker et al.,[32] Stanga

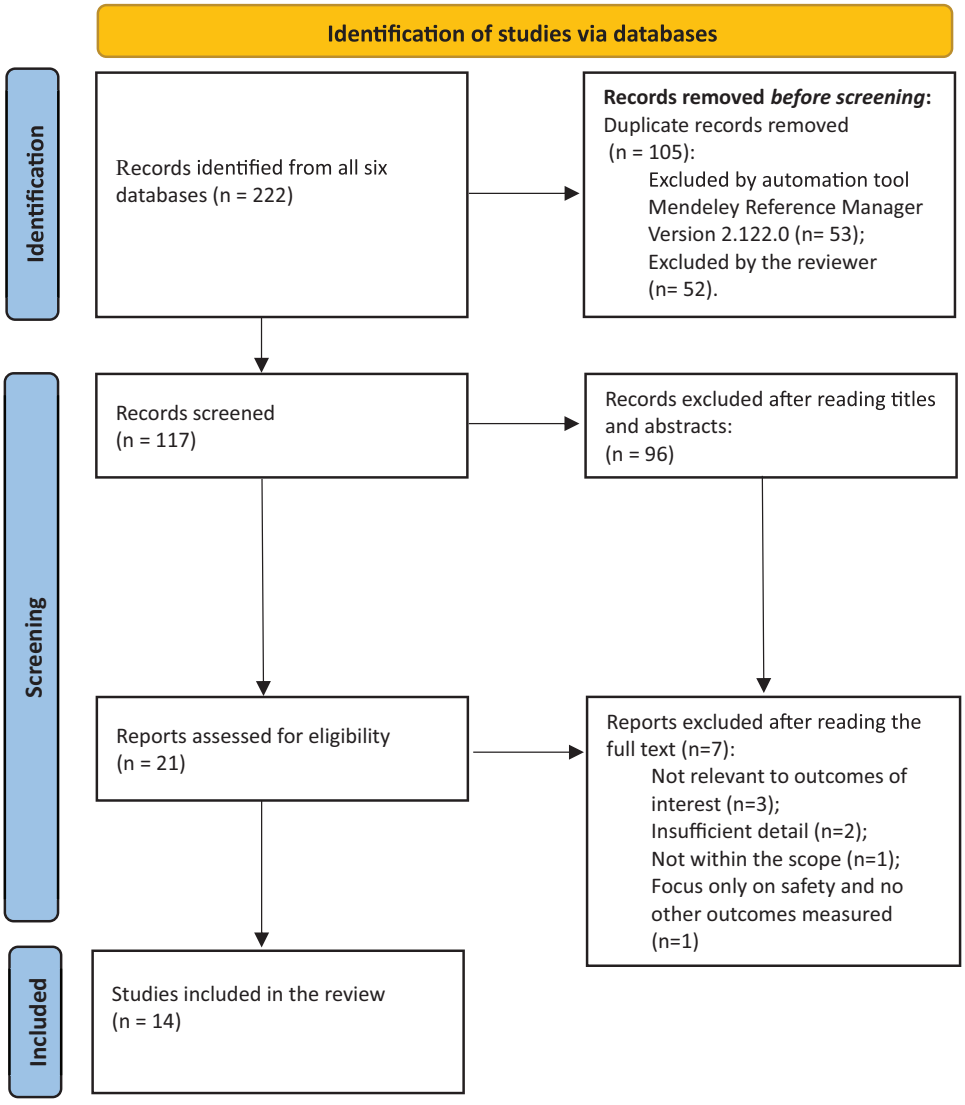

Figure 1. PRISMA flow diagram of the study selection process.

et al.,[33] Delyfer et al.,[42] Muqit et al.,[34] and Petoe et al.[30] were judged to have low-to-moderate selection bias due to their small sample sizes and lack of randomised control groups. These factors limited the strength of the studies' conclusions and the generalizability of their findings to wider groups of visually impaired individuals. However, some of the studies justified the small sample sizes by pointing out the rarity of the RP condition.[37–39] All 12 trials had well-defined inclusion and exclusion criteria which helped to reduce some aspects of selection bias.[43] In addition, the comparators were within-subject controls between implants on and off or between pre- and post-implant, thereby ensuring no differences in the baseline characteristics.

Performance bias occurs when the study groups are treated systematically differently or when the participants' behaviour varies due to their awareness of the assigned interventions.[44] Therefore, this risk of bias can be minimised by blinding the participants or researchers to the intervention received. Such masking helps to reduce the risk of the outcomes being influenced by their knowledge of the interventions. However, masking or blinding is not always feasible, such as in cases where the participants are required to undergo significant surgery.[25] In the trials included in the current systematic review, blinding was not feasible because of the flashes or auditory cues evoked by the implants, so the participants and researchers were aware of whether or not the retinal

Table 4. Characteristics of the included studies.

Study	Design	Sample size	Mean age (years)	Male/ female	Baseline vision	Follow-up duration (months)	Intervention	Comparator
Ho et al.[37]	Single-arm, prospective, unmasked clinical trial	30	58	21/9	BLP ($n=29$), NLP ($n=1$)	36	The Argus II Retinal Prosthesis System: **Epiretinal implant.**	Implanted eye versus fellow eye; system on versus system off.
da Cruz et al.[38]	Prospective, multi-centre, single-arm clinical trial	30	58	21/9	BLP ($n=29$), NLP ($n=1$)	60	The Argus II Retinal Prosthesis System: **Epiretinal implant.**	Within-patient controls; implant on versus off.
Fujikado et al.[29]	Single-arm, prospective, unmasked pilot clinical trial	3	56	2/1	LP ($n=2$), HM ($n=1$)	12	49-channel STS: **Suprachoroidal implant.**	Implant on versus off.
Stingl et al.[40]	Prospective clinical trial	15	55.2	5/10	LPWP ($n=14$), NLP ($n=1$)	12	Retina implant Alpha AMS: **Subretinal implant.**	Implant on versus off.
Duncan et al.[39]	Single-arm, prospective, unmasked clinical trial	30	58.3	21/9	Worse than 2.9 logMAR in both eyes	36	The Argus II prosthesis: **Epiretinal implant**.	Baseline versus post-implant follow-up measurements or implant on versus off.
Edwards et al.[41]	Prospective, single-arm, investigator-sponsored interventional clinical trial	6	53	1/5	Non-useful LP or NLP	12	The Alpha AMS device: **Subretinal implant.**	Within-participant control; implant on versus off.
Schaffrath et al.[35]	Multi-centre, post-approval, single-arm, clinical trial	47	56	27/20	LP	12	The Argus II retinal prosthesis: **Epiretinal implant.**	Within-subject control; implant on versus off.
Palanker et al.[32]	First-in-human clinical trial	5	n.d.	n.d.	Mean of baseline vision was logMAR of 1.48 or 20/600	12	PRIMA implantation: **Subretinal implant.**	System on versus off.
Stanga et al.[33]	Single arm, non-randomised, controlled feasibility study at a single site	5	75	2/3	n.d. (inclusion criteria: HM or worse in the study eye)	12	The Argus II Retinal Prosthesis System: **Epiretinal implant.**	System on versus off; implanted eyes versus fellow eyes; pre-surgery versus post-surgery performance.
Arevalo et al.[23]	Retrospective, interventional case series	10	41.3	7/3	LP ($n=5$), BLP ($n=5$)	Mean follow-up duration was 2.1 years	The Argus II Retinal Prosthesis System: **Epiretinal implant.**	System on versus off.

