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Systematic Review

A Systematic Review and Meta-Analyses of Interventional Clinical Trial Studies for Gene Therapies for the Inherited Retinal Degenerations (IRDs)

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Abstract: IRDs are one of the leading causes of visual loss in children and young adults. Mutations in over 271 genes lead to retinal dysfunction, degeneration and sight loss. Though no cure exists, gene augmentation therapy has brought hope to the field. This systematic review sought to assess the efficacy of available gene therapy treatments for IRDs. Databases and public resources were searched for randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs). Standard methodological procedures were used, including a risk-of-bias assessment. One RCT and five NRSIs were assessed, all for adeno-associated virus two (AAV2)-mediated treatment of RPE-specific 65 kDa (RPE65)-associated LCA (Leber congenital amaurosis). Five outcomes were reported for meta-analyses. Modest improvements in visual acuity, ambulatory navigation/mobility testing or central retinal thickness was observed. There was significant improvement in red and blue light full-field stimulus testing (FST) (red light risk ratio of 1.89, treated v control, $p = 0.04$; and blue light risk ratio of 2.01, treated v control, $p = 0.001$). Study design assessment using a ROBIN-I tool (Cochrane Library) showed risk-of-bias judgement to be “low/moderate”, whilst there were “some concerns” for the RCT using a RoB-2 tool (Cochrane Library). Although comparison by meta-analysis is compromised by, amongst other issues, a variable amount of vector delivered in each trial, FST improvements demonstrate a proof-of-principle for treating IRDs with gene therapy.

Keywords: IRDs; retinitis pigmentosa; Leber congenital amaurosis (LCA); gene therapy; RCT; clinical trial; visual acuity (VA); mobility; multi-luminance mobility testing (MLMT); full-field stimulus testing (FST)



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1. Introduction

The IRDs are a heterogeneous group of overwhelmingly monogenic eye conditions that cause premature sight loss [1]. Currently, 271 causal genes have been identified (last updated 8 April 2021 [2]) which have roles in various aspects of photoreceptor and/or retinal pigment epithelium (RPE) function. Dominant, recessive, X-linked, digenic and mitochondrial modes of inheritance have all been described [3–14]. IRDs cause progressive retinal degeneration, which results in a variety of progressive symptoms including night blindness (nyctalopia), visual field constriction, central visual loss, dark adaptation problems, photophobia, nystagmus and pupillary abnormalities [14].

There is considerable phenotypic variability between IRDs and historically they have been grouped into several different disease patterns, including retinitis pigmentosa (RP), cone dystrophies, cone-rod dystrophies and Leber congenital amaurosis (LCA) [15]. Further, many attempts have been made at genotype-phenotype correlation. However, in reality, there is both considerable inter-allelic disease overlap and marked intra-allelic disease variability. Thus, the progress made in genetic diagnosis of IRDs has been invaluable.

LCA is a severe congenital or early infant-onset IRD characterised by vision loss, nystagmus, an absence of a normal pupil response and an almost non-recordable ERG [16–19]. Known genes associated with LCA includes *GUCY2D* (estimated 10–20% patients), *CEP290* (15–20%), *CRB* (10%), *AIPL1* (4–8%) and *NMNAT1* (uncertain). Following the original description of the infantile disorder, a subsequent milder form of disease, considered to be on the LCA spectrum, was described that presents in the 6th or 7th year of life and leads to blindness by the age of 30 [20]. Whilst this later-onset disease has been referred to by several different names [21–25], there is considerable overlap with LCA in both genotype and phenotype, with causal genes including *RPE65* (5–10%), *LRAT* (<1%) and *RDH12* (4–5%) [18].

Mutations in *RPE65* are estimated to account for approximately 5–10% of LCA and approximately 1–2% of retinitis pigmentosa [26]. *RPE65* is localized to chromosome 1p31, comprising 14 exons and encoding a 65-Kd protein [23]. *RPE65* is a key component of the retinoid visual cycle. It is expressed in the retinal pigment epithelium (RPE) which, together with LRAT, is involved in continuous regeneration of the visual chromophore [24]. LCA-mediated IRDs have a prevalence of between 1 in 33,000 [25] and 1 in 81,000 [27]. In Ireland, there are an estimated ~130 LCA patients [28], while NICE has reported there may be 86 LCA2 patients potentially eligible for EMA-approved gene augmentation therapy [29] in England [30].

Gene augmentation therapy is a novel therapeutic approach for genetic disease that seeks to replace null or loss-of-function protein by expressing wild-type copies of the gene of interest, typically through delivery via a viral capsid [31]. The approach is most applicable to recessive traits, and decades-long efforts have demonstrated the approach efficient at rescuing visual loss in animal models of achromatopsia, X-linked and recessive RP, LCA and Stargardt’ disease, amongst others [32,33].

Subsequently, gene augmentation therapy has begun to be translated in clinical trials. [ClinicalTrials.gov](https://www.clinicaltrials.gov) have estimated 250 listed studies focused on IRDs, including patient registry studies, natural histories, observational and interventional trials [34]. One of the first genes to be targeted was *RPE65*-LCA, so chosen because of the relative delay in the development of retinal degeneration despite early-onset visual loss, thus offering a wide treatment window. Gene augmentation therapy (voretigene neparovec-rzyl/*Luxturna* [35]) has now received FDA approval in the USA (2017) and EMA approval in Europe (2018) for adult and paediatric disease. This first-in-class treatment gives the field hope that a new class of drugs may arise for IRDs [36,37].

Gene augmentation therapies used to date to treat IRDs are based around similar basic adeno-associated virus (AAV) vectors and their capsids, with a variety of promoters chosen by different research groups and companies. To rigorously determine the efficacies of these new therapies it is critical to assess how results show benefit. This requires that methodology, study design and outcome measures provide a clear and reasonable conclusion for the impact on the patient. To this end, we performed a systematic review and meta-analyses of clinical trials for RP patients undergoing gene therapy.

2. Materials and Methods

2.1. Criteria for Considering Studies for This Review

2.1.1. Types of Studies

Articles eligible for inclusion in this systematic review were interventional clinical trials, either randomized or non-randomized, for gene therapy treatments for IRD patients, published in English searched in the relevant databases from <1946 to 2020 Week 5>.

2.1.2. Types of Participants

All patients who have been diagnosed with IRDs, either non-syndromic or syndromic, were included with no restrictions of age, gender or ethnicity. Clinical trials were excluded from patients with ocular comorbidities, or excluded from patients with complications

known to influence visual function. Women who were pregnant or lactating or any participants unwilling to use effective contraception were also ineligible.

2.1.3. Types of Interventions

Studies included any investigational gene therapy interventions for IRDs. There were no comparators available for any approved interventions for IRD patients.

2.2. Types of Outcome Measures

2.2.1. Primary Outcomes

The primary outcome of intervention was a mean change from baseline best corrected visual acuity (BCVA) at one year, as measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and measured by logMAR (standard logarithm of the minimum angle of resolution) [38–41].

Ambulatory navigation/mobility mazes have been developed by a number of research groups and were included as a primary outcome. However, several methodologies exist. To allow comparison between trials, reporting of these assays used a mean difference, i.e., comparing the proportion of improved performances post-operatively, between groups (a risk ratio [RR]).

2.2.2. Secondary Outcomes

Secondary outcomes included full-field light sensitivity threshold (FST) [42], visual field, visual perception, electroretinogram (ERG), Goldmann visual fields, fundus photography, nystagmus testing, central retinal thickness (as measured by optical coherence tomography (OCT)), pupillary light reflex response (PLR) and diagnostic ophthalmic techniques [38,43,44].

2.2.3. Adverse Events

Adverse events were not searched for vector administration, due to a considerable volume of literature for AAV safety outcomes from several authors [45–49].

2.3. Search Methods for Identification of Studies

2.3.1. Electronic Searches

The literature search used the Cochrane Handbook for Systematic Reviews of Interventions [50], using the Ovid database for MEDLINE and EMBASE.

We used a PICOS strategy to identify a systematic review of interventional clinical trials (*the study design*) for gene therapies (*the intervention*) for IRD patients (*the population*), for the purpose of improving the disorder (*the outcomes*), given there were no treatments available (*the comparison*). The PICOS search terms and search strings included 36 words and phrases using MeSH terms and Boolean operators, identified in Table S1 (Supplemental).

Structuring and collection of the relevant studies used the PRISMA checklist process [51]. We used the ROBINS-I risk of bias in non-randomised studies of interventions tool [52,53] and the RoB-2 tool for the Cochrane Collaboration's process for assessing risk of bias in randomised trials [54].

2.3.2. Searching Other Resources

We searched FDA and clinicaltrials.gov databases, including the Biologics License Application resource (BLA) at FDA.

2.4. Data Collection and Analysis

2.4.1. Selection of Studies

Following database searching, each article was assessed as being definitely relevant, possibly relevant or definitively not relevant. Duplicates were removed and all articles assessed for exclusion and inclusion. All included articles were evaluated for study design and reports and final studies reviewed in depth.

2.4.2. Data Extraction and Management

All relevant data (intervention characteristics, study design, primary and secondary outcomes) were extracted and collected in Excel prior to analysis [55] of all available data with Review Manager (RevMan) 5.4 software [56].

2.4.3. Assessment of Risk of Bias in Included Studies

Selected studies were independently assessed for sources of systematic bias according to the guidelines in the relevant sections for the Cochrane Handbook for the Systematic Reviews of Interventions [50] using ROBINS-I and Rob-2 tools.

2.4.4. Measures of Treatment Effect

Primary and secondary outcome data was assessed in accordance with the methods within each selected study. Number of BCVA letters/logMAR at one year (or more) was used to collect the mean difference (MD), standard deviations [SD] and corresponding 95% confidence intervals (CI), comparing mean change from baseline between groups. Continuous data was additionally recorded for improvements (with 95% CIs) for full-field stimulus testing data (red and blue wavelengths) and retinal thickness. Risk ratios (RRs) (with 95% CIs) for dichotomous outcomes were reported, including the proportion of participants with improved/worsening mobility/ambulatory navigation. A random-effects model in RevMan 5.4 meta-analysis [57] was used for meta-analysis.

2.4.5. Unit of Analysis Issues

For most studies, the unit of analysis was the individual participant (one study eye per participant). Five of six studies used a design with one treated eye compared to an untreated control eye. One study (Russell, 2017 [58]), used a crossover design where both eyes received interventions one year apart.

2.4.6. Missing Data

Missing data was not imputed for the purpose of the analysis while only one study (Russell, 2017 [58]) used both an intent-to-treat (ITT) and a modified intent-to-treat (mITT) model.

2.4.7. Heterogeneity

Heterogeneity was tested between the studies using chi-square analysis with significant heterogeneity ($p < 0.05$) precluding meta-analysis. An I^2 value of greater than 50% indicated a substantial statistical heterogeneity.

2.4.8. Assessment of Reporting Biases

ROBIN-I and ROB tools were used to assess risk of bias in the five NSRIs and one RCT respectively. Assessments were made by 2 independent examiners.

