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# BMJ Open Perspectives of people with inherited retinal diseases on ocular gene therapy in Australia: protocol for a national survey

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## ABSTRACT

**Introduction** Voretigene neparvovec-rzyl (Luxturna) was approved by the Australian Therapeutic Goods Administration on 4 August 2020 for the treatment of biallelic mutations in the *RPE65* gene, a rare cause of congenital and adult-onset retinal dystrophy (predominantly Leber congenital amaurosis). Previous studies have shown that individuals who might participate in gene therapy trials overestimate clinical effect and underestimate risks. However, little is known about the perspectives of patients who may be offered approved gene therapy treatment for ocular conditions (as distinct from participating in clinical trials of gene therapy). The main objective of this study is to develop a tool to assess knowledge, attitudes and perceptions of approved and future genetic therapies among potential recipients of ocular gene therapy. In addition, we aim to assess the quality of life, attitudes towards clinical trials and vision-related quality of life among this cohort.

**Methods and analysis** A new 'Attitudes to Gene Therapy for the Eye' tool will be developed following consultation with people with inherited retinal disease (IRD) and content matter experts. Australians with IRD or their guardians will be asked to complete an internet-based survey comprising existing quality of life and visual function instruments and items for the newly proposed tool. We expect to recruit 500 survey participants from patient support groups, the practices of Australian ophthalmologists who are specialists in IRD and Australian ophthalmic research institutions. Launch is anticipated early 2021. Responses will be analysed using item response theory methodology.

**Ethics and dissemination** This study has received ethics approval from the University of Melbourne (#2057534). The results of the study will be published in a peer-reviewed journal and will be presented at relevant conferences. Organisations involved in recruitment, and the Patient Engagement Advisory committee will assist the research team with dissemination of the study outcomes.

## INTRODUCTION

Inherited retinal diseases (IRDs) are a group of heterogenous degenerative retinal conditions estimated to occur in up to 1 in 1000

## Strengths and limitations of this study

- This is the first study to discern the perspectives of individuals who may be offered gene therapy for inherited retinal disease (IRD) in a standard care setting (outside a clinical trial).
- Recruiting participants with a spectrum of IRD across all ages from multiple sources across Australia, including patient support groups, will allow a comprehensive analysis of participant understanding of and interest in both currently approved and future clinical trials of gene therapies for IRD.
- Collection of utility data (EQ-5D-5L data) will allow health economic calculations for government and insurers who pay for gene therapy.
- The study relies on self-reported diagnosis of IRD.
- The recruitment of self-selecting rather than randomly sampled participants may skew results towards positive views of research given their interest in participating in surveys and/or biases from parents of children affected by IRD.

individuals,<sup>1 2</sup> with the major subtype retinitis pigmentosa (RP) occurring in about 1 in 4000 individuals.<sup>3 4</sup> IRDs are now the most common cause of legal blindness of adults of working age in Australia<sup>5</sup> and the UK.<sup>6</sup> Thus, there is an urgent need for interventions that are aimed at preventing or reversing the ocular manifestations of these genetic conditions.

IRDs predominantly affect the retinal photoreceptors and retinal pigment epithelium (RPE), with variable phenotypes.<sup>7</sup> Most cases are limited to the eye, but 20%–30% have systemic associations.<sup>8</sup> In RP rod photoreceptors degenerate first, followed by cones and affected people experience nyctalopia (night blindness), constriction of the visual field and then reduction in visual acuity. Symptoms of RP may appear at birth (Leber congenital



amaurosis (LCA) phenotype), during childhood (severe early childhood onset retinal dystrophy phenotype) or in adulthood (typical RP phenotype). In cone and cone-rod dystrophy, the cones are affected first, and later the rods may be involved. Affected people may also experience haemeralopia (extreme glare) and loss of central and colour vision. The phenotype may vary between different family members with the same mutation, as exemplified in *ABCA4* mutations where a single mutation in family members can result in macular dystrophy, and cone-rod dystrophy phenotypes.<sup>9 10</sup>

The *RPE65* gene (OMIM 180069) is expressed in RPE cells (supporting cells for the photoreceptors), and encodes RPE65 protein, a critical component of the visual cycle and necessary for vitamin A metabolism in cells.<sup>11</sup> Biallelic mutations in *RPE65* lead to degeneration of photoreceptors in humans.<sup>12–14</sup> Natural history studies show variability in age of onset, degree of severity and disease progression.<sup>15 16</sup> Biallelic *RPE65* mutations are responsible for about 10% of RP cases with LCA phenotype (LCA type 2), and about 2% of adults with typical RP phenotype (RP 20).<sup>17</sup>