(Continued)

Table 4. (Continued)

Study	Design	Sample size	Mean age (years)	Male/ female	Baseline vision	Follow-up duration (months)	Intervention	Comparator
Delyfer et al.[42]	Prospective, multi-centre, single-arm, post-approval study	18	56	11/7	BLP in all cases	24	Argus II retinal prosthesis: **Epiretinal implant.**	Within-patient controls; system on versus off.
Petoe et al.[30]	Phase II, prospective, single-centre, interim clinical trial	4	53.8	3/1	LP	13	Bionic Vision Technologies Second-Generation (44-Channel)**: Suprachoroidal implant**	Within-subject comparison: device on versus off (with scrambled condition for some tasks)
Muqit et al.[34]	Feasibility clinical trial	5	74.8	2/3	Mean of baseline vision was logMAR of 1.48 or 20/600	48	PRIMA implantation: **Subretinal implant.**	System on versus off across participants.

Bold text indicates the implantation site of the retinal implants (epiretinal, subretinal, or suprachoroidal).
BLP, bare light perception; HM, hand motion; LogMAR, logarithm of the minimum angle of resolution; LP, light perception; LPWP, light perception without projection; n.d., no data; NLP, no light perception.

prostheses were switched on. This may introduce performance bias because their knowledge of the status of the implants could influence their behaviours, thereby motivating them to report better when the implant was on as a placebo effect.[42,45] In one trial by Petoe et al.,[30] a scrambled stimulation condition was included for some visual function assessments (the location and motion discrimination tasks), in which the implant remained active but the mapping between visual field locations and specific electrodes was re-randomised every few seconds. This technique helped determine whether improvements in performance were due to the implant providing accurate spatial information or to non-visual guessing and placebo effects, by comparing results between the normal and scrambled conditions. Moreover, participants were blinded to whether the test condition was scrambled or normal, but not to when the implant was deactivated. Therefore, the risk of performance bias was reduced in this trial.

Detection bias may arise if the evaluators and participants cannot be masked. This bias describes systematic differences in how outcomes are measured. The assessors of the included trials were aware of whether or not the implants were active, which could unconsciously affect how they measured the outcomes, especially the subjective ones, such as QoL evaluation. However, using clinical tools such as visual acuities for visual function outcomes helped to minimise this bias risk.[25]

Attrition bias occurs when participants withdraw or miss follow-up measurements during the trial, leading to incomplete outcome data.[25,46] All prospective clinical trials should report and document any participants' loss to follow-up or dropout during the studies and explain the reasons for this. This helps to minimise the risk of bias and helps the reader to evaluate the studies' validity and reliability.[47] Attrition rates were low in studies of Ho et al.,[37] Duncan et al.[39] and Delyfer et al.[42] where only one participant out of 30, 30 and 18, respectively, did not complete the trial. This minor rate of attrition was well reported and explained, thereby reducing the risk of attrition bias and indicating that the results were still valid. Moreover, as a percentage, this accounted for just 3%–5% of the enrolled participants, which means that the risk of attrition bias was not a concern.[48] In contrast, the studies of Stingl et al.,[40] Edwards et al.,[41] Schaffrath et al.,[35] Stanga et al.[33] and Muqit et al.[34] demonstrated

Table 5. Efficacy, safety and QoL from the included studies.

Paper	Implant's type	Number of subjects (disease)	Efficacy: visual functions*	Safety profile	QoL/functional vision outcomes*	Notes
Ho et al.[37]	**(Argus II), epiretinal implant**	30 (RP, CHM)	**SLT:** 89% ($p < 0.05$) **DOM:** 55.6% ($p < 0.05$) **GVA:** 33.3% ($p < 0.05$)	23 SAEs among 11 subjects. One explant.	**DT**: 54.2% versus 19% ($p < 0.05$) **LT:** 67.9 versus 14.3% ($p < 0.05$) **FLORA:** 65.20% (positive or mildly positive).	Subjects were able to perform better with the system on than off.
da Cruz et al.[38]	**(Argus II), epi retinal implant**	30 (RP, CHM)	**SLT:** 80.9% ($p < 0.05$) **DOM:** 50% ($p < 0.05$) **GVA:** 38.1% ($p < 0.05$)	24 SAEs among 12 patients. Two implant failures. Three explants.	**DT:** 52% versus 23% ($p < 0.05$) **LT:** 66% versus 17% ($p < 0.05$)	Patients were able to perform significantly better with the system on than off.
Duncan et al.[39]	**(Argus II), epi retinal implant**	30 (RP)	n.d.	n.d.	Significant improvement in three dimensions: injury, life and roles in patients with affected QoL at baseline. The other dimensions (except friendships) improved but were statistically insignificant.	Argus II can result in significant sustained and long-term improvement in QoL.
Schaffrath et al.[35]	**(Argus II), epi retinal implant**	47 (RP, CHM, CRD)	**SLT:** 46% **DOM:** 35.4%. As a group, patients' accuracy was not significantly improved when system was on versus off. **GVA:** More patients had measurable acuity at or better than 2.9 logMAR with implant on versus off.	51 nonserious AEs among 23 patients. 13 SAEs among 12 patients were related to the device or procedure. Two explants.	n.d.	When averaged across the group, patients' accuracy at SLT appeared better with the system on versus off.
Stanga et al.[33]	**(Argus II), epi retinal implant**	5 (AMD)	**SLT:** One patient had significantly better performance with the system on versus off at two visits. **DOM:** Two patients had significantly better performance with system on versus off at one visit. **GVA:** No significant difference with system on versus off.	Seven AEs. Four out of seven were SAEs related to the device or procedure.	**FLORA:** 80% (positive or mildly positive).	AMD patients with GA can achieve visual benefits from epiretinal implantation.
Arevalo et al.[23]	**(Argus II), epi retinal implant**	10 (RP)	80% of patients exhibited significant improvement in visual function tests with the system on relative to off. **SLT:** Mean error with system on versus off (8.83 vs 16.11, $p < 0.05$). **DOM:** Mean error with system on versus off (81.32 vs 90.60, $p > 0.05$). **GVA:** Nine out of ten patients had GVA of 2.9 or 3.0 LogMAR post-implantation.	3 AEs.	All patients exhibited improvement in functional vision by achieving the following: Locating a bright light on the ceiling. Detecting/avoiding obstacles. Detecting people in front of them in the majority of cases.	Patients' performance was significantly better with the system on than off.