3. Results

3.1. Systematic-Review of Search Results

Following the structured search approach (Appendix A.1), 115 peer-reviewed research articles were screened and assessed (Figure 1; Appendix A.2), seven articles were removed due to duplication, leaving one hundred and eight articles to be screened. Eighty-seven records were excluded that did not include relevant information. Twenty-one articles were accessed for eligibility; fifteen articles were excluded: one was not applicable for meta-analysis (a study on gene therapy for choroideremia), five were follow-up studies and nine articles included duplicate data. This left six final articles (Appendix A.3) for review and meta-analysis:

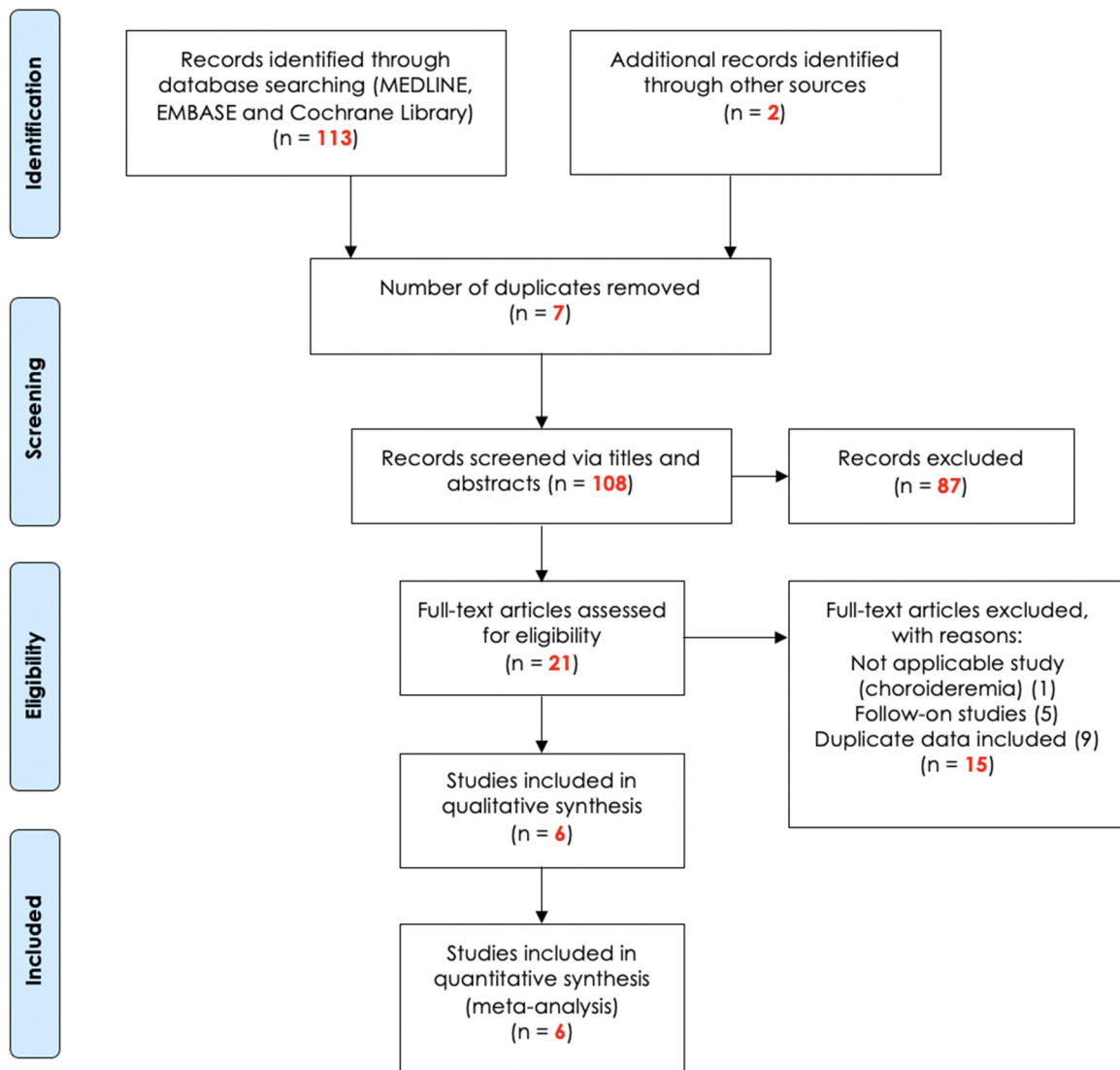


Figure 1. PRISMA flowchart of 115 studies identified, excluded, reviewed and selected.

3.2. Outcomes

In total, 23 different assays were reported and analysed across the six studies in Figure 2 and Table 1 (including Figure S1a–c, Appendix A.4 and Table A1). Safety data was not collected on specific AAV2 vectors, having been examined in other independent studies on interventional clinical studies in the retina [37,59–62]. Only one assay, visual acuity (VA), was common to all six papers. Of the 23 assays reviewed, only five outcomes were reported for meta-analysis—VA (logMAR), mobility, red light full-field stimulus (FST) testing ($\log_{10}(\text{cd.s}/\text{m}^2)$), blue light full-field stimulus (FST) testing ($\log_{10}(\text{cd.s}/\text{m}^2)$) and central retinal thickness (CRT).

Authors on clinical trial studies on gene therapy for LCA2	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
Bainbridge <i>et al</i> 2015	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗
Jacobson <i>et al</i> 2012	✓	✗	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	✓	✗
Le Meur <i>et al</i> 2018	✗	✗	✗	✗	✗	✗	✓	✗	✗	✓	✓	✓	✗	✗	✓	✓	✗	✓	✓	✗	✗	✓	✗
Russell <i>et al</i> 2017	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✓	✗
Testa <i>et al</i> 2013	✓	✗	✗	✓	✓	✓	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	✗	✓	✗
Weleber <i>et al</i> 2016	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✓	✓
Number of assays assessed for meta-analyses*	4	1	1	2	3	2	1	2	2	1	1	5	1	1	1	2	2	2	3	1	1	6	1

* not all assays were comparable between different studies

Figure 2. A summary of the assays collated from the six (6) studies, arranged alphabetically.

All continuous and dichotomous data was reported. If either continuous and dichotomous data were available, then analysis was used to compare and contrast the models. However, continuous data was preferred from a statistical perspective as some information risked being lost in categorical data.

Table 1. Study selection of six (6) research articles for review and meta-analysis outcomes for LCA2-RPE65 gene therapy.

Studies (n = 6) (Journal)	Trial Identifier (Clinical-Trials.gov)	Study Type/Viral Vector	Titre (vg ^(a))/Injection Vol.	Population (ITT ^(b))	Age Range (in Years)	BCVA ^(c) (logMAR)	Ambulatory Navigation, Low Light Ambient Level (<4 lux) (RR ^{(d)(e)})	FST ^(f) (Red Light), log10(cd.s/m ²)	FST ^(f) (Blue Light), log10(cd.s/m ²)	Retinal Thickness (OCT, µm)
Bainbridge et al., 2015 (NEJM)	NCT00643747	Phase 1–2, open-label, non-randomized; rAAV 2/2. hRPE65p.hRPE65	1.0 × 10 ¹¹ to 1.0 × 10 ¹² vg; injection volume of 900 µL to 1 mL	12	6–23 years (Median, 15y; Mean, 14.4y; CI 95%, 3.8)	Mean change BCVA of −0.008 logMAR (treated eyes) vs. −0.063 logMAR (untreated eyes), a difference of 0.06 logMAR (95% CI −0.14, 0.02)	Risk ratio of 5.00 (95% CI 0.27, 93.55)	Data unavailable	Data unavailable	Risk of ratio of 1.50 (95% CI 0.30, 7.43)
Jacobson et al., 2012 (Arch Ophthalmol)	NCT00481546	Phase 1, open-label, non-randomized; rAAV2-RPE65	5.96 × 10 ¹⁰ to 17.88 × 10 ¹⁰ vg; injection volume of 150 µL to 450 µL	15	11–30 years (Median, 20y; Mean, 19.6y; CI 95%, 3.1)	Mean change BCVA of −0.12 logMAR (treated eyes) vs. −0.05 logMAR (untreated eyes), a difference of −0.07 logMAR (95% CI −0.18, 0.04)	Risk ratio of 1.18 (95% CI 0.86, 1.61)	Mean change FST of 0.45 log10(cd.s/m ²) (treated eyes) vs. −0.02 log10(cd.s/m ²) (untreated eyes), a difference of 0.47 log10(cd.s/m ²) (95% CI 0.24, 0.70)	Mean change FST of 1.59 log10(cd.s/m ²) (treated eyes) vs. −0.05 log10(cd.s/m ²) (untreated eyes), a difference of 1.64 log10(cd.s/m ²) (95% CI 1.14, 2.14)	Risk of ratio of 1.00 (95% CI 0.31, 3.28)
Le Meur et al., 2018 (Mol Ther)	NCT01496040	Phase 1/2, open, non-randomized; AAV2/4-RPE65-RPE65	1.22 × 10 ¹⁰ to 4.8 × 10 ¹⁰ vg; injection volume of 200 µL to 800 µL	9	9–42 years (Median, 22y; Mean, 24.1y; CI 95%, 7.8)	Mean change BCVA of −0.05 logMAR (treated eyes) vs. −0.02 logMAR (untreated eyes), a difference of −0.03 logMAR (95% CI −0.18, 0.12)	Data unavailable	Data unavailable	Data unavailable	Data unavailable
Russell et al., 2017 (Lancet)	NCT00999609	Phase 3, open-labelled, randomised (RCT); AAV2-hRPE65v2	1.5 × 10 ¹¹ vg; injection volume of 300 µL	31	4–44 years (Median, 11y; Mean, 14.4y; CI 95%, 4.1)	Mean change BCVA of −0.163 logMAR (treated eyes) vs. −0.031 logMAR (untreated eyes), a difference of −0.13 logMAR (95% CI −0.29, 0.03)	Risk ratio of 3.6 (95% CI 1.04, 12.46)	Mean change FST of 1.29 log10(cd.s/m ²) (treated eyes) vs. −0.16 log10(cd.s/m ²) (untreated eyes), a difference of 1.45 log10(cd.s/m ²) (95% CI 0.69, 2.21)	Mean change FST of 1.96 log10(cd.s/m ²) (treated eyes) vs. −0.13 log10(cd.s/m ²) (untreated eyes), a difference of 2.09 log10(cd.s/m ²) (95% CI 0.61, 3.57)	Data unavailable
Testa et al., 2013 (Ophthalmology)	NCT00516477	Phase 1, open-label, non-randomized (3-year study); AAV2-hRPE65v2	1.0 × 10 ⁸ to 5.0 × 10 ⁸ vg; injection volume of 150 µL to 300 µL	5	11–26 years (Median, 19y; Mean, 19.8y; CI 95%, 7.9)	Mean change BCVA of −0.486 logMAR (treated eyes) vs. −0.264 logMAR (untreated eyes), a difference of −0.22 logMAR (95% CI −0.34, −0.10)	Risk ratio of 1.0 (95% CI 0.71, 1.41)	Data unavailable	Data unavailable	Data unavailable
Weleber et al., 2016 (Ophthalmology)	NCT00749957	Phase 1–2, open-label, non-randomized; rAAV2-CB-hRPE65	1.0 × 10 ⁸ to 5.0 × 10 ⁸ vg	12	6–39 years (Median, 31y; Mean, 24.8y; CI 95%, 8.5)	Mean change BCVA of −0.025 logMAR (treated eyes) vs. −0.046 logMAR (untreated eyes), a difference of 0.02 logMAR (95% CI −0.06, 0.11)	Data unavailable	Data unavailable	Data unavailable	Data unavailable
Summary meta-analyses		Phase 1, 1/2, 3; AAV2	Range from 1.0 × 10 ⁸ to 1.0 × 10 ¹² vg; injection vol. 150 µL to 1 mL	Population n = 84	Range 4–44 years	Summary weighted mean difference (MD) of −0.06 logMAR improvement over treated vs. untreated eye (95% CI −0.14, 0.02), p = 0.16	RR improvement of 1.35 , over treated vs. untreated eye (95% CI 0.78, 2.2.35), p = 0.29	Summary weighted mean difference (MD) of FST (red) 0.89 log10(cd.s/m ²) over treated vs. untreated eye (95% CI −0.06, 1.84), p = 0.07	Summary weighted mean difference (MD) of FST (blue) 1.69 log10(cd.s/m ²) over treated vs. untreated eye (95% CI 1.21, 2.16), p = 0.00001	RR improvement of 1.15 (95% CI 0.45, 3.00), p = 0.77

(a) vg—vector genomes; (b) ITT—intention to treat; (c) BCVA—Best corrected visual acuity, (logMAR); (d) RR—risk ratio; (e) 95% CI—95% confidence interval; (f) FST—full-field stimulus testing (red and blue wavelength), log10(cd.s/m²).

3.3. Visual Acuity Measured by logMAR

A 0.30 logMAR (3 line) mean post-operative change of VA was accepted as being a “clinically meaningful” improvement [43]. VA results were reported in Figure 3. Overall, outcomes showed a benefit of treatment compared to control eyes, but did not meet statistical significance.

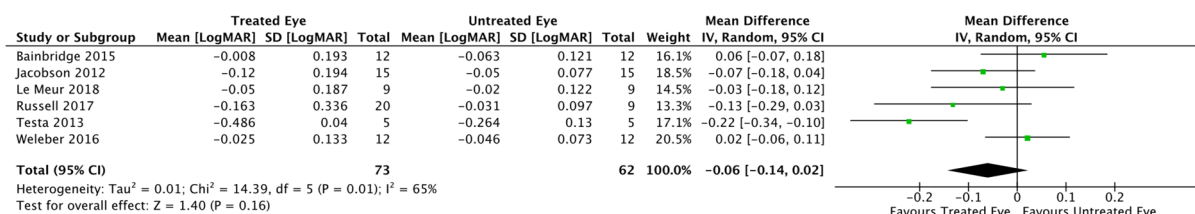


Figure 3. Meta-analysis shows no significant improvement in visual acuity following treatment. RevMan analysis of logMAR visual acuity, using a random effects model and summary statistic for continuous data, shows a modest improvement (mean difference $-0.06 [-0.14, 0.02]$) that does not reach statistical significance ($p = 0.16$).

There was a mean [SD] improvement of $-0.142[0.181]$ logMAR letters in treated eyes ($n = 73$), compared to $-0.079[0.103]$ logMAR letters in untreated ($n = 62$), showing a difference of logMAR -0.063 (including Table S2 (Supplemental)). RevMan 5.4 analysis showed a statistical difference of -0.06 logMAR (95% CI $[-0.14, 0.02]$, $p = 0.16$) above. Individually, only one study (Testa, 2013), reported a clinically meaningful improvement in VA, with a mean [SD] improvement of $-0.49 [0.04]$ logMAR letters in the treated eye, compared to a mean [SD] improvement of $-0.26 [0.13]$ logMAR in the untreated eye.