IRDs are genetically diverse, with over 300 responsible genes and loci identified to date in genomic and mitochondrial DNA.<sup>18</sup> Gene therapy refers to a set of strategies that modify the expression of an individual's genes or repair abnormal genes.<sup>19</sup> Over 20 gene therapy products have been approved globally for systemic indications, with the two principal approaches including direct in vivo administration of a viral vehicle for gene delivery, and ex vivo therapies generating genetically engineered cells for reintroduction to the patient.<sup>20</sup> Voretigene neparvovec-rzyl (Luxturna) has recently been approved in several jurisdictions for the treatment of biallelic mutations in *RPE65* causing retinal dystrophy.<sup>21–26</sup> Trials of ocular gene therapy for at least 10 IRD are underway.<sup>27 28</sup> Gene therapy in IRD is thought to have a 'therapeutic window' in that it must be performed while there are residual viable photoreceptors, retinal interneurons and optic nerve.<sup>29</sup>

There is limited data on the potential gains and risks of ocular gene therapy, with results limited to published clinical trials, and no long-term studies available.<sup>21–26</sup> In general treatments of direct in vivo administration via subretinal injection of a viral vehicle for gene augmentation appear to have an acceptable safety profile. Immunogenicity is low, but inflammation can be triggered, and immunosuppression may be necessary in some cases. Future RNA-based therapies may have less risk of immune reaction.<sup>30</sup>

Currently, there is limited understanding of the potential participant perspective for *approved* ocular gene therapy. Ganne *et al*<sup>31</sup> demonstrated that members of the public have a low level of knowledge of genetic eye disease. Studies to date have focused on participants in early-stage *clinical trials of experimental therapies*, rather than those receiving approved treatments. The only study of patient-reported outcomes among potential *RPE65* gene therapy trial recipients found a high information need

and wish to take part in medical decisions.<sup>32</sup> A 2012 study of potential participants in a choroideraemia gene therapy Phase I trial revealed participant misconceptions of the value of trial participation in safety studies. Participants tended to overestimate treatment effect, underestimate possible risks and show misconceptions about the timing of treatment.<sup>33</sup> A later study of potential choroideraemia trial participants (NCT02077361) confirmed these findings and noted the value of early-stage published data in influencing treatment decisions and the need to improve postoperative experiences of trial participants.<sup>34</sup> Similarly, Turriff *et al*<sup>35</sup> found potential participants in a Phase I/IIa gene therapy trial for X-linked retinoschisis were motivated by therapeutic hope, although the authors considered the individuals to be realistic in their assessments.

There is an evidence-gap for understanding participant views on receiving an *approved* ocular gene therapy treatment, compared with participating in a *clinical trial*. Even in standard trials of treatments of retinal conditions, participants may have an incomplete understanding of their rights and the process.<sup>36</sup> Ocular gene therapy for IRD has the potential to provide significant improvements in quality of life to patients and their families. However, like most medical and surgical procedures, there are associated risks. Hence, it is imperative that researchers and clinicians are aware of patient perspectives on the imminent arrival of approved ocular gene therapies, and use this information to facilitate patient informed consent processes, and to better inform regulatory bodies and reimbursement strategies. Thus, we aim to develop a tool to investigate the knowledge, attitudes and perceptions of the risks and benefits associated with approved and future gene augmentation therapies among people with IRDs. In addition, we aim to assess the quality of life, attitudes towards clinical trials, and vision-related quality of life among this cohort.

## METHODS AND ANALYSES

### Objectives

The primary objective of this study is to survey Australian patients with an IRD and/or their guardians (for minors) to identify their perceptions and understanding regarding receiving gene therapy treatment for IRD, and to evaluate the effect of key variables, such as quality of life, on perceptions and understanding.

The secondary objective is to develop a novel survey instrument to assess understanding of approved ocular gene therapy (Attitudes to Gene Therapy for the Eye (AGT-Eye) Tool), with instrument calibration and item reduction after survey responses have been received.

### Study design

This will be a structured survey with non-random sampling, primarily administered via internet with a paper-based alternative available as needed. To fulfil the above objectives, we have developed a battery of survey tools, including previously validated questionnaires and

a newly developed tool, AGT-Eye, survey. The following previously validated survey tools were selected for inclusion