(Continued)

Table 5. (Continued)

Paper	Implant's type	Number of subjects (disease)	Efficacy: visual functions*	Safety profile	QoL/functional vision outcomes*	Notes
Delyfer et al.[42]	**(Argus II), epi retinal implant**	18 (RP)	**SLT:** Performance was better with the system on. **DOM:** As a group, patients' accuracy was not significantly improved when the system was on versus off. Mean error with system on versus off (approximately 60 vs 70, $p > 0.05$). **GVA:** More patients had measurable acuity at or better than 2.9 LogMAR with implant on versus off.	21 AEs among 12 patients. 8/21 were related to the device or procedure. Two out of eight were SAEs.	**FLORA:** 71% (positive or mildly positive). **Orientation:** 67%. **Mobility:** 80%. **ADLs:** 58%.	Most of the patients benefited from the implant and approximately 50% exhibited improvements in functional vision and well-being.
Stingl et al.[40]	**(Alpha AMS), subretinal implant**	15 (RP, CRD).	**Light perception:** 100% versus 17% ($p < 0.05$). **Light localisation:** At month 12, 85% versus 0% ($p < 0.05$). Performance was better with the system on versus off at one, two, 3 and 12 months ($p < 0.05$). **Motion detection:** Two participants achieved a pass level when the implant was on at one out of 11 months. **BaGA:** Performance was better with the implant on. **Landolt-C VA:** 20/546 and 20/1111 were achieved in two patients.	Eight SAEs among four patients. Two device failures. Two explants.	**ADLs:** In detection and localisation tasks, seven out of eight patients performed significantly better with the system on than off. **Hand-eye coordination:** Performance was significantly better with the system on than off at months 2 and 12 ($p < 0.05$).	The durability of the Alpha AMS appeared to be longer than that of the Alpha IMS. This system demonstrated an ability to restore some limited vision to blind patients.
Edwards et al.[41]	**(Alpha AMS), subretinal implant**	6 (RP)	**Light perception:** 100% versus 0% ($p < 0.05$). **Light localisation:** At month 12, 100% versus 0% ($p < 0.05$). **Motion detection:** 0% of the participants achieved the pass level for both the on and off status of the implants. **BaGA:** Performance was better with the implant on.	Five AEs. Four out of five were related to the device. Two explants.	**ADLs:** Five patients could only locate shapes and tableware items when the implants were on. Other findings were mentioned in the results section. **IMQ:** The implant in three subjects positively affected the activity of walking in familiar areas.	The Alpha AMS achieved superior longevity than the Alpha IMS. Visual performance improved in 83% of subjects.
Palanker et al.[32]	**(PRIMA), subretinal implant**	5 (AMD)	**Light perception in the scotoma area:** 100% versus 0%. Landolt-C VA: Three patients had measurable VA ranging from 20/460 to 20/550 post-implant.	Three intraoperative complications.	n.d.	Visual sensitivity was restored in each patient's previous scotoma area.

(Continued)

Table 5. (Continued)

Paper	Implant's type	Number of subjects (disease)	Efficacy: visual functions*	Safety profile	QoL/functional vision outcomes*	Notes
Muqit et al.[34]	**(PRIMA), subretinal implant**	5 (AMD)	**Light perception in the scotoma area:** 100% versus 0%. ETDRS VA: Improved with zoom in all subjects by 32 letters from the baseline ($p < 0.05$).	Four SAEs among five patients.	n.d.	No decline in the natural peripheral vision was noted during the study period.
Fujikado et al.[29]	**(49-channel STS), supra-choroidal implant**	3 (RP, STGD)	**SLT:** Performance was better with the system on during the entire study period ($p < 0.05$) in one patient. This was observed in another patient but only at month 1. No significant difference was noted at all in the third patient.	Three AEs.	**Mobility test:** Patient performance was significantly better with the system on versus off in only two patients: one at nine and 11 months and the other at 2, 5, and 8 months. **Table test:** Two out of three patients performed significantly better with the system on versus off: one at 6 months postoperatively and the other during the entire study period.	Visual function outcomes were better in cases with implants closer to the fovea.
Petoe et al.[30]	**(44-Channel), suprachoroi-dal implant**	4 (RP)	**SLT:** 100% ($p < 0.001$) **DOM:** 50% ($p < 0.001$) **GVA:** 50% ($p < 0.05$)	**SAEs:** None **Mild post-operative events:** 3 No explants	**MDT:** 75% ($p < 0.001$) **Tabletop:** 100% for localising ($p < 0.001$ for 75% and $p < 0.01$ for 25%). 50% for identification ($p < 0.05$) **Obstacle avoidance:** 75% ($p < 0.01$-0.001) **FLORA:** Positive impact (orientation tasks and ADLs) **IVI-VLV:** Stable for emotional well-being in 3/4, decline in 1/4.	Functional vision, ADLs, and QoL improved with the suprachoroidal implant, and no SAEs were documented.

*Results were presented as the percentage of the participants who performed better with the implant turned on versus turned off.
Bold values is used only for visual emphasis to distinguish implant types and names and test abbreviations.
ADLs, activities of daily living; AEs, adverse events; AMD, age-related macular degeneration; BaGA, basic grating acuity; CHM, choroideremia; CRD, cone rod dystrophy; DOM, direction of motion; DT, door task; ETDRS, early treatment of diabetic retinopathy study; FLORA, functional low-vision rated assessment; GVA, grating visual acuity; IMQ, independent mobility questionnaire; IVI-VLV, the Impact of Vision Impairment – Very Low Vision questionnaire; LogMAR, logarithm of the minimum angle of resolution; LT, line task; MDT, modified door task; n.d., no data; QoL, quality of life; RP, retinitis pigmentosa; SAEs, serious adverse events; SLT, square localisation test; STGD, Stargardt disease; VA, visual acuity.

Table 6. Outcomes of the included studies.

Study	Outcomes
Ho et al.[37]	• Visual function assessments (SLT, DOM and GVA). • Functional vision outcomes (line task (LT) and door task (DT)). • Safety profile (adverse event evaluation). • QoL assessment (FLORA).
da Cruz et al.[38]	• Visual function assessments (SLT, DOM and GVA). • Functional vision outcomes (LT and DT). • Safety profile (adverse event evaluation).
Fujikado et al.[29]	• Visual function assessments. • Safety profile (adverse event evaluation). • Functional vision outcomes (mobility and table tests).
Stingl et al.[40]	• Visual function assessments (BaLM, BaGA and Landolt-C VA). • Safety profile (adverse event evaluation). • Functional vision outcomes (ADLs and hand-eye coordination).
Duncan et al.[39]	• QoL assessment (VisQoL).
Edwards et al.[41]	• Visual function assessments (BaLM, BaGA and Landolt-C VA). • Safety profile (adverse event evaluation). • Functional vision outcomes (ADLs and clock face recognition). • IMQ.
Schaffrath et al.[35]	• Visual function assessments (SLT, DOM and GVA). • Safety profile (adverse event evaluation).
Palanker et al.[32]	• Visual function assessments. • Safety profile (adverse event evaluation).
Stanga et al.[33]	• Visual function assessments (SLT, DOM and GVA). • Safety profile (adverse event evaluation). • QoL assessment (FLORA).
Arevalo et al.[23]	• Visual function assessments (SLT, DOM and GVA). • Safety profile (adverse event evaluation). • Functional vision assessments (orientation and mobility)
Delyfer et al.[42]	• Visual function assessments (SLT, DOM and GVA). • Safety profile (adverse event evaluation). • QoL assessment (FLORA).
Petoe et al.[30]	• Visual function assessments (SLT, DOM, and GVA). • Functional vision outcomes (Modified door task (MDT), tabletop, and obstacle avoidance. • Safety profile (adverse event evaluation). • QoL assessment (FLORA and IVI-VLV).
Muqit et al.[34]	• Visual function assessments. • Safety profile (adverse event evaluation).