Finally, an analysis of dichotomous data on visual outcomes post treatment (better or worse) was performed. Five studies provided individual patient data to allow this analysis ($n = 58$ treated eyes; $n = 47$ untreated eyes). The line of no effect showed an RR of 1.13 (95% CI 0.83, 1.53), indicating an improvement with treatment that did not reach clinical significance ($p = 0.44$) (Figure S2 (Supplemental)).

3.4. Mobility

Given the disparity between the four different mobility methods used in the studies in terms of size, light intensity, scoring and reporting, no direct comparison was possible. Instead, a meta-analysis of dichotomous data (better/worse post-treatment) was performed. To do so, four sub-groups were defined, according to light intensity used to illuminate the mobility mazes: (a): mobility under a single light of intensity of 4 lux; (b): mobility under a “low” ambient light level (0.2, 0.6, 1, 2 or 4 lux), broadly scotopic light; (c): mobility under a “high” ambient light level (10, 15, 50, 100 or 125 lux), broadly photopic light vision function; (d): mobility under all ambient light levels ranging from 0.2 to 100 lux. Results are summarised in Figure 4 (and in Table S3 (Supplemental)).

Under a light intensity of 4 lux (Figure 4, “Lux 4”), analysis of 4 studies showed an RR of 1.03 (95% CI 0.75, 1.42), indicating an improvement with treatment that did not reach clinical significance ($p = 0.84$). Under low ambient light (“Low Lux 0.2 to 4”), analysis of 4 studies showed an RR of 1.35 (95% CI 0.78, 2.35), indicating an improvement with treatment that did not reach clinical significance ($p = 0.29$). Under high ambient light (“High Lux 10 to 100”), analysis of 4 studies showed an RR of 0.42 (95% CI 0.12, 1.50), indicating a worsening with treatment that did not reach clinical significance ($p = 0.18$). Analysis of all ambient light levels (“All lux levels 0.2 to 100”) of 4 studies showed an RR of 1.15 (95% CI 0.84, 1.58), indicating an improvement with treatment that did not reach clinical significance ($p = 0.39$).

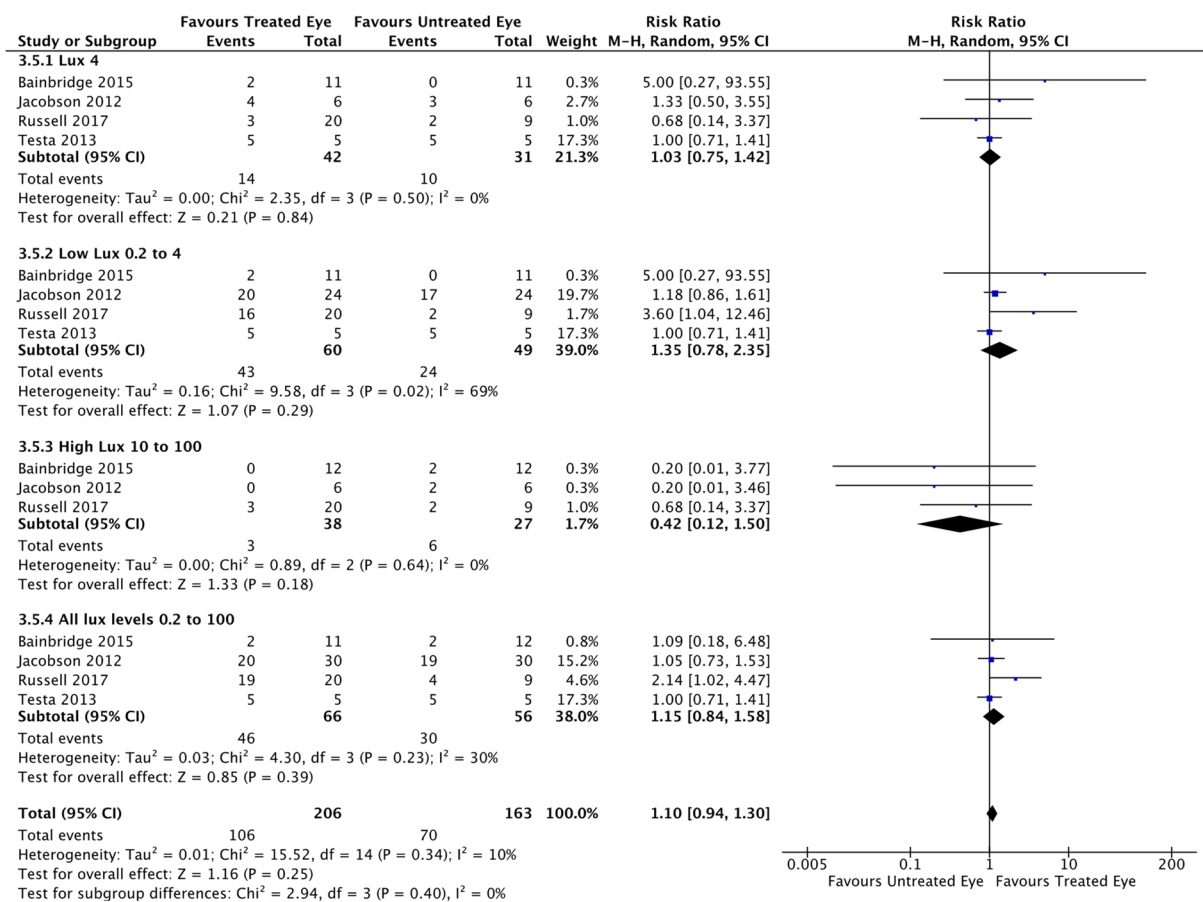


Figure 4. Meta-analysis shows no significant improvement in ambulatory navigation/mobility following treatment. RevMan meta-analysis of dichotomous data showed no significant improvement in performance across all light intensities analysed.

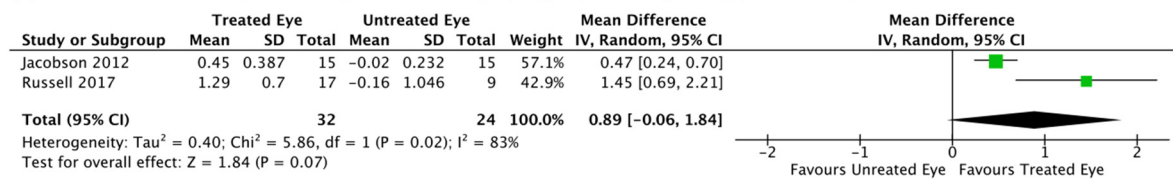
3.5. Full-Field Stimulus (FST) Testing for Red and Blue Wavelength

Only two studies used FST testing that allowed for a meta-analysis. Both continuous and dichotomous (better/worse) data was analysed (Figure 5a–d).

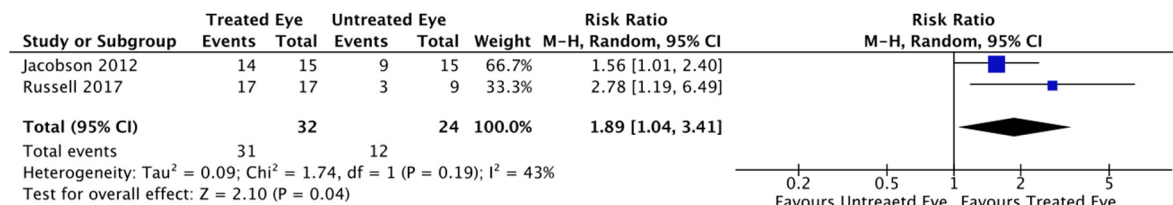
Under red light FST results, analysis of continuous data, showed a mean difference [MD] of 0.89 log₁₀(cd.s/m²) (95% CI −0.06, 1.84) in treated eyes compared to control, indicating an improvement with treatment that did not reach clinical significance (*p* = 0.07). Analysis of dichotomous data (better/worse) for red light FST showed a RR of 1.89 (95% CI 1.04, 3.41), indicating an improvement with treatment that reached clinical significance (*p* = 0.04).

Under blue light FST results, analysis of continuous data, showed a difference of 1.69 log₁₀(cd.s/m²) (95% CI 1.21, 2.16) in treated eyes compared to control, indicating an improvement with treatment that reached clinical significance (*p* = 0.00001). Analysis of dichotomous data (better/worse) showed a RR of 2.01 (95% CI 1.32, 3.06), indicating an improvement with treatment that reached clinical significance (*p* = 0.001).

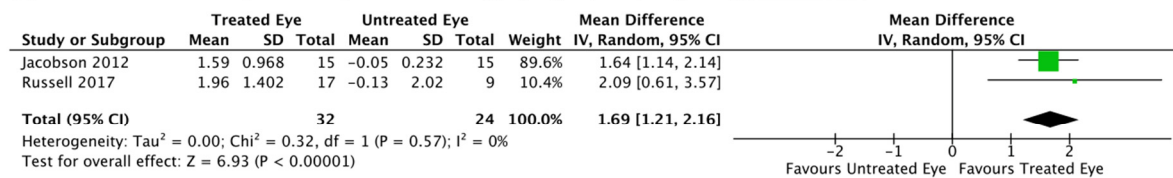
(a) RevMan meta-analysis of FST (red wavelength) log₁₀(cd.s/m²), using continuous data.



(b) RevMan meta-analysis of FST (red wavelength) log₁₀(cd.s/m²), using dichotomous data.



(c) RevMan meta-analysis of FST (blue wavelength) log₁₀(cd.s/m²), using continuous data.



(d) RevMan meta-analysis of FST (blue wavelength) log₁₀(cd.s/m²), using dichotomous data.

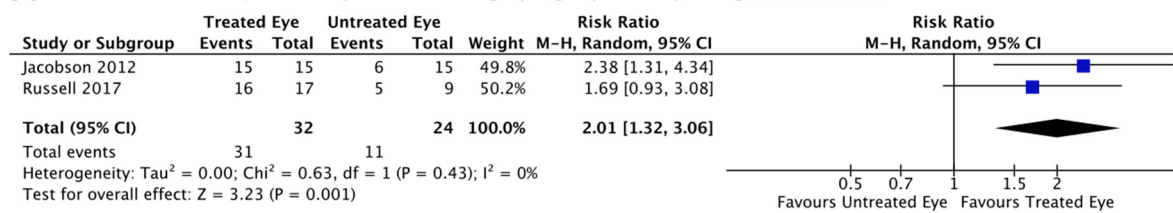
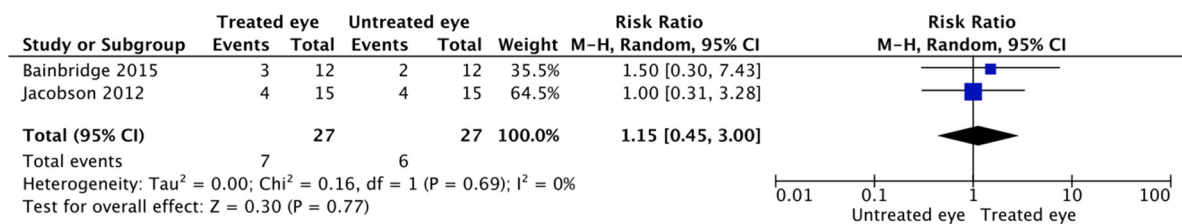


Figure 5. Meta-analysis shows significant improvement in full field sensitivity in response to red and blue light (log₁₀(cd.s/m²)) following treatment [(a–d)]. RevMan analysis of dichotomous FST data shows significant improvement with red (RR1.89; p = 0.04) and blue (RR 2.01; p = 0.001) stimuli. Continuous data shows improvement with blue (mean difference 1.69, p < 0.00001) but not red (mean difference 0.89, p = 0.07) light.

3.6. Central Retinal Thickness (CRT)

Three studies reported CRT outcomes as measured by optical coherence tomography (OCT), but only two included quantitative data that allowed for meta-analysis. Analysis of dichotomous data (thinner/thicker) at 1 year post treatment, showed a RR of 1.15 (95% CI 0.45, 3.00), indicating an increase of CRT with treatment that did not reach clinical significance (p = 0.77) (Figure 6a). Analysis of dichotomous data for a long term timepoint (3 years), showed a RR of 1.29 (95% CI 0.33, 5.10), indicating an increase of CRT with treatment that did not reach clinical significance (p = 0.72) (Figure 6b).

(a) RevMan meta-analysis of CRT results show dichotomous data between the treated and untreated eye groups in a 1-year timepoint.



(b) RevMan meta-analysis of CRT results show dichotomous data between the treated and untreated eye groups in a 3-year timepoint.