ADLs, activities of daily living; BaGA, basic grating acuity; BaLM, basic light and motion; DOM, direction of motion; FLORA, functional low-vision rated assessment; GVA, grating visual acuity; IVI-VLV, the Impact of Vision Impairment – Very Low Vision questionnaire; SLT, square localisation test.

significantly higher attrition rates of 46.7%, 66.7%, 44.7%, 40% and 40% of their participants, respectively, who withdrew their consents or did not complete the full duration of follow-up. These significant attrition rates may introduce attrition bias because those who did not complete the study may differ from those who remained in the trials.[49] However, all of these studies clearly

reported the number of subjects who completed the entire process in their reports. Similarly, da Cruz et al.[38] reported the safety findings for 27 of the 30 participants because three subjects' devices were removed. Furthermore, they reported visual function performance findings for 20 to 21 of their 30 subjects and explained why. Attrition bias was not a concern in the three remaining studies by Fujikado et al.,[29] Palanker et al.,[32] and Petoe et al.[30] because all enrolled participants completed the trials. However, there were a few missing data points in the trial by Petoe et al.[30] for some tasks, but the reasons were clearly documented, which limited the risk of attrition bias.

Reporting bias occurs when published trials fail to transparently report insignificant outcomes or unfavourable findings.[50] This bias was minimised in all of the included trials because the authors reported the serious and non-serious adverse events, the technical failures of the implants and any unsuccessful implantations.

Sources of bias in the case series. Selection bias was considered in the included interventional case series study by Arevalo et al.[23] due to the small number of included cases, thereby limiting the applicability of the results beyond the specific population studied. Although strict inclusion criteria are recommended to ensure the quality of the findings (Arevalo et al.[23]), this could introduce selection bias. For example, Arevalo et al.[23] included participants with a specific education level and excluded illiterate subjects in their case series. This could make generalising the findings to all patients who may be eligible for these interventions difficult. However, the consecutive sampling used in this case series enhanced its quality and reduced selection bias because all eligible subjects were enrolled during the study period.[51,52]

As previously discussed, the lack of blinding in interventional case series could introduce performance and detection biases. Moreover, in Arevalo et al.'s[23] study, the implantation surgeries for the ten participants were performed by four different surgeons. This could also result in performance bias because the outcomes may be affected by the surgeons' respective experiences, skills and techniques, even if they followed the same procedure. The risk of reporting bias was minimised in this study by transparently reporting both the positive and negative findings in a balanced manner and identifying the study's limitations.

Although these included studies had certain limitations, it was felt that these biases were acceptable due to the nature of the implants, which meant that it was not possible to mask the participants or researchers, as well as the first-in-human and early-phase design of some trials, the difficulty of enrolling a large number of participants, and the rarity of the eligible subjects. Given the paucity of papers that have studied retinal implants, it was important to include these papers in the synthesis. Tables 1 to 3 show the CASP and JBI critical appraisal checklists for the included studies depending on each study design.

The current review aims to determine the efficacy and safety of various retinal implants in restoring vision over the long term and their impact on patients' QoL. Table 5 presents details of the efficacy, safety and QoL of the studies included in the systematic review: Argus II epi-retinal implants studies, subretinal implants studies and suprachoroidal implant studies.

Results for efficacy: Visual function

All of the studies included in this systematic review reported improved patient performance in the visual function tests when the system was turned on compared to when it was turned off. The Argus II studies (see Table 5) investigated visual function through three objective assessments: square localisation (SL), direction of motion (DOM) and grating visual acuity (GVA) tests. In the SL test, the participants were required to touch a white square displayed at random on a black monitor to identify its location twice: once with the system turned on and once with the system turned off. In the DOM test, the patients were asked to trace the direction of a white moving bar on a black monitor. Meanwhile, in the GVA test, the patients were asked to differentiate the orientation (horizontal, vertical or oblique) of black and white bars displayed with different spatial frequencies.[23,33,35,37,38,42]

The SL results in the studies of Ho et al.,[37] da Cruz et al.[38] and Arevalo et al.[23] indicated similar findings: 89.3%, 80.9% and 80% of subjects, respectively, performed substantially better when the device was switched on than when it was switched off. However, the percentage of participants who performed better with the implant turned on declined over time by 8.4% in the 5-year follow-up trial of da Cruz et al.[38] compared

to what was reported by Ho et al.[37] who relied on a 3-year follow-up trial. This was consistent with the study by Schaffrath et al.[35] which found that a smaller percentage (approximately 46%) performed significantly better when the Argus II implant was on than when it was off. In addition, Delyfer et al.[42] reported that the mean error of the SL test when the system was on was lower than when it was off (7–8 cm vs 14 cm), thereby indicating that performance improved when the implant was activated. In contrast, Stanga et al.[33] reported that performance was significantly enhanced when the system was activated compared to when it was off only in one subject at two follow-up visits (6 and 12 months). This can be explained by the fact that their patients' demographics were not comparable with those of the other studies because they enrolled patients with AMD, had a smaller sample size of five subjects and had a mean age greater than that of the other Argus II studies (see Table 4).

For the DOM results, more than half (55.6%) of the participants in Ho et al.'s[37] study performed substantially better when the implant was activated than when it was off. This percentage decreased over time to 50% in the trial of da Cruz et al.[38] Schaffrath et al.[35] found that a smaller proportion of subjects (35.4%) significantly benefited from having the system on when carrying out the DOM tests. The mean errors with the implant on versus off (see Table 5) when performing DOM reported by Arevalo et al.[23] and Delyfer et al.[42] indicated that the participants' performance improved when the system was on compared to when it was off, albeit that this difference was not statistically significant. In Stanga et al.,[33] two patients demonstrated significant improvement at one visit each when performing the DOM with the implant activated compared to when it was off.

For the GVA test, Ho et al.,[37] da Cruz et al.[38] and Arevalo et al.[23] reported similar findings: 33.3%, 38.1%, and 40% of participants, respectively, had measurable visual acuity (VA) equal to or better than 2.9 logarithm of the minimum angle of resolution (logMAR) with the system on. None of the participants had measurable VA (Ho et al.[37]) or scored 2.9 LogMAR or better when the implant was off (da Cruz et al.,[38] Arevalo et al.[23]). Ho et al.[37] reported that the participants were presented with the GVA test for 5 s, likely to be the same amount of time employed by da Cruz et al.[38] This was consistent with the findings reported by Schaffrath et al.[35] and Delyfer et al.[42] who found that more participants scored 2.9 logMAR or better when the implants were activated than when they were off. In contrast to the previous findings, Stanga et al.[33] found no substantial difference in patients' performance on the GVA test with the implant on or off.