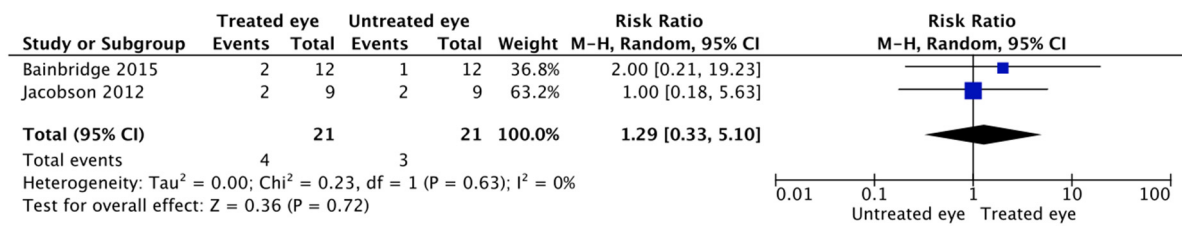


Figure 6. Meta-analysis shows no significant improvement in central retinal thickness following treatment [(a,b)]. RevMan meta-analysis of dichotomous data showed no significant improvement in CRT measurement.

3.7. Risk of Bias Tools within Studies

Cochrane risk-of-bias tools were used to assess study reliability; ROBINS-I methods [52], for non-randomised study designs, and RoB-2 methods [63], for randomised clinical trials. Overall, a risk-of-bias judgement was reported “low/moderate”, with a predicted direction of bias “towards null/unpredictable” for the 5 NRSIs, and a report with “some concerns” and a predicted direction of bias with “favours experimental” for the RCT (Table 2; Appendix A.5, Table A2. and Appendix A.6, Table A3).

Table 2. Analysis of risk of bias studies for five (5) NRSIs and one (1) RCT.

Study Author & Year	ROBIN-I (Risk of Bias in Non-Randomised Studies of Interventions)		RoB-2 (Risk of Bias in Randomised Studies of Interventions [RCT])	
	Risk-of-Bias Judgement	Overall Predicted Direction of Bias	Risk-of-Bias Judgement	Overall Predicted Direction of Bias
Bainbridge et al., 2015	Low/Moderate	Towards null/Unpredictable	N/A	N/A
Jacobson et al., 2012	Low/Moderate	Towards null/Unpredictable	N/A	N/A
Le Meur et al., 2018	Low/Moderate	Towards null/Unpredictable	N/A	N/A
Russell et al., 2017	N/A	N/A	Some concerns	Favours experimental
Testa et al., 2013	Low/Moderate	Towards null/Unpredictable	N/A	N/A
Weleber et al., 2016	Low/Moderate	Towards null/Unpredictable	N/A	N/A

Finally, Table 3 provided a summary of 12 meta-analyses reported for each of the outcomes, a PRISMA summary of a structured abstract in Appendix A.7, and a PRISMA checklist in Appendix A.8 (Table A4).

Table 3. Summary table of 12 meta-analyses with a total of all treated and untreated eyes showed that three meta-analyses have reported statistical significance within the table below *. Of the 3 of the 12 meta-analyses that reached statistical significance, FST (red light) had an RR improvement of 1.89 (95% CI 1.04, 3.41) $p = 0.04$; FST (blue light) had a MD improvement of 1.69 (95% CI 1.21, 2.16) $p = 0.00001$, and finally; FST (blue light) had an RR improvement of 2.01, (95% CI 1.32, 3.06), $p = 0.001$.

No.	Meta Analyses	Number of Studies for Meta-Analysis	Treated Eyes	Untreated Eyes	Study Author	Continuous (C)/Dichotomous (D)	Formal Result (MD or RR)	95% Confidence Interval	Chi ²	I ²	Z Effect	p Value
1	LogMAR visual acuity	6	73	62	Bainbridge, Jacobson, Le Meur, Russell, Testa, Weleber	C	MD −0.06	CI (−0.14, 0.02)	14.39	65%	1.40	0.16
2	LogMAR visual acuity	6	58	47	Bainbridge, Jacobson, Le Meur, Russell, Testa, Weleber	D	RR 1.13	CI (0.83, 1.53)	3.92	0%	0.77	0.44
3	Ambulatory navigation/mobility: Sub-group A (4 lux)	4	42	31	Bainbridge, Jacobson, Russell, Testa,	D	RR 1.03	CI (0.75, 1.42)	2.35	0%	0.21	0.84
4	Ambulatory navigation/mobility: Sub-group B (0.2, 0.6, 1, 2, 4 lux)	4	60	49	Bainbridge, Jacobson, Russell, Testa,	D	RR 1.35	CI (0.78, 2.35)	9.58	69%	1.07	0.29
5	Ambulatory navigation/mobility: Sub-group C (10, 15, 50, 100, 125 lux)	3	38	27	Bainbridge, Jacobson, Russell	D	RR 0.42	CI (0.12, 1.50)	0.89	0%	1.33	0.18
6	Ambulatory navigation/mobility: Sub-group D (0.2–125 lux)	4	66	56	Bainbridge, Russell	D	RR 1.15	CI (0.84, 1.58)	4.30	30%	0.85	0.39
7	FST (red light) measurement of log ₁₀ (cd.s/m ²)	2	32	24	Bainbridge, Russell	C	MD 0.89	CI (−0.6, 1.84)	5.86	83%	1.84	0.07
8	FST (red light) measurement of log ₁₀ (cd.s/m ²)	2	32	24	Bainbridge, Russell	D	RR 1.89	CI (1.04, 3.41)	1.74	43%	2.10	* 0.04
9	FST (blue light) measurement of log ₁₀ (cd.s/m ²)	2	32	24	Bainbridge, Russell	C	MD 1.69	CI (1.21, 2.16)	0.32	0%	6.93	* 0.00001
10	FST (blue light) measurement of log ₁₀ (cd.s/m ²)	2	32	24	Bainbridge, Russell	D	RR 2.01	CI (1.32, 3.06)	0.63	0%	3.23	* 0.001
11	Central retinal thickness (CRT) (1 year)	2	27	27	Bainbridge, Jacobson	D	RR 1.15	CI (0.45, 3.00)	0.16	0%	0.30	0.77
12	Central retinal thickness (CRT) (3 year)	2	21	21	Bainbridge, Jacobson	D	RR 1.29	CI (0.33, 5.10)	0.23	0%	0.36	0.72

4. Discussion

Inherited retinal dystrophies (IRDs) are a leading cause of visual loss in children and adults of working age. Formerly untreatable, the emergence of gene augmentation therapy represents a real paradigm shift in patient care. We thus performed a systematic review and meta-analysis of interventional clinical trials to assess the efficacy of gene therapies for IRDs, thus delivering useful information for both clinicians and patients. The purpose of this systematic review is also based on a “fair test” [64], grounded in evidence-based medicine [65,66] (and Figure S1). To test such new therapies, it is critical to assess how transparent results show clear benefit for the patient. This requires that methodology, study design and outcome measures have to provide a clear and reasonable conclusion for the impact on the patient. A systematic review and meta-analysis of IRD patient outcomes for gene therapy is critical in order to support the field [67].

A search of peer-reviewed literature found that only gene therapies to treat Leber congenital amaurosis (LCA) met the criteria for addressing the original question (Appendix A.1). LCA is a rare disorder and gene therapy is an expensive treatment, which led to studies with small patient numbers. Further, the particularly severe phenotype of the disease, with low visual acuity from birth, led to difficulties in assessing the effect of treatment.

Of the 6 studies analysed, a significant drawback to the meta-analysis performed here is the variability in vector design and concentration of virus injected sub-retinally. All studies analysed used an AAV2 serotype, with most using an AAV2/2 capsid. However, one study used an AAV2/4 capsid. Further, some studies used a hybrid chicken β -actin promoter with a cytomegalovirus enhancer, whilst some used the human RPE65 promoter. Treatment doses ranged from 10^8 to 10^{12} vg, in volumes from 0.15 to 1.0 mL. This spans a number of logarithmic steps in each dose, potentially compromising the comparison of the results within the 6 studies. Despite all this, in our view, the similarities in products compared in the meta-analyses outweigh the differences. All contain the same recombinant human *RPE65* gene, all are packaged in a similar AAV2 vector and all use a similar sub-retinal surgical procedure for delivery. All were used to treat the same trial population (RPE65-LCA2 patients). Further, there were similar criteria for controls and there was considerable overlap in trial duration and endpoints. Finally, we felt the comparison appropriate as pre-clinical work has shown good photoreceptor transduction and expression efficiency. As such, despite the analyses' obvious limitations, we felt it appropriate in order to increase numbers of this rare disease and thus improve statistical power. Given the differences outlined, it is extremely encouraging to note the significant improvements in full-field stimulus (FST) testing that are seen following meta-analysis.

With gene augmentation in its infancy, it is perhaps unsurprising that there were variabilities in the biomarkers used to determine treatment efficacy. In total, 23 outcome assays were used. Visual acuity was the only outcome used in all six studies analysed. Five studies used Goldmann perimetry, four used ambulatory navigation/mobility and three used electroretinography. A further nineteen assays were used in two or less studies. Many of the assays were not comparable for several reasons. Five studies assessed visual fields using Goldmann perimetry, although different studies presented different isopters with variable follow up time. Further, a lack of quantitative data in some studies meant overall meta-analysis was not possible. Three studies used electroretinography as an assay, but two provided no data. Other assays used in two or more studies were unsuitable for meta-analysis due to a lack of quantitative data or irreconcilable differences in the way data was presented. As the field evolves, it is hoped agreed standards for methods and reporting will be established, allowing for easier meta-analyses of trials.

Visual acuity is the gold standard assay by which retinal disease treatments are assessed. Though our meta-analysis showed only modest improvement with gene therapy (in terms of clinical or statistical significance), the result is perhaps not surprising given the low-vision phenotype of LCA patients. Two studies (Bainbridge and Testa) did not provide raw visual acuity data and instead patient vision was determined from results presented in study graphs. This was undertaken by two independent researchers, with a mean of the

two readings being used, but an element of uncertainty remains with the overall result due to the unavailability of raw data within the actual papers. It should be noted that an I^2 value 65% indicates substantial statistical heterogeneity within the VA assays (Figure 3). As such, little weight can be placed upon the outcome of our VA analyses.

The study designs often dictated that the eye with the worse vision was treated, with control eyes having a better baseline vision. Although logMAR vision charts determine a linear improvement in vision with each letter or line gained, if treatment and control arms have different baseline values, bias is introduced and outcomes may be influenced as a result. Without adjustment, it may be unclear what impact arises from the treatment effect, as opposed to the treated eye being worse at baseline. Even adjusted data may not be robust enough to eliminate this confounding factor. Emerging gene therapy trials, where both eyes are treated and compared for one year to a deferred treatment group, should address this issue.

Four studies reported mobility testing as a key outcome. Mobility testing for the MLMT assay (Russell et al.) received criticism by an independent commentator [68] and reviewers in the FDA regarding uneven luminance levels [29]. In addition, we note that the MLMT assay results were indirect. A “passing level” of the assay compared baselines between 1-year timepoints however, the original data for measuring speed, time, accuracy (and further components) for assessment, were not included in the paper or the Biologicals License Application (BLA). Further, the MLMT assay used a logarithmic scale, based on light intensity (lux), which was then subsequently converted to an ordinal scale (ranging from -1 to 6), such that a two-point change in the ordinal scale may have a different interpretation depending on the baseline score (Table S4 (Supplemental)) [68].

Due to disparate methodologies (maze size and design, measurement, quantification and reporting), only analysis of dichotomous data (better/worse post treatment) was possible. This risks overestimating the benefit in certain studies. For example, Russell et al. reasoned that results in their maze required at least 2 levels of improvement on their assessment scale to accept the result as showing therapeutic benefit, whereas we defined even a 1 level gain post-operatively as performing ‘better’.

Some studies had datapoints missing, while quantitative data was missing from others, and required interpretation from results presented in study graphs (Jacobson et al.). Though RevMan analysis of dichotomous data suggested overall improvement in mobility, statistical significance was not reached. At present, there is no better test available for assessing the impact of gene therapy on visual function and so, as the field develops, it would be advantageous if some standardisation of the test could be agreed upon, recently supported by other literature [69–71].

The use of full-field stimulus (FST) testing (white, red and blue wavelength) is highly relevant because few research tools can quantify changes in visual perception if sight loss is as severe as it is in an RPE65/LCA2 population. Thus, the FST data carries extra significance. FST results presented in the studies was at times confusing. One study (Russell et al.) alternately presented white light FST results in $\log_{10}(\text{cd.s/m}^2)$ units and $-\log_{10}(\text{cd.s/m}^2)$ units, whilst not commenting on their red and blue light FST results (Russell et al.). A further study only described results in terms of “log10” units, which we interpreted as $\log_{10}(\text{cd.s/m}^2)$ units (Jacobson et al.), thus allowing for meta-analysis. Although the FDA, as part of the Biologicals Licence Application (BLA) review for Luxturna [29], stated ‘the direct clinical benefit of FST is not clear’, it is apparent from meta-analysis of these two studies that retinal sensitivity improves with AAV-mediated gene augmentation therapy for RPE65-mediated LCA2. The significance of this cannot be underestimated. It is proof of principle that visual improvement is achievable with this technology and gives us hope that similar benefit could be achieved when other alleles are targeted.