Conversely, studies investigating subretinal implants (see Table 5) examined visual function using the basic light and motion (BaLM) test, basic grating acuity (BaGA) test or Landolt C-rings. The BaLM test consists of three elements: light perception, light localisation and motion detection. Two studies investigating the subretinal Alpha AMS prosthesis (Stingl et al.,[40] and Edwards et al.[41]) found that all of their subjects passed the light perception element when the implants were turned on, whereas 17% and 0% passed the test when the implants were off, respectively, ($p < 0.05$). For the light localisation test, approximately 85% and 100% of their subjects, respectively, passed this element at month 12 when the implants were on. In contrast, none of the participants passed it when the implants were off ($p < 0.05$). On the motion detection module, Stingl et al.[40] found that two patients only passed this component when their implants were on at month one and none of the subjects passed this component when the implants were turned off during the entire study period. In Edwards et al.'s[41] study, none of the patients passed the test with the implant either on or off.

For the BaGA test, Stingl et al.[40] reported that the patients' performance was significantly better when the Alpha AMS implants were on than when off at three time points (two, three, and 12 months; $p < 0.05$). On the remaining time points, more than 50% of the participants performed better with the implant on than off, but this difference was not statistically significant. There was a variation in the subjects' performance with the implant on because 26.7%, 20%, 13.3%, 13.3% and 6.7% of the participants achieved grating detection acuity of 0.1, 0.33, 0.66, 1.0 and 3.3 cycles per degree, respectively. Similarly, in Edwards et al.,[41] the subjects performed at most 50% correct answers (chance level) when the implants were off. However, with the implants switched on, five participants achieved grating detection acuity ranging from 0.1 to 3.33 cycles per degree. Performance varied among the participants, but it was generally better when the implants were activated than when

they were off. For the Landolt C-rings test, only two patients in the study by Stingl et al.[40] had measurable VA, achieving 20/1111 and 20/546. In contrast, none of the patients in the study by Edwards et al.[41] was able to recognise letters on the Landolt C-rings test. Neither of these studies imposed time limits when displaying the tests for the participants.

Two studies (Palanker et al.,[32] and Muqit et al.[34]) investigating PRIMA subretinal implants found that all of the participants perceived light in the central atrophic area when the implants were on but not when turned off. In Palanker et al.'s[32] study, three patients postimplant had measurable VA ranging from 20/460 to 20/550 within the 12-month study period. Of the two remaining patients, one achieved a VA of 20/800 and the other could not recognise letters of any size. In Muqit et al.'s[34] study, the VA postimplant significantly improved from the mean baseline VA, which was 1.48 LogMAR (20/600) to 1.33 LogMAR (20/430) at 4 years. By 48 months post-implantation, the subjects' VA significantly improved using Zoom by 32 letters from the baseline.

As shown in Table 5, only two studies included in this systematic review (Fujikado et al.[29] and Petoe et al.[30]) investigated suprachoroidal implants. The trial by Fujikado et al.[29] found that one out of three patients demonstrated better performance in the SL test when the implant was on than when off ($p < 0.05$) during all of the follow-up visits. For the remaining two patients, one demonstrated significant improvement when the implant was on compared to when it was off in only one follow-up visit and the other did not demonstrate a substantial difference in terms of performance between when it was on or off. In contrast, 100% of the participants in the trial by Petoe et al.,[30] performed significantly more accurately in the SLT with the device on compared to off ($p < 0.001$). They also performed significantly worse in the scrambled condition than in the normal condition, but still better than with the device was off. In the motion discrimination task, 50% of the participants showed significantly higher accuracy with the implant on than off at all tested speeds (7°/s, 15°/s and 30°/s), with accuracy reduced in the scrambled condition compared to the normal mapping. In the spatial discrimination task, two participants passed once and three times, respectively ($p < 0.05$).

In general, trials involving RP patients showed greater and more consistent improvements in visual function assessments when the implants were activated compared to when they were off. In contrast, the three AMD trials[32–34] reported more variable results, with smaller sample sizes, older participant ages, and, in some tests such as GVA, no statistically significant improvements.

Results for safety profile

As demonstrated in Table 5, all of the studies investigating Argus II implants reported adverse events ranging from three (Arevalo et al.[23]) to 51 (Schaffrath et al.[35]). In the clinical trial by Ho et al.,[37] 18 severe adverse events (SAEs) were developed in ten out of 30 participants during the first year after implantation. Among these SAEs, four conditions were more common than the others: conjunctival erosion, dehiscence, hypotony and presumed endophthalmitis. As a result of recurrent conjunctival erosion in one subject, the implant was explanted at 1.2 years. At 3 years post-implantation, 23 SAEs were reported in 11 out of 29 subjects. Therefore, only five SAEs occurred in four participants after 1 year. These five conditions were hypotony in two participants, infective keratitis, corneal melt and conjunctival erosions. In the trial by da Cruz et al.,[38] at 5 years post-implantation, there was only 1 SAE (rhegmatogenous RD) in the study eye, which developed after 3 years post-implantation. In addition, they reported two implant failures 4 years after implantation and two implant removals at 3.5 and 4.3 years. This indicates that during the 5 years of follow-up, there were a total of 24 SAEs, 2 device failures and 3 explants. All of these SAEs were successfully treated and managed.

Schaffrath et al.[35] reported that 23 out of 47 participants experienced 51 nonserious AEs and 12 subjects experienced 13 SAEs related to the implant or procedure. Conjunctival erosions, retinal detachment (RD) and hypotony were the most frequent SAEs in this trial. During the entire study period, two devices were removed: one due to failure and the other due to ocular pain.

Stanga et al.[33] reported seven AEs, four of which were SAEs related to the implant or procedure. These four conditions included non-rhegmatogenous RD in one patient, PVR/RD in two patients and hypotony in one case. All were treated with surgical interventions, including gas injection,

silicone oil injection or pars plana vitrectomy. In addition, macular oedema (MO) developed in all of the enrolled participants with no effect on prosthetic vision and, therefore, no treatment was required. Conversely, Arevalo et al.[23] found that none of the participants experienced any SAEs that required surgical intervention or prosthesis explantation. They reported that a mild vitreous haemorrhage was developed in one case post-implantation, which resolved within 2 weeks without intervention. Moreover, suture exposure occurred in one participant and an elevated intraocular pressure (IOP) due to a tight scleral band (SB) was reported in another case. The high IOP was resolved with SB relaxation, so no medication was required.

Delyfer et al.[42] reported that 12 patients had experienced 21 AEs, eight of which were related to the implant or procedure, which occurred in five patients. Two of these eight AEs were classified as SAEs: endophthalmitis and vitreous haemorrhage. All of the AEs were resolved spontaneously or following treatment, except for one condition of mild ptosis.

Regarding the studies investigating subretinal implants, Stingl et al.[40] reported that eight SAEs occurred among four subjects. Two patients experienced implant movement following implantation, which required a second operation to readjust it. Four cases of conjunctival dehiscence were successfully treated with surgical interventions. One patient experienced ocular pain close to the coil and an issue with the silicone oil tamponade, which required surgery to be refilled. In the other study by Edwards et al.,[41] five AEs were reported, four of which related to the implant. These AEs were conjunctival erosion, peripheral RD and contact dermatitis. Two devices were removed: one due to damage that occurred during the surgical intervention to treat recurrent conjunctival erosion and one due to device failure.

Palanker et al.[32] reported intraoperative complications, including choroidal bleeding and focal subretinal haemorrhage, which were resolved spontaneously within 6 months or a matter of weeks, respectively. In addition, one patient experienced an acute elevated IOP as a result of not taking their medications postoperatively. This case was adequately managed with antiglaucoma drops and intravenous injections. Muqit et al.[34] found four SAEs unrelated to the implant among the enrolled patients. These SAEs included MNV and OHT in the study eye at 2 years post-implantation, both of which were classified as being related to the procedure.

Fujikado et al.[29] found that iridocyclitis developed in two cases at two, 4 and 6 months postoperatively, both of which were treated successfully. They also reported an acute loss of hearing in one subject at 7 months post-implantation, which was treated with intravenous corticosteroids. In the trial by Petoe et al.,[30] no device-related SAEs were reported during the study period. Small subretinal haemorrhages developed postoperatively in two cases and resolved spontaneously within 2 weeks. Other minor adverse events included swollen eyelids, pain, conjunctival injection, increased IOP, and mild anterior chamber inflammation, all of which were expected.

There were no significant differences in the safety profile outcomes between RP and AMD studies, with the majority of AEs being treatable. Although the AMD trials had limited sample sizes, they appeared to demonstrate more significant surgical complications. This may be explained by the fact that two[32,34] out of the three AMD studies investigated subretinal implants, which are surgically more challenging and less familiar to surgeons due to their placement.[53]

Results for functional vision

As demonstrated in Table 5, patients' performances in the orientation and mobility tasks, including the door task (DT) and line task (LT), were significantly better when the Argus II was on than when it was off.[37,38] The results for these tasks were shown as the mean percentage of success in both tests with the Argus II on versus off (see Table 5). In addition, Ho et al.[37] reported the results for DT and LT at 1 year follow-up, which were 53.0% versus 30.8% and 72.8% versus 17.1%, respectively. In comparison, the percentage of success when the Argus II systems were on for both tasks appeared to decline over time. However, the lack of individual data made it unclear whether or not this decline was statistically significant. Arevalo et al.[23] reported that all participants post-implantation achieved the following daily life conditions: locating a bright light on the ceiling, avoiding obstacles and detecting people in front of them.

Stingl et al.[40] reported that the activities of daily living (ADL) were significantly improved with the system on versus when it was off. They found that the patients' ability to detect and localise geometric shapes or items on the table was significantly better with the system on than when it was off during the entire study period ($p < 0.05$). However, there was no statistically significant difference in terms of recognising the shapes or table items between when the system was on and off during the entire study period, except for month 3 when identifying the table items was significantly better with the implant on than off. Moreover, with regard to the hand-eye coordination test, the number of participants who successfully performed this test was greater when the system was on than off. However, this difference was only statistically significant at months 2 and 12.

Similar findings were reported by Edwards et al.[41] who found that five of their participants could locate geometric shapes and tableware items with the system on, but not when the system was off. Furthermore, at month 3, two patients could correctly identify three-to-four geometric shapes and table objects with the system on but not when the system was off. The most challenging task was clock face recognition, whereby the participants were presented with clock hands showing 12 various times and required to tell the time with the implant on and off. They found that only one patient correctly recognised all 12 times at three follow-up visits when the system was on. The same patient's performance declined when the system switched off to correctly identify only two, one and six times at the same three follow-up visits. For the remaining patients, the median results were calculated for the number of correct times given with the implant on versus off, as follows: 3.5 versus 1.0; 0.0 versus 0.0; 0.0 versus 0.0; 0.5 versus 0.0; and 5.0 versus 1.0.

Fujikado et al.[29] performed a mobility test on the trial participants to assess their ability to walk along a predefined straight line with the implants. The participants were asked to stop if they deviated from the line whilst walking. This test was performed monocularly with only the implanted eye and with the implant switched on and off. They reported that one participant's mobility accuracy was not significantly different when the system was on compared to off. However, another participant demonstrated that their deviation was reduced when the implant was on than when it was off at 9 and 11 months post-implantation ($p < 0.05$). This significant difference was also noted in the third patient at 2, 5, and 8 months post-implantation. This study also performed a table test to evaluate the participants' ability to distinguish a rice bowl from chopsticks. Two of the enrolled subjects performed better when the implants were on than when they were off at 6 months post-implantation and during the entire study period, respectively.

Similarly, Petoe et al.[30] reported that all participants were better at localising objects with the device on than off ($p < 0.001$ and $p < 0.01$ for 75% and 25% of subjects, respectively). For object identification, performance improved for half of the participants with the implant on ($p < 0.05$), although the average accuracy remained below 40%. In addition, this trial assessed subjects' ability to detect obstacles with the device on versus off. They found that participants were significantly better at detecting obstacles with the implant on; however, they walked more slowly, possibly due to additional head scanning and spatial assessment.

Results for quality of life

The functional low-vision rated assessment (FLORA) tool was developed to assess the effect of visual restoration by the Argus II prosthesis on the implanted patients' QoL. The FLORA consists of three parts: an interview to assess the patient's self-reported experience with the implants; observation of the subjects performing ADL and orientation and mobility tasks with and without the system; and a narrative case study summarising the results of the previous parts for subjective judgement.[54] Based on this, the evaluators rated the effect that the implants had on the subjects' QoL as being positive (when the implant had improved both functional vision and well-being of the patient), mildly positive (either functional vision or well-being improved), neutral or negative.[42]

Ho et al.[37] reported that 1 year post-implantation, 12 out of the 15 subjects (80%) rated their outcomes as positive or mildly positive based on the FLORA results. At 3 years post-surgery, 65.20% of the 23 subjects rated their outcomes as positive or mildly positive. None of the participants rated their outcomes as negative at any time point during the follow-up process. This is consistent with the findings by Stanga et al.[33] who found that the

implant's effect on the patients' QoL was rated as positive or mildly positive for one and three of their participants, respectively. Delyfer et al.[42] reported that the implants' effect was positive or mildly positive in 70% and 71% of their participants at 1 and 2 years follow-up, respectively. The percentage of subjects who rated their experiences as positive increased from 41% at the 1-year time point to 53% at the 2-year time point. In contrast, the percentage of subjects who rated their experiences as mildly positive declined from 29% to 18%, respectively. The patients' performance significantly improved in three domains: orientation, mobility and daily living activities as a result of the implants ($p < 0.05$), as shown in Table 5. Similar to what was reported in the other studies, none of their participants experienced any negative effect on their QoL as a result of the implant.