The first attempt to use gene augmentation therapy for retinal disease has led to an FDA and EMA approved product (voretigene neparvovec-rzyl [Luxturna]). Improvements in surgical technique and improved knowledge of treatment technicalities (e.g., virus concentration) could mean subsequent iterations of these therapies show improved efficacy. Further, the more novel outcomes for mobility may drive innovative end-points. Though

some concerns were raised by our Cochrane risk of bias analysis, further treatments targeting more common disease-causing genes [37] will mean increased patient numbers in trials and may allow for blinded evaluations, resulting in more robust studies.

As of April 2021, there are > 40 interventional gene therapy trials for IRDs reported at clinicaltrials.gov, from both academic and commercial institutions targeting several different IRD genes [72–76]. This meta-analysis highlights the need for consistency of trial design to allow comparison of gene products, but also shows the potential this technology has for addressing a leading cause of blindness in children and adults of working age.

5. Conclusions

The objective of this work was to conduct a systematic review of interventional clinical trial studies for IRDs and to assess and compare the effectiveness of available gene therapy treatments. Following the search, review and analysis of the relevant studies, the systematic review concluded that a meta-analysis for AAV-RPE65 gene therapy for LCA2 reported a modest improvement for visual acuity, mobility and full-field stimulus testing (FST), with FST improvements reaching statistical significance. In terms of a recommendation to support the IRD patient communities and researchers, we propose that full and open-access data is key. If the field is to be progressed and improved, then objective and transparent results need to be shared in order to improve outcomes, analysis, reporting and interpretation.

Supplementary Materials: The following are available online at <https://www.mdpi.com/article/10.3390/biom11050760/s1>, Figure S1: (a) A simple hierarchy of evidence; (b) A list of 23 assays from the 6 selected studies; (c) Each of the 23 assays re-grouped and colour coded to clearly distinguish how the specific assays were to be used in the study, Figure S2: Visual acuity logMAR, with a random effects model and summary statistic for dichotomous data showed, Table S1: PICOS results. The PICOS search terms, keywords, MeSH terms, search strings and Boolean operators were used and identified in Materials & Method (using Ovid Database), additionally de-defined Appendices A.1–A.3, Table S2: All mean difference (MD) values for all visual acuity logMAR changes across all six (6) papers. All data was retrieved and analysed by two independent authors, Table S3: All ambulatory navigation/mobility across all six (6) papers. All data was retrieved and analysed by two independent authors, Table S4: (a) MLMT (Russell et al. 2017) and (b) derived data from FDA (BLA No. 125610).

Author Contributions: Conceptualization, G.P.T. and R.M.; methodology, G.P.T. and R.M.; software, G.P.T. and R.M.; validation, G.P.T. and R.M.; formal analysis, G.P.T. and R.M.; investigation, G.P.T. and R.M.; resources, University of Edinburgh; data curation, RevMan, Cochrane Library; writing—original draft preparation, G.P.T.; writing—review and editing, G.P.T. and R.M.; visualization, G.P.T. and R.M.; supervision, G.P.T. and R.M.; project administration, G.P.T. and R.M.; funding acquisition, none. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Appendix A

Appendix A.1. Ovid Search Results in MEDLINE and EMBASE

The overall aim of this study was to identify a systematic review and meta-analyses of interventional clinical trial studies for gene therapies for IRDs. The aims of the study were to identify, extract, analyse and critique outcomes for gene therapy treatments from a relevant and specific population, in particular:

(i) identify, search and collate the available research data from IRD patients for gene therapy treatment;

(ii) extract and assess the relevant data from an IRD population and prepare a meta-analysis of the available outcomes and potential impact of the research reporting;

(iii) analyse and critique relevant outcomes from key IRD studies.

This systematic review and meta-analyses were performed for interventional clinical trial outcomes for approved gene therapies for IRDs. The systematic review used a structured search approach with a PICOS process (*Population, Intervention, Comparison, Outcomes and Study*). The specific research question was to search interventional clinical trials (*the study design*) for published gene therapies (*the intervention*) for IRD patients (*the population*), for the purpose of improving the disorder (*the outcomes*), given there was little or no treatment available (*the comparison*).

The search used the Ovid platform to search the MEDLINE, EMBASE and Cochrane databases. The PICOS search terms and search strings included 36 words and phrases using MESH terms and Boolean operators (within this Appendix A.1), and subsequently reported in Appendix A.2.

Database: Ovid MEDLINE(R) <1946 to June Week 5 2020>

Search Strategy:

1. retinitis pigmentosa.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (9772)
2. leber* congenital amaurosis.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1147)
3. inherited retinal disease.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (150)
4. inherited retinal disorder.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (26)
5. X-linked retinitis pigmentosa.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (311)
6. blindness.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (37,460)
7. rpe65.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (720)
8. exp Eye Diseases, Hereditary / (50,296)
9. **1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (85,822)**
10. gene therapy.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (41,640)
11. gene replacement.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2273)

12. recombinant gene.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (733)
13. gene delivery.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (15,306)
14. adeno-associated virus.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (7095)
15. AAV.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6906)
16. viral delivery.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (630)
17. exp Genetic Therapy/(48,858)
18. **10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (80,450)**
19. visual acuity.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (90,996)
20. best-corrected visual acuity.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10,388)
21. standard logarithm of the minimum angle of resolution.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (0)
22. visual field.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (27,503)
23. visual perception.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (64,654)
24. electroretinogram.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (6127)
25. Goldmann visual fields.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (91)
26. microperimetry.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism

- supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (828)
27. fundus photography.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2908)
 28. nystagmus testing.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (18)
 29. central retinal thickness.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (1088)
 30. optical coherence tomography.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (26,996)
 31. pupillary light reflex response.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (10)
 32. full-field light sensitivity threshold.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2)
 33. exp Diagnostic Techniques, Ophthalmological/(169,167)
 34. **19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (267,300)**
 35. clinical trial.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (684,554)
 36. randomised clinical trial.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (2676)
 37. non-randomised.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (3207)
 38. rct.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (18,015)
 39. clinical trial/(523,108)
 40. **35 or 36 or 37 or 38 or 39 (702,125)**
 41. **9 and 18 and 34 and 40 (58)**

Database: Embase <1980 to 2020 Week 28 >

Search Strategy:

1. retinitis pigmentosa.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (12,771)

2. leber* congenital amaurosis.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2206)
3. inherited retinal disease.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (365)
4. inherited retinal disorder.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (49)
5. X-linked retinitis pigmentosa.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (435)
6. blindness.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (56,507)
7. rpe65.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1412)
8. exp eye disease/(860,410)
9. **1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (867,550)**
10. gene therapy.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (98,379)
11. gene replacement.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (3771)
12. recombinant gene.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2354)
13. gene delivery.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (45,914)
14. adeno-associated virus.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (16,154)
15. AAV.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (15,822)
16. viral delivery.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1057)
17. gene therapy/(60,417)
18. **10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 (138,881)**
19. visual acuity.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (133,479)
20. best-corrected visual acuity.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (22,009)
21. standard logarithm of the minimum angle of resolution.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (3)

22. visual field.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (50,559)
23. visual perception.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (8084)
24. electroretinogram.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (12,950)
25. Goldmann visual fields.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (144)
26. microperimetry.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1575)
27. fundus photography.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (4794)
28. nystagmus testing.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (24)
29. central retinal thickness.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (2714)
30. optical coherence tomography.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (66,975)
31. pupillary light reflex response.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (13)
32. full-field light sensitivity threshold.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (10)
33. exp visual system examination/or exp visual system function/or exp visual system parameters/or exp visual threshold/(472,418)
34. **19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (520,911)**
35. clinical trial.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (1,537,834)
36. randomised clinical trial.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (4255)
37. non-randomised.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (5299)
38. rct.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (39,586)
39. clinical trial/(966,569)
40. **35 or 36 or 37 or 38 or 39 (1,567,775)**
41. **exp controlled clinical trial/(792,290)**
42. **9 and 18 and 34 and 40 and 41 (55)**

Appendix A.2. Results of Searches, Papers and Assessment of Data Using Ovid in MEDLINE and EMBASE

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Appendix A.3. Selected Studies (6) for Meta-Analyses

- (1) **Bainbridge et al., 2015 NEJM.** Long-Term Effect of Gene Therapy on Leber’s Congenital Amaurosis. James W B Bainbridge, Manjit S Mehat, Venki Sundaram, Scott J Robbie, Susie E Barker, Caterina Ripamonti, Anastasios Georgiadis, Freya M Mowat, Stuart G Beattie, Peter J Gardner, Kecia L Feathers, Vy A Luong, Suzanne Yzer, Kamaljit Balaggan, Ananth Viswanathan, Thomy J L de Ravel, Ingele Casteels, Graham E Holder, Nick Tyler, Fred W Fitzke, Richard G Weleber, Marko Nardini, Anthony T Moore, Debra A Thompson, Simon M Petersen-Jones, Michel Michaelides, L Ingeborgh van den Born, Andrew Stockman, Alexander J Smith, Gary Rubin, Robin R Ali. *N Engl J Med* 2015 May 14;372(20):1887–97, doi:10.1056/NEJMoa1414221. Epub 2015 May 4.5 [77].
- (2) **Le Meur et al., 2018 Mol Ther.** Safety and Long-Term Efficacy of AAV4 Gene Therapy in Patients with RPE65 Leber Congenital Amaurosis. Guylène Le Meur, Pierre Lebranchu, Fanny Billaud, Oumeya Adjali, Sébastien Schmitt, Stéphane Bézieau, Yann Péréon, Romain Valabregue, Catherine Ivan, Christophe Darmon, Philippe Moullier, Fabienne Rolling, Michel Weber. *Mol Ther.* 2018 Jan 3;26(1):256–268, doi:10.1016/j.ymthe.2017.09.014. Epub 2017 Sep 19 [78].
- (3) **Jacobson et al., 2012 Arch Ophthalmol.** Gene Therapy for Leber Congenital Amaurosis Caused by RPE65 Mutations—Safety and Efficacy in 15 Children and Adults Followed Up to 3 Years. Samuel G Jacobson, Artur V Cideciyan, Ramakrishna Ratnakaram, Elise Heon, Sharon B Schwartz, Alejandro J Roman, Marc C Peden, Tomas S Aleman, Sanford L Boye, Alexander Sumaroka, Thomas J Conlon, Roberto Calcedo, Ji-Jing Pang, Kirsten E Erger, Melani B Olivares, Cristina L Mullins, Malgorzata Swider, Shalesh Kaushal, William J Feuer, Alessandro Iannaccone, Gerald A Fishman, Edwin M Stone, Barry J Byrne, William W Hauswirth; *Arch Ophthalmol.* 2012 Jan;130(1):9–24, doi:10.1001/archophthalmol.2011.298. Epub 2011 Sep 12. [79].
- (4) **Russell et al., 2017 The Lancet.** Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Stephen Russell, Jean Bennett, Jennifer A Wellman, Daniel C Chung, Zi-Fan Yu, Amy Tillman, Janet Wittes, Julie Pappas, Okan Elci, Sarah McCague, Dominique Cross, Kathleen A Marshall, Jean Walshire, Taylor L Kehoe, Hannah Reichert, Maria Davis, Leslie Raffini, Lindsey A George, F Parker Hudson, Laura Dingfield, Xiaosong Zhu, Julia A Haller, Elliott H Sohn, Vinit B Mahajan, Wanda Pfeifer, Michelle Weckmann, Chris Johnson, Dina Gewaily, Arlene Drack, Edwin Stone, Katie Wachtel, Francesca Simonelli, Bart P Leroy, J Fraser Wright, Katherine A High, Albert M Maguire. 2017 Aug 26;390(10097):849–860, doi:10.1016/S0140-6736(17)31868-8. Epub 2017 Jul 14. [58].
- (5) **Testa et al., 2013 Ophthalmology.** Three-Year Follow-up after Unilateral Subretinal Delivery of Adeno-Associated Virus in Patients with Leber Congenital Amaurosis Type 2. Francesco Testa, Albert M Maguire, Settimio Rossi, Eric A Pierce, Paolo Melillo, Kathleen Marshall, Sandro Banfi, Enrico M Surace, Junwei Sun, Carmela Acerra, J Fraser Wright, Jennifer Wellman, Katherine A High, Alberto Auricchio, Jean Bennett, Francesca Simonelli. *Ophthalmology*, 2013 Jun;120(6):1283–91, doi:10.1016/j.ophtha.2012.11.048. Epub 2013 Mar 6. [80].
- (6) **Weleber et al., 2016 Ophthalmology.** Results at 2 Years after Gene Therapy for RPE65-Deficient Leber Congenital Amaurosis and Severe Early-Childhood Onset Retinal Dystrophy. Richard G Weleber, Mark E Pennesi, David J Wilson, Shalesh Kaushal, Laura R Erker, Lauren Jensen, Maureen T McBride, Terence R Flotte, Margaret Humphries, Roberto Calcedo, William W Hauswirth, Jeffrey D Chulay, J Timothy Stout. *Ophthalmology* 2016 Jul;123(7):1606–20, doi:10.1016/j.ophtha.2016.03.003. Epub 2016 Apr 19. [81].