Duncan et al.[39] employed the VisQoL survey to assess the effect that the Argus II system had on the patients' QoL. They used this tool to compare changes in the patient's QoL pre- and post-implantation. This survey has six dimensions: injury, life, friendships, assistance, roles and activities. They found that the mean VisQoL utility score post-implant, ranged from 0.63 to 0.67 and was not significantly different from the baseline pre-implant score of 0.62. However, the Argus II implant significantly improved the injury, life and roles dimensions of the VisQoL ($p = 0.0362$, $p = 0.0069$ and $p = 0.0012$, respectively). No difficulty was reported in the dimension of friendship at pre- or post-implant. The remaining two dimensions (assistance and activities) showed improvement post-implantation, but this was not statistically significant.

Edwards et al.[41] utilised the Turano Independent Mobility Questionnaire (IMQ), enabling patients to report their experiences with the implants when used in familiar environments. The enrolled subjects were required to rate the difficulty of various activities as none, mild, moderate, severe or extremely difficult. They found that walking in familiar areas was the most positively affected activity post-implantation.

For the suprachoroidal implants, Petoe et al.[30] assessed QoL outcomes using FLORA and the Impact of Vision Impairment – Very Low Vision (IVI-VLV)24 questionnaire. The FLORA assessment indicated that orientation tasks and activities of daily living became easier with the implant on, being rated as moderate, whereas they remained difficult with the device off over time. In contrast, there were no significant improvements in mobility tasks or social interactions with the device on compared to off. However, two participants showed improvement in some social interactions, such as detecting when a person was approaching at 11 and 14 months post-implantation. The IVI-VLV outcomes showed no changes in the emotional well-being component postoperatively for three subjects. Moreover, little to no additional impact of vision loss was reported on activities of daily living, mobility, and safety.

In general, there was no difference in the overall proportion of participants reporting positive or mildly positive outcomes between RP and AMD studies. However, the AMD study[33] reported a greater proportion of mildly positive ratings than positive ratings.

Discussion

This systematic review identified 13 studies that met the criteria to answer the research question. Of these studies, 53.85% focused on the Argus II system, 30.77% studied subretinal implants and only 15.38% investigated suprachoroidal implants. All of the included studies indicated that retinal implants may offer an effective and safe means of restoring some degree of useful vision for blind patients from end-stage RP or dry AMD. The retinal prostheses enabled implanted participants in the included studies to perceive light, localise objects, identify the direction of motion, find the door, follow a line on the floor or perform grating acuity or optotype visual acuity tests with the implants on. These improvements appeared to be sustained over time. This was observed through the participants' performance because more participants were able to perform better with the system on than off up to 5 years after implantation.[38] This indicates that the effectiveness of retinal implants is sustained over time rather than merely offering a short-term improvement.

However, there was variation in the patients' performance between SL, DOM and GVA. The percentages of patients who performed better with the system on versus off in SL were higher than in DOM and GVA. Only two studies (Schaffrath et al.,[35] Delyfer et al.[42]) explained this, reporting that the difference was expected due to the difficulty of the DOM and GVA tasks compared to the SL. Some degree of spatial vision (i.e. the

capacity to recognise and use spatial information within a scene) was required to recognise the direction of movement and pass this task. This was different and more difficult than merely detecting light, which is what was required to pass the SL test.[42,55] In addition, the visual performance of the participants in the studies differed. This variability was explained by Schaffrath et al.,[35] who reported that it is likely to be due to several factors, such as the participant's age when they experienced complete visual loss and received their implant, the genetic subtype of the retinal condition and the position of the electrodes, among others.

Moreover, the vision outcome measures differed among the included studies. Some studies (Ho et al.,[37] da Cruz et al.,[38] Arevalo et al.,[23] Schaffrath et al.,[35] Delyfer et al.,[42] and Stanga et al.[33]) reported the implanted subjects' vision with the implant on and off using GVA and reported whether they scored 2.9 logMAR or better. Meanwhile, Stingl et al.[40] and Edwards et al.[41] reported the subjects' vision in units of cycles per degree. Furthermore, Palanker et al.[32] and Muqit et al.[34] reported the subjects' vision in Snellen using optotype acuity. Given this wide variation and because grating acuity does not always match optotype acuity, the findings of these studies were not comparable.[7,56] The highest visual acuities reported among the included studies were 20/460 and 20/430 for the PRIMA subretinal implants in Palanker et al.[32] and Muqit et al.,[34] respectively. Other subretinal implants, such as Alpha AMS, demonstrated visual acuity of up to 20/546.[40] These findings suggest that subretinal prostheses may provide greater visual acuity than the outcomes reported in the literature for Argus II epiretinal implants. This supports the findings of Chuang et al.[57] who reported that Argus II delivered 20/1262 visual acuity, which was lower than that achieved by the Alpha-IMS subretinal implant. However, these levels of visual acuities, which were worse than 20/200, were still regarded as legal blindness.[58]

The above differences in visual outcomes between the various types of retinal implants can be attributed to their anatomical positions. Subretinal devices are implanted beneath the retina, closer to the target neurons (the degenerated photoreceptors), which allows for better spatial resolution.[59–62] In comparison, epiretinal implants are placed on the retina, farther from the photoreceptors, and directly stimulate the ganglion cells. This positioning results in lower spatial resolution compared to subretinal implants, due to their proximity to the passing axonal nerve fibres, which may stimulate these fibres and lead to ectopic visual percepts.[53,62] Suprachoroidal implants are positioned within the suprachoroidal space, at an even greater distance from the target neural tissue, and therefore provide lower spatial resolution than other implant types.[62,63] However, suprachoroidal prostheses have some advantages, such as safer, less invasive and simpler surgical procedures, making them preferable in some cases to other types.[62]

Regarding the safety profile, epiretinal Argus II demonstrated higher adverse event rates than the subretinal and suprachoroidal implants. The most commonly reported adverse effects were conjunctival erosion/dehiscence, hypotony, presumed endophthalmitis and retinal detachment. None of the reported adverse effects were unexpected, except for elevated IOP due to a tight scleral band.[23] Therefore, they proposed evaluating the scleral band tension prior to the conclusion of the procedure. Most of the reported adverse events occurred within the first year and were successfully treated.[33,35,37,38,42] This is consistent with the findings of Humayun et al.[64] who reported that 70% and 82% of SAEs occurred during the first 3 to 6 months following implantation. During the follow-up, 18 SAEs developed within 1 year, compared to five SAEs which occurred from 1 to 3 years and only one from 3 to 5 years.[37,38] This suggests that the occurrence of adverse events may decrease over time. The reduction in the development of SAEs may be due to enhancements in implant design and surgical techniques.[65] However, the risk of developing new or reoccurring SAEs remains, thereby indicating that regular follow-ups are required for patients with chronic retinal implants.[38]

For subretinal implants, the most frequent SAEs reported were conjunctival dehiscence, retinal detachment, subretinal haemorrhage and elevated IOP. Based on the included studies, subretinal implants were associated with relatively fewer AEs than the Argus II epiretinal. This result is similar to that reported by Chow,[66] who found that the incidence of SAEs appeared to be lower with subretinal implants than with epiretinal implants. However, in the current review, there were fewer studies investigating subretinal implants than those investigating Argus II. Furthermore, the follow-up durations varied

among the included studies. Most of the Argus II studies had follow-ups of more than 24 months, whereas most of the subretinal implant studies had follow-ups of just 12 months. Therefore, the comparison may not be fair because of such variations. One study in the current review reported iridocyclitis and hearing loss related to suprachoroidal implants (Fujikado et al.[29]), which were not reported in the other included studies. A review by Wu et al.[67] reported that suprachoroidal prostheses had the fewest adverse events compared to other types of retinal implants. However, in the current review, comparing suprachoroidal implants with other types of retinal implants in terms of safety was not feasible because only two studies were included and had a very small sample size ($n = 3$ and 4).