Appendix A.4. Summary Trial Inclusion, Exclusion Eligibility and Endpoints

Table A1. Summary Trial Inclusion, Exclusion Eligibility and Endpoints.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957
Principal Investigator	Study Director: Robin R Ali , PhD University College, London	Samuel G. Jacobson , MD, PhD; University of Pennsylvania	Michel WEBER , Professor; CHU Nantes	Albert M Maguire , MD (Children’s Hospital of Philadelphia) and Stephen R Russell , MD (University of Iowa).	Study Director: Clinical Director, Spark Therapeutics	J Timothy Stout , MD, PhD, MBA; Casey Eye Institute, Oregon Health & Science University
Sponsor (Academic/ Industry)	University College, London; (Moorfields Eye Hospital NHS Foundation Trust; Targeted Genetics Corporation)	University of Pennsylvania	Nantes University Hospital	Spark Therapeutics	Spark Therapeutics	Applied Genetic Technologies Corporation; (Oregon Health and Science University; University of Massachusetts, Worcester.
Official title	An Open-Label Dose Escalation Study of an Adeno-associated Virus Vector (AAV2/2-hRPE65p-hRPE65) for Gene Therapy of Severe Early-Onset Retinal Degeneration	Phase I Trial of Ocular Subretinal Injection of a Recombinant Adeno-Associated Virus (rAAV2-CBSB-hRPE65) Gene Vector to Patients With Retinal Disease Due to RPE65 Mutations (Clinical Trials of Gene Therapy for Leber Congenital Amaurosis)	Prospective Monocentric Open Label Non Randomized Uncontrolled Phase I/II Clinical Gene Therapy Protocol for the Treatment of Retinal Dystrophy Caused by Defects in RPE65	A Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 to the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-301]	A Phase 1 Safety Study in Subjects With Leber Congenital Amaurosis (LCA) Using Adeno-Associated Viral Vector to Deliver the Gene for Human RPE65 Into the Retinal Pigment Epithelium (RPE) [AAV2-hRPE65v2-101]	A Multiple-Site, Phase 1/2, Safety and Efficacy Trial of a Recombinant Adeno-associated Virus Vector Expressing RPE65 (rAAV2-CB-hRPE65) in Patients With Leber Congenital Amaurosis Type 2
Study design	Phase 1–2, open-label, non-randomized;	Phase 1, open-label, non-randomized;	Phase 1/2, open, non-randomized;	Phase 3, open-labelled, randomised (RCT);	Phase 1, open-label, non-randomized (3-year study);	Phase 1–2, open-label, non-randomized;
Treatment	rAAV 2/2. hRPE65p.hRPE65	rAAV2-RPE65	AAV2/4.-RPE65-RPE65	AAV2-hRPE65v2	AAV2-hRPE65v2	rAAV2-CB-hRPE65
Inclusion Criteria:	1 Clinical diagnosis of severe early-onset retinal dystrophy confirmed missense mutation(s) in RPE65	1 RPE65-associated retinal disease (two disease-causing RPE65 mutations);	1 Mutations that code for abnormal RPE65 protein	1 Willingness to adhere to protocol and long-term follow-up as evidenced by written informed consent or parental permission and subject assent (where applicable).	1 Male and female subjects of any ethnic group are eligible for participation in this study, providing they meet the following criteria:	1 Retinal disease consistent with a diagnosis of Leber congenital amaurosis and documented mutations in the RPE65 gene (including null mutations and mutations that code for abnormal RPE65 protein);
		2 Clinical diagnosis of Leber congenital amaurosis (LCA)/early-onset retinal degeneration (EORD) and of severely impaired visual and retinal function, and best corrected visual acuity of 20/40 or worse in the study eye;	2 Presence of characteristic abnormalities in fundus	2 Diagnosis of LCA due to RPE65 mutations; molecular diagnosis is to be performed, or confirmed, by a CLIA-approved laboratory.	2 Must be willing to adhere to protocol and companion protocol for long-term follow-up as evidenced by written informed consent or parental permission and subject assent.	2 At least 6 years of age;
		3 Ability to perform tests of visual and retinal function;	3 Dramatic reduction of both rods and cones ERG responses	3 Age three years old or older.	3 Adults and children diagnosed with LCA.	3 Good general health without significant physical examination findings or clinically significant abnormal laboratory results;

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957				
	4	Visible photoreceptor layer on a standard OCT scan;	4	Low visual acuity <0.32	4	Visual acuity worse than 20/60 (both eyes) and/or visual field less than 20 degrees in any meridian as measured by a III4e isopter or equivalent (both eyes). Sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Must have either: 1) an area of retina within the posterior pole of >100 µm thickness shown on OCT; 2) ≥ 3 disc areas of retina without atrophy or pigmentary degeneration within the posterior pole; or 3) remaining visual field within 30 degrees of fixation as measured by a III4e isopter or equivalent.	4	Molecular diagnosis of LCA due to RPE65 mutations (homozygotes or compound heterozygotes) by a CLIA-approved laboratory.	4	Able to perform tests of visual and retinal function;
	5	Good general health;	5	inform consent signed	5	Subjects must be evaluable on mobility testing (the primary efficacy endpoint) to be eligible for the study. Evaluable is defined as: 1) The ability to perform mobility testing within the luminance range evaluated in the study. Individuals must receive an accuracy score of ≤ 1 during screening mobility testing at 400 lux or less to be eligible; individuals with an accuracy score of > 1 on all screening mobility test runs at 400 lux, or those who refuse to perform mobility testing at screening, will be excluded. 2) The inability to pass mobility testing at 1 lux. Individuals must fail screening mobility testing at 1 lux to be eligible; individuals that pass one or more screening mobility test runs at 1 lux will be excluded.	5	Age eight years old or older at the time of administration.	5	Visual acuity not better than 20/60 and not worse than hand motion in both the treated eye and the fellow eye;
	6	Ability to comply with research procedures;	6		6	Visual acuity ≤ 20/160 or visual field less than 20 degrees in the eye to be injected.	6	Visible photoreceptor (outer nuclear) layer on a standard optical coherence tomography (OCT) scan;		
	7	Specific for Cohorts 1, 2 and 4: 18 years of age and older;	7		7	Acceptable hematology, clinical chemistry and urine laboratory parameters;				

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957
		8 Specific for Cohorts 3 and 5: Between 8 and 17 years of age, inclusive.				8 For females of childbearing potential, a negative pregnancy test at screening and at baseline, and agreement to use effective contraception for 12 months after administration of rAAV2-CB-hRPE65, for sexual activity that could lead to pregnancy;
						9 For males of reproductive potential, agreement to use effective contraception for 12 months after administration of rAAV2-CB-hRPE65, for sexual activity that could lead to pregnancy
Exclusion Criteria:	1 Visual acuity in the study eye better than 6/36 Snellen	1 AAV antibody titers greater than two standard deviations above normal at baseline;	1 Patients with chronic conditions such a haematological, cardiac, renal diseases	1 Unable or unwilling to meet requirements of the study, including receiving bilateral subretinal vector administrations.	1 SUBJECTS WILL NOT BE EXCLUDED BASED ON THEIR GENDER, RACE OR ETHNICITY. Subjects who meet any of the following conditions are excluded from the clinical study: Subjects who meet any of the following conditions are excluded from the clinical study:	1 Pre-existing eye conditions that would preclude the planned surgery or interfere with interpretation of study endpoints or complications of surgery (e.g., glaucoma, corneal or lenticular opacities, or history or retinal detachment);
	2 Hypertension	2 Humoral immune deficiency as evidenced by low tetanus toxoid IgG antibody titers;	2 Patients with, within the past 6 months, a clinically significant cardiac disease or known congestive heart failure, cardiac rhythm and conduction abnormalities	2 Any prior participation in a study in which a gene therapy vector was administered.	2 Unable or unwilling to meet requirements of the study.	2 Presence of epiretinal membrane on OCT;
	3 Diabetes mellitus	3 Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints or surgical complications;	3 Patients with pulmonaty dysfunction	3 Participation in a clinical study with an investigational drug in the past six months.	3	3 History of immunodeficiency or other medical conditions that might increase the risk of rAAV2-CB-hRPE65 administration;

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957
4	Tuberculosis	4 Complicating systemic diseases;	4 Patients with suspected rheumatoid arthritis	4 Use of retinoid compounds or precursors that could potentially interact with the biochemical activity of the RPE65 enzyme; individuals who discontinue use of these compounds for 18 months may become eligible.	4 Participation in a clinical study with an investigational drug in the past six months.	4 Use of anticoagulants or anti-platelet agents within 7 days prior to study agent administration;
5	Renal impairment	5 Use of anti-platelet agents that may alter coagulation within 7 days prior to study agent administration;	5 Patients with current systemic infection	5 Prior intraocular surgery within six months.	5 Pre-existing eye conditions that would preclude the planned surgery or interfere with the interpretation of study endpoints (for example, glaucoma, corneal or lenticular opacities). Lack of sufficient viable retinal cells as determined by non-invasive means, such as optical coherence tomography (OCT) and/or ophthalmoscopy. Specifically, if indirect ophthalmoscopy reveals less than 1 disc area of retina which is not involved by complete retinal degeneration (indicated by geographic atrophy, thinning with tapetal sheen, or confluent intraretinal pigment migration), these eyes will be excluded. In addition, in eyes where optical coherence tomography (OCT) scans of sufficient quality can be obtained, areas of retina with thickness measurements less than 100 µm, or absence of neural retina, will not be targeted for delivery of AAV2-hRPE65v2.	5 History of allergy or sensitivity to medications planned for use in the peri-operative period;
6	Immunocompromise	6 Use of immunosuppressive medications;		6 Known sensitivity to medications planned for use in the peri-operative period.	6	6 For females of childbearing potential, a positive pregnancy test at screening or baseline (within 2 days before rAAV2-CB-hRPE65 administration);

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957			
7	Osteoporosis	7	Pregnancy or breastfeeding;	7	Pre-existing eye conditions or complicating systemic diseases that would preclude the planned surgery or interfere with the interpretation of study. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (for example: radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g., macular edema or proliferative changes). Also excluded would be subjects with immunodeficiency (acquired or congenital) as there could be susceptibility to opportunistic infection (such as CMV retinitis).	7	Complicating systemic diseases or clinically significant abnormal baseline laboratory values. Complicating systemic diseases would include those in which the disease itself, or the treatment for the disease, can alter ocular function. Examples are malignancies whose treatment could affect central nervous system function (for example, radiation treatment of the orbit; leukemia with CNS/optic nerve involvement). Also excluded would be subjects with immuno-compromising diseases, as there could be susceptibility to opportunistic infection (such as CMV retinitis). Subjects with diabetes or sickle cell disease would be excluded if they had any manifestation of advanced retinopathy (e.g., macular edema or proliferative changes). Subjects with juvenile rheumatoid arthritis could be excluded due to increased infection risk after surgery due to poor wound healing. Subjects who are positive for hepatitis B, C, and HIV will be excluded.	7	Females who are breast feeding;

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957			
8	Gastric ulceration	8	Individuals (males and females) of childbearing potential who are unwilling to use effective contraception;	8	Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for four months following vector administration.	8	Prior ocular surgery within six months.	8	Use of any investigational agent, or systemic corticosteroids or other immunosuppressive drug(s), within 3 months prior to enrollment;
9	Severe affective disorder)	9	Any condition that would prevent a subject from completing follow-up examinations during the course of the study;	9	Individuals incapable of performing mobility testing (the primary efficacy endpoint) for reason other than poor vision, including physical or attentional limitations.	9	Known sensitivity to medications planned for use in the peri-operative period.	9	Prior receipt of any AAV gene therapy product;
10	Pregnancy or lactation	10	Any condition that makes the subject unsuitable for the study;	10	Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study or, in the opinion of the investigator, makes the potential subject unsuitable for the study.	10	Individuals of childbearing potential who are pregnant or unwilling to use effective contraception for the duration of the study.	10	Any condition which leads the investigator to believe that the participant cannot comply with the protocol requirements or that may place the participant at an unacceptable risk for participation.
		11	Current, or recent participation, in any other research protocol involving investigational agents or therapies;	11	Subjects will not be excluded based on their gender, race, or ethnicity.	11	Any other condition that would not allow the potential subject to complete follow-up examinations during the course of the study and, in the opinion of the investigator, makes the potential subject unsuitable for the study.		
		12	Recent receipt of an investigational biologic therapeutic agent.			12	Subjects will be excluded if immunological studies show presence of neutralizing antibodies to AAV2 above 1:1000.		

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957
Primary Outcome Measures:	1 intraocular inflammation [Time Frame: at intervals up to 12 months]	1 The primary safety endpoint in this trial is the standard ocular examination. Toxicity will also be assessed by measurement of vision, hematology and serum chemistries, assays for vector genomes, reported subject history of symptoms and adverse events. [Time Frame: 15 years]	1 The drug safety evaluation after administration of the gene therapy product. The patient will be followed for the duration of the hospital stay, an average of 7 days]	1 Multi-luminance Mobility Testing (MLMT), Bilateral [Time Frame: One year (change from baseline)]; The MLMT measures changes in functional vision, as assessed by the ability to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. MLMT was assessed using both eyes at 1 or more of 7 levels of illumination, ranging from 400 lux (a brightly lit office) to 1 lux (a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to those who could not pass MLMT at 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level.	1 The primary outcome measures are safety and tolerability. Secondary outcome measure(s) include changes in visual function as measured by subjective, psychophysical tests and by objective, physiologic tests. [Time Frame: Visual function will be measured at designated intervals from baseline visits through 5 years as stated in the protocol.]	1 Number of Participants Experiencing Ocular or Non-ocular Adverse Events [Time Frame: 2 years]
Secondary Outcome Measures:	1 visual function [Time Frame: intervals up to 12 months]	1 Visual function will be quantified prior to and after vector administration in order to determine whether vector administration affects visual function. [Time Frame: 15 years]	2 Biodistribution: Urine sampling and nasal secretion will be collected at several time points after administration of the gene therapy product during all the duration of hospital stay, an average of 7 days.	1 Full-field Light Sensitivity Threshold (FST) Testing: White Light [Time Frame: One year (change from baseline)]; Measures the light sensitivity of the entire visual field by recording the luminance at which a subject reliably reports seeing the dimmest flash.	2 Participants With Changes in Visual Fields [Time Frame: 2 years]; Improvement in the central 30 degree visual field, measured by static perimetry, at one or more time points after treatment, that was greater than the limit of agreement for baseline values.	

Table A1. Cont.

Study Author	Bainbridge et al., 2015 (NEJM). NCT00643747	Jacobson et al., 2012 (Arch Ophthalmol). NCT00481546	Le Meur et al., 2018 (Mol Ther). NCT01496040	Russell et al., 2017 (Lancet). NCT00999609	Testa et al., 2013 (Ophthalmology). NCT00516477	Weleber et al., 2016 (Ophthalmology). NCT00749957
			Different efficacy parameters and immune parameters have to be measured to conclude on the overall amelioration of quality of life of enrolled patients [Time Frame: Between Day -120 and Day -7, Day 5, Day 14, Day 30 Day 60, Day 90, Day 120, Day 180, Day 360]	Multi-luminance Mobility Testing (Monocular) [Time Frame: One year (change from baseline)]; The MLMT measures changes in functional vision, as assessed by the ability to navigate a course accurately and at a reasonable pace at different levels of environmental illumination. MLMT was assessed using the first eye at 1 or more of 7 levels of illumination, ranging from 400 lux (a brightly lit office) to 1 lux (a moonless summer night). Each light level was assigned a score code ranging from 0 to 6. A higher score indicated that a subject was able to pass the MLMT at a lower light level. A score of -1 was assigned to those who could not pass MLMT at 400 lux. The MLMT of each subject was videotaped and assessed by independent graders. The MLMT score was determined by the lowest light level at which the subject was able to pass the MLMT. The MLMT score change was defined as the difference between the score at Baseline and the score at Year 1. A positive MLMT score change from Baseline to Year 1 visit indicated that the subject was able to complete the MLMT at a lower light level.		Participants With Changes in Best Corrected Visual Acuity [Time Frame: 2 years]; Increase in BCVA of 7 or more letters at Year 2 visit compared to average baseline value
		3		2		3
		4	Recording global ERG (electroretinogram)	3	Visual Acuity [Time Frame: One year (change from baseline)]; Measurement of the sharpness of vision, determined by the ability to read letters on a standardized chart from a specified distance.	
		5	Patient efficacy questionnaire			
		6	Testing of far and near visual acuity, color vision, pupillometry, microperimetry and dark adaptation.			

Appendix A.5. ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions

Table A2. ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B		C		D	E			
	Bainbridge et al., 2015	Jacobson et al., 2012		Le Meur et al., 2018		Testa et al., 2013	Weleber et al., 2016			
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
Bias due to confounding										
<u>1.1 Is there potential for confounding of the effect of intervention in this study?</u>	4 of the 12 patients used the better eye, contradicting the text suggesting that the poorer eye should be the treated eye, Table 1 (page 1889); the concentration of vector genomes (vg) have different cohorts;	Y	Y; "worse" vs. "better" eyes was logMAR 1.09 vs. 0.96, respectively, and there was no adjustment;	Y	Y; "worse" had an average of 31.5 letters while "better" eyes had 41.1 letters and there was no adjustment;	Y	Y; "worse" had a logMAR of 1.47 while "better" eyes had 1.14 logMAR, and there was no adjustment;	Y	Y; "worse" had an average of 24.0 letters while "better" eyes had 28.4 letters and there was no adjustment;	Y
1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	Not significant time split between control vs. intervention;	N		N		N		N		N
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?		NI		NI		NI		NI		NI
Questions relating to baseline confounding only										
<u>1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?</u>	There was no information that controlled a confounding domain;	N	See comment on Jacobson, page 21;	N		N		N		N

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B	C	D	E					
	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
<u>1.5. If Y/PY to 1.4:</u> Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	There was no controlled confounding domains.	N		N		N		N		N
<u>1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?</u>	No information;	NI		N		NI		NI		NI
Questions relating to baseline and time-varying confounding										
<u>1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?</u>	There is no control or adjustment that might impact the outcome between the worse eye vs. the better eye;	N		N		N		N		N
<u>1.8. If Y/PY to 1.7:</u> Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N, see comment above re: better eye of 4 patients were used;	N		N		N		N		N

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A		B		C		D		E	
	Bainbridge et al., 2015		Jacobson et al., 2012		Le Meur et al., 2018		Testa et al., 2013		Weleber et al., 2016	
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
Risk of bias judgement	Moderate/(?); confounding occurs due to uncorrected baselines for treated vs. control;	Low/Moderate		Low/Moderate		Low/Moderate		Low/Moderate		Low/Moderate
Optional: What is the predicted direction of bias due to confounding?	Unpredictable/ Favours experimental	Unpredictable		Unpredictable		Unpredictable		Unpredictable		Unpredictable
Bias in selection of participants into the study	Bainbridge et al., 2015		Jacobson et al., 2012		Le Meur et al., 2018		Testa et al., 2013		Weleber et al., 2016	
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?		N		N		N		N		N
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?		N		N		N		N		N
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		N		N		N		N		N

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B	C	D	E					
	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
2.4. Do start of follow-up and start of intervention coincide for most participants?		NI		NI		NI		NI		NI
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?		NI		N		NI		NI		NI
Risk of bias judgement	Low	Low		Low		Low		Low		Low
Optional: What is the predicted direction of bias due to selection of participants into the study?		Towards null		Towards null		Towards null		Towards null		Towards null
Bias in classification of interventions	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
3.1 Were intervention groups clearly defined?		Y		Y		Y		Y		Y
3.2 Was the information used to define intervention groups recorded at the start of the intervention?		Y		Y		Y		Y		Y
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?		PN		PN		PN		PN		PN

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B	C	D	E					
	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
Risk of bias judgement	Low/Moderate	Low		Low		Low		Low		Low
Optional: What is the predicted direction of bias due to classification of interventions?		Towards null		Towards null		Towards null		Towards null		Towards null
Bias due to deviations from intended interventions	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2										
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	N	N	N	N	N					N
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	N	N	N	N	N					N

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B	C	D	E					
	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6										
4.3. Were important co-interventions balanced across intervention groups?		NI		NI		NI		NI		NI
4.4. Was the intervention implemented successfully for most participants?		PY		PY		PY		PY		PY
4.5. Did study participants adhere to the assigned intervention regimen?		Y		Y		Y		Y		Y
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		Y		Y		Y		Y		Y
Risk of bias judgement	Low	Low		Low		Low		Low		Low
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Towards null		Towards null		Towards null		Towards null		Towards null

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A	B	C	D	E					
	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
Bias due to missing data	Bainbridge et al., 2015	Jacobson et al., 2012	Le Meur et al., 2018	Testa et al., 2013	Weleber et al., 2016					
5.1 Were outcome data available for all, or nearly all, participants?	N/PN; some partial missing data (see mobility data in Figure 2, pg 1892);	<u>Y</u>		<u>Y</u>		<u>Y</u>		<u>Y</u>		<u>Y</u>
5.2 Were participants excluded due to missing data on intervention status?		<u>N</u>		<u>N</u>		<u>N</u>		<u>N</u>		<u>N</u>
5.3 Were participants excluded due to missing data on other variables needed for the analysis?		<u>NI</u>		<u>NI</u>		<u>NI</u>		<u>NI</u>		<u>NI</u>
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?		<u>NA</u>		<u>NA</u>		<u>NA</u>		<u>NA</u>		<u>NA</u>
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?		<u>NI</u>		<u>NI</u>		<u>NI</u>		<u>NI</u>		<u>NI</u>
Risk of bias judgement	Low	<u>Low</u>		<u>Low</u>		<u>Low</u>		<u>Low</u>		<u>Low</u>
Optional: What is the predicted direction of bias due to missing data?		<u>Towards null</u>		<u>Towards null</u>		<u>Towards null</u>		<u>Towards null</u>		<u>Towards null</u>

Table A2. Cont.

ROBINS-I Risk of Bias in Non-Randomised Studies of Interventions (NRSI)										
(1)Yes[Y]; (2) Probably Yes[PY]; (3)Probably no[PN]; (4)No[No]; and (5) No information[NI].										
Risk of bias assessment Responses <u>underlined in green</u> are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.	A		B		C		D		E	
	Bainbridge et al., 2015		Jacobson et al., 2012		Le Meur et al., 2018		Testa et al., 2013		Weleber et al., 2016	
Signalling questions	Description	Response options	Description	Response options	Description	Response options	Description	Response options	Description	Response options
<u>7.1 ... multiple outcome measurements within the outcome domain?</u>	Y; some outcomes were reported to collect some data (e.g., ERG, contrast sensitivity, or FAF) but the outcomes did not show the data; see this main paper of Tuohy & Megaw, Figure 2, showing 23 assays, arranged alphabetically; estimate of 10 of 23 outcomes identified;	NI	See this main paper of Tuohy & Megaw, Figure 2, showing 23 assays, arranged alphabetically; estimate of 8 of 23 outcomes identified;	NI	See this main paper of Tuohy & Megaw, Figure 2, showing 23 assays, arranged alphabetically; estimate of 6 of 23 outcomes identified;	NI	See this main paper of Tuohy & Megaw, Figure 2, showing 23 assays, arranged alphabetically; estimate of 9 of 23 outcomes identified;	NI	See this main paper of Tuohy & Megaw, Figure 2, showing 23 assays, arranged alphabetically; estimate of 5 of 23 outcomes identified;	NI
<u>7.2 ... multiple analyses of the intervention-outcome relationship?</u>	Y; there was no adjusted data	NI		NI		NI		NI		NI
<u>7.3 ... different subgroups?</u>		NI		NI		NI		NI		NI
Risk of bias judgement	Low/Moderate	Low		Low		Low		Low		Low
Optional: What is the predicted direction of bias due to selection of the reported result?	Towards null/Unpredictable	Towards null		Towards null		Towards null		Towards null		Towards null
Overall bias	Bainbridge et al., 2015		Jacobson et al., 2012		Le Meur et al., 2018		Testa et al., 2013		Weleber et al., 2016	
Risk of bias judgement	Low		Low		Low		Low		Low	
Optional: What is the overall predicted direction of bias for this outcome?	Towards null		Towards null		Towards null		Towards null		Towards null	

Appendix A.6. RoB-2—Risk of Bias in Randomised Studies of Interventions

Table A3. RoB-2—Risk of Bias in Randomised Studies of Interventions.