In terms of QoL, several studies have demonstrated that retinal implants improve patients' quality of life.[33,37,39,42] However, the percentage of patients who rated their experiences on FLORA as positive or mildly positive in Ho et al.'s[37] study decreased by 14.8% from year one to year three. Although a general observation of the reduction in the participants' performance with the system turned on in some measures was reported, the reason for this decline was not clearly explained. The authors were unsure whether this was an actual decline in performance. However, they suggested that the implantation of a new prosthetic design in some subjects who enrolled after 1 year might have affected the performance results. In contrast, Delyfer et al.[42] reported no decline in the percentage of recipients who rated their experiences as positive or mildly positive from year one to year two. There are several explanations for this variation. First, the number of subjects who enrolled in Delyfer et al.'s[42] study was fewer than those included in the study by Ho et al.[37] Second, the decline occurred at year three (Ho et al.[37]), whereas the follow-up duration in the study by Delyfer et al.[42] was only 2 years. Finally, no participants were enrolled after the start date and received retinal implants with a new design in Delyfer et al.'s[42] study, which was different to what happened in the study by Ho et al.,[37] as previously mentioned. In general, most of the participants benefited from the implants in many aspects of their quality of life.[33,37,42] The Argus II system's benefits in terms of patients' QoL were sustained for up to 3 years.[39] The results suggest that the implantation of Argus II prostheses enabled patients to move around familiar environments such as their home, district, yard and workroom, as well as navigating streets and pavements whilst avoiding obstructions. This means that patients became more self-dependent with a lower risk of injury when the system was turned on.[39]

The noted differences in visual function and QoL outcomes between RP and AMD studies may be explained by two key factors. First, the pattern of visual field (VF) loss differs between the conditions: RP typically causes peripheral VF loss that progresses to involve the central VF in the advanced stages, whereas dry AMD affects the macula, leading to central VF loss.[68] Second, the age of onset for AMD is generally older than that for RP, as reflected in the participants' demographics in the included trials.[68]

Although the included studies demonstrated promising results, there was a high risk of bias. First, neither the researchers nor the subjects were blinded to the system's status (whether it was turned on or off). Second, there were no control groups in any of the included studies for the purpose of comparison. Most of the included studies compared the outcomes for the subjects with the system on versus off; few studies compared pre- and post-implantation outcomes. This comparison is unable to confirm the efficacy of retinal implants and whether they are beneficial compared to no therapy being received. The implantation of retinal prostheses may adversely affect the participants' residual vision. Therefore, the benefits of the implants may remain unclear without a control (no treatment) group or pre-implantation comparison.[15] Moreover, the results may be biased due to the lack of blinding. Awareness about the operational status of the implants may influence the participants' behaviours, encouraging them to perform better when the prostheses are switched on as a placebo effect.[15,42,45] Also, the evaluators' awareness of whether the implants were turned on or off may have affected their interactions with the subjects or how they measured the outcomes based on the device's status.[15,25] Only two of the included studies (Duncan et al.,[39] Delyfer et al.[42]) discussed the placebo effect and reported that it was less likely to be significant because the improvements were sustained throughout the study periods. Third, the tests were performed twice for each individual in the included studies: first with the system on and then with the system off. This approach could bias the results as the participants became familiar with the task and this familiarity may enable

them to perform better when the system was switched off.[45]

There are several limitations associated with the current systematic review. Ideally, the systematic review should be carried out by at least two independent reviewers in order to help minimise bias and enhance the review's validity.[69] The current review was conducted by one reviewer, which could introduce a risk of bias. Moreover, only studies published in English were included, whereas those in other languages were omitted, which could induce some language bias.[70] In addition, grey literature was excluded from the current review, which may induce some degree of publication bias and reduce the review's validity. The unpublished literature may indicate negative or insignificant findings, so including them could confer a more balanced and accurate conclusion on the review.[71]

The strength of the systematic review depends on the validity of the included primary studies.[72] The included studies had several limitations and were at risk of bias, as previously discussed in this dissertation. Consequently, the overall quality of the current review may be adversely affected.

All of the included studies enrolled RP patients except for three which focused on subjects with AMD. This imbalance could limit the review's generalisability to the AMD population or those with other retinal degenerative diseases.

As previously mentioned, most of the included studies compared the outcomes post-implantation within subjects when the implants were switched on and off. This approach cannot confirm whether or not the implants were truly beneficial.[15] Consequently, trials comparing the visual outcomes of the participants before and after implantation are needed. In addition, the included studies had small sample sizes and were followed up for a maximum of 5 years. Therefore, a trial with a large sample size and an extended follow-up period (more than 5 years) would need to be conducted for future retinal implant studies, especially for subretinal and suprachoroidal prostheses. This would help to better understand this emerging solution's long-term efficacy and safety. Given the paucity of trials investigating the efficacy and safety profile of these technologies in AMD patients, further research is needed. Moreover, future research should use more robust selection criteria in an attempt to reduce the variations noted in the visual performance outcomes,[15] and improve the findings. Given that prosthetic vision is different from natural vision, there is a demand for further research focusing on rehabilitation programmes post-implantation because these programmes can enhance the benefits of retinal implants.[67] Finally, further research into the recipients' QoL post-implantation is needed because most of the available trials focused on the efficacy and safety of these technologies.

Conclusion

This systematic review has yielded valuable insights regarding the long-term efficacy, safety, and impact of retinal implants on patients' QoL. While subretinal implants appeared to offer better VA compared to other implant types, all types showed a generally acceptable safety profile, with adverse events being mostly treatable and declining over time. Patients' QoL improved in most implanted individuals and was sustained throughout the follow-up periods. However, although retinal implants confer some functional vision, this regained vision remains severely limited, and patients continue to meet the criteria for legal blindness.

Declarations

Ethics approval and consent to participate

Not applicable. This study is a non-interventional systematic review of existing research literature on retinal implants. According to Cardiff University Research Ethics Committee, such research is exempt from requiring ethics approval.

Not applicable.

Consent for publication

Not applicable. This manuscript does not include any data from individual persons.

Author contributions

Hanan B. Alqahtani: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Visualisation; Writing – original draft.

Marcela Votruba: Supervision; Writing – review & editing.

Justyn Regini: Methodology; Project administration; Supervision; Writing – review & editing.

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