Cochrane Tool for RoB-2—Risk of Bias in Randomised Studies of Interventions (RoB 2)			
(1) Yes[Y]; (2) Probably Yes[PY]; (3) Probably No[PN]; (4) No[No]; and (5) No Information[NI].			
Domain 1: Risk of bias arising from the randomization process			
Signalling questions	Comments	Response options	Actual responses—Russell et al., 2017
1.1 Was the allocation sequence random?	The study was randomized; the allocation sequence was performed under direction of an independent biostatistician assigned to either intervention or control and the list of patients was created before enrolment.	Y/PY/PN/N/NI	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y/PY/PN/N/NI	Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?		Y/PY/PN/N/NI	Y
Risk-of-bias judgement	There is a risk-of-bias due to the small sample and this concern was identified the issue from the authors themselves (see Russell, 2017, page 858).	Low/High/Some concerns	Low/Some concerns
Optional: What is the predicted direction of bias arising from the randomization process?	Favours experimental; change of LogMAR, ambulatory navigation/mobility and full-field sensitivity improves visual function	NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)			
Signalling questions	Comments	Response options	Actual responses—Russell et al., 2017
2.1. Were participants aware of their assigned intervention during the trial?	The study was “open-label” therefore the patients were unblinded.	Y/PY/PN/N/NI	N
2.2. Were carers and people delivering the interventions aware of participants’ assigned intervention during the trial?		Y/PY/PN/N/NI	N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		Deviations may arise on the basis of being unblinded due to the “trial context”, specifically the absence of unequal baselines) (see interpretation in the Cochrane advice, Rob-2 explanation no. 2.3)	NA/Y/PY/PN/N/NI

Table A3. Cont.

Cochrane Tool for RoB-2—Risk of Bias in Randomised Studies of Interventions (RoB 2)			
(1) Yes[Y]; (2) Probably Yes[PY]; (3) Probably No[PN]; (4) No[No]; and (5) No Information[NI].			
2.4 If <u>Y/PY</u> to 2.3: Were these deviations likely to have affected the outcome?	There is “NI”; there was no trial protocol available in the Russell paper, or no IND 13804 document or not included in the BLA 125610 (FDA)	NA/ <u>Y/PY</u> / <u>PN/N</u> /NI	NI
2.5. If <u>Y/PY</u> /NI to 2.4: Were these deviations from intended intervention balanced between groups?	See question above, 2.4	NA/ <u>Y/PY</u> / <u>PN/N</u> /NI	NI
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		<u>Y/PY</u> / <u>PN/N</u> /NI	Y
2.7 If <u>N/PN</u> /NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA/ <u>Y/PY</u> / <u>PN/N</u> /NI	N
Risk-of-bias judgement		Low/High/Some concerns	Some concerns
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental
Domain 3: Missing outcome data			
Signalling questions	Comments	Response options	Actual responses—Russell et al., 2017
3.1 Were data for this outcome available for all, or nearly all, participants randomized?		<u>Y/PY</u> / <u>PN/N</u> /NI	Y
3.2 If <u>N/PN</u> /NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA/ <u>Y/PY</u> / <u>PN/N</u>	N
3.3 If <u>N/PN</u> to 3.2: Could missingness in the outcome depend on its true value?		NA/ <u>Y/PY</u> / <u>PN/N</u> /NI	N
3.4 If <u>Y/PY</u> /NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA/ <u>Y/PY</u> / <u>PN/N</u> /NI	N
Risk-of-bias judgement		Low/High/Some concerns	Low

Table A3. Cont.

Cochrane Tool for RoB-2—Risk of Bias in Randomised Studies of Interventions (RoB 2)			
(1) Yes[Y]; (2) Probably Yes[PY]; (3) Probably No[PN]; (4) No[No]; and (5) No Information[NI].			
Optional: What is the predicted direction of bias due to missing outcome data?		NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental
Domain 4: Risk of bias in measurement of the outcome			
Signalling questions	Comments	Response options	Actual responses—Russell et al., 2017
4.1 Was the method of measuring the outcome inappropriate?	The outcome methods for the mobility test (MLMT) had several measurements rolled into one final outcome without sufficient data including: (i) speed; (ii) time; (iii) accuracy; (iv) obstacles; (v) time penalties; (vi) lux, and; (vii) the scales of ordinal vs. logarithmic interpretation. Consequently, (a) the full direct data and measurements were not available, and; (b) the final outcome may have different interpretations; see comments from FDA reviewers in the BLA 125610.	Y/PY/PN/N/N	Y
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	As above.	Y/PY/PN/N/N	PY
4.3 If N/PN/N to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Open-label, therefore there was no blinding.	NA/Y/PY/PN/N/N	Y
4.4 If Y/PY/N to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	The study is an open-label, unblinded and approved design; while there may be some unconscious influence, there is no evidence for such, therefore was no influence reported; PN or N.	NA/Y/PY/PN/N/N	PN/N
4.5 If Y/PY/N to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA/Y/PY/PN/N/N	PN/N
Risk-of-bias judgement		Low/High/Some concerns	Some concerns
Optional: What is the predicted direction of bias in measurement of the outcome?		NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental

Table A3. Cont.

Cochrane Tool for RoB-2—Risk of Bias in Randomised Studies of Interventions (RoB 2)			
(1) Yes[Y]; (2) Probably Yes[PY]; (3) Probably No[PN]; (4) No[No]; and (5) No Information[NI].			
Domain 5: Risk of bias in selection of the reported result			
Signalling questions	Comments	Response options	Actual responses—Russell et al., 2017
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	There was no pre-specified analysis plan (a protocol) so there is: NI.	Y/PY/PN/N/NI	NI
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...	The MLMT assay is a novel primary outcome; see question and response above in 4.2	Y/PY/PN/N/NI	NI
5.2 . . . multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?		Y/PY/PN/N/NI	NI
5.3 . . . multiple eligible analyses of the data?		Y/PY/PN/N/NI	
Risk-of-bias judgement		Low/High/Some concerns	Some concerns
Optional: What is the predicted direction of bias due to selection of the reported result?		NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental
Overall risk of bias			
Risk-of-bias judgement	Comments	Response options	Actual responses—Russell et al., 2017
Risk-of-bias judgement	Further data would be valuable to conclude an overall risk of bias/judgement.	Low/High/Some concerns	Some concerns
Optional: What is the overall predicted direction of bias for this outcome?		NA/Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable	Favours experimental

Appendix A.7. PRISMA—Structured Summary

Title A systematic review and meta-analyses of interventional clinical trial studies for gene therapies for the Inherited Retinal Degenerations (IRDs)

Abstract

Background

Retinitis pigmentosa (RP) is a group of inherited retinal degenerations (IRDs) causing the deterioration of rod and cone photoreceptor cells in the retina leading to visual impairment or blindness. There is currently no cure for RP. Leber Congenital Amaurosis (LCA), a juvenile form of RP, shows an early infant-onset form of the disease characterised by severe retinal dystrophy, vision loss, nystagmus and an almost non-recordable ERG. Gene therapy is a potential treatment for LCA with previously published trials aimed at addressing several clinical outcomes, including visual acuity, mobility, visual field testing and retinal thickness, amongst others.

Objectives

To conduct a systematic review of interventional clinical trial studies for RP and to assess and compare the effectiveness of available gene therapy treatments.

Search methods

Ovid databases were searched in MEDLINE (from Jan. 1946 to Jun. 2020), EMBASE (Jan. 1980 to Jun. 2020), FDA and [ClinicalTrials.gov](https://www.clinicaltrials.gov).

Selection criteria

Randomised controlled trials (RCTs) and non-randomised studies of the effects of interventions (NRSIs) with any gene therapy treatment for any human patients diagnosed with any syndromic or non-syndromic RP.

Data collection and analysis

Standard methodological procedures of the Cochrane Collaboration for screening, data abstraction, and study assessment. A structured PICOS search strategy used screened records and abstracted data following with a review and assessment of risk-of-bias tools with included studies (with two independent authors). 115 records were found, 7 articles were duplicated and removed, 108 publications were screened, 87 were excluded and 21 articles were accessed for eligibility; of these, 15 articles were excluded: one (1) was not applicable (choroideremia), five (5) were follow-up studies and nine (9) articles included duplicate data. A final six (6) primary articles were conducted for review and meta-analyses, summarised in a PRISMA flowchart.

Main results

Six (6) clinical trial studies reported one (1) RCT and five (5) NRSIs, including a sample of $n = 84$ LCA2 (RPE65) patients across three countries (UK, France and the USA). A gene therapy augmentation treatment for recombinant AAV-RPE65 was sub-retinally transfected for a range of subjects spanning ages from 4–44 years. Twenty-three (23) outcomes were assessed and only five (5) outcomes were reported for meta-analyses: visual acuity (logMAR), ambulatory navigation/mobility, full-field stimulus (FST) testing (red wavelength) measuring $\log_{10}(\text{cd.s/m}^2)$, full-field stimulus (FST) testing (blue wavelength) measuring $\log_{10}(\text{cd.s/m}^2)$, and a final measurement of retinal thickness (evaluating OCT at the fovea). Twelve meta-analyses were reported but only one (1) assay, visual acuity (VA), was common to all six (6) papers.

ETDRS logMAR results found a summary weighted mean difference (MD) of -0.06 logMAR improvement over treated vs. untreated eyes (95% CI $-0.14, 0.02$), $p = 0.16$, including six (6) studies with a I^2 heterogeneity of 65%. An ambulatory navigation/mobility test across a light-intensity level of 4 lux showed an RR (risk ratio) improvement of 1.03, over treated vs. untreated eyes (95% CI 0.75, 1.42), $p = 0.84$, including four studies with a I^2 heterogeneity of 0%. A summary weighted mean difference (MD) of FST (full-field stimulus testing) (red) showed $0.89 \log_{10}(\text{cd.s/m}^2)$ over treated vs. untreated eyes (95% CI $-0.06, 1.84$), $p = 0.07$, and; a summary weighted mean difference (MD) of FST (blue) showed $1.69 \log_{10}(\text{cd.s/m}^2)$ over treated vs. untreated eyes (95% CI 1.21, 2.16), $p = 0.00001$. Finally, an RR improvement of retinal thickness was 1.15 (95% CI 0.45, 3.00), $p = 0.77$. Of

the 12 meta-analyses, only three of the meta-analyses met statistical significance: FST (red light) with an RR improvement of 1.89 (95% CI 1.04, 3.41), $p = 0.04$; FST (blue light) with a MD improvement of 1.69 highlighted above, with a $p = 0.00001$, and finally; FST (blue light) reported an RR improvement of 2.01, (95% CI 1.32, 3.06), $p = 0.001$. All other assays did not reach statistical significance.

Study design quality and an overall risk-of-bias judgement showed “Low/Moderate” and “Towards to null/Unpredictable” with the ROBIN-I tool (NRSIs), and “Some concerns” and “Favours experimental” with the RoB-2 tool (RCT).

Conclusions

The objective of this work was to conduct a systematic review of interventional clinical trial studies for IRDs and to assess and compare the effectiveness of available gene therapy treatments. Following the search, review and analysis of the relevant studies, the systematic review concluded that a meta-analysis for AAV-RPE65 gene therapy for LCA2 reported a modest improvement for visual acuity, mobility and full-field stimulus testing (FST). However, other than FST, there was no clinically meaningful benefit and no statistical significance from the six collected studies. One RCT found a clinically meaningful benefit for an assessment for a primary endpoint for mobility, a MD of 1.6 (95% CI 0.72–2.41), $p = 0.0013$.

In terms of a recommendation to support the IRD patient communities and researchers, we propose that full and open-access data is key. If the field is to be progressed and improved, then objective and transparent results need to be shared in order to improve outcomes, analysis, reporting and interpretation.

Appendix A.8. PRISMA List for LCA2 Studies

Table A4. PRISMA List for LCA2 Studies.

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 53, (Appendix A.7)
BACKGROUND			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 1–2 (Introduction)
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 2 (Materials and Methods); page 4 (Results); Table S1 (Supplemental).
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Informal proposal/protocol assessed and peer-reviewed at the University of Edinburgh.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Table S1 (Supplemental); Appendix A.4.

Table A4. Cont.

Section/Topic	#	Checklist Item	Reported on Page #
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Table S1 (Supplemental); Appendix A.1, page 15.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A.1, page 15; Appendix A.2, page 21.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Appendix A.2, page 21; Appendix A.3, page 31.
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4 (Materials and Methods).
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	2 NRSI studies were supported by academic funding (Jacobson 2012, Le Meur 2018); 1 NRSI was supported by both academic and industry funding (Bainbridge 2015); 2 NRSI studies were supported by industry funding (Testa 2013, Weleber 2016); 1 RCT was supported by industry funding (Russell 2017).
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 4 (Materials and Methods); Appendices A.5 and A.6.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 4 (Materials and Methods).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	Page 4 (Materials and Methods); Page 8–16.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 4 (Materials and Methods); Appendices A.5 and A.6.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	n/a
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 5, Figure 1 (Results)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table S1 (Supplemental); Appendix A.2.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Appendices A.5 and A.6.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3, page 13.

Table A4. Cont.

Section/Topic	#	Checklist Item	Reported on Page #
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3, page 12.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2, page 11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 15 (Conclusion); Appendix A.7 (Structured summary).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Table 2, Page 11; Appendices A.5 and A.6.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15 (Conclusion); Table S4a,b.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None.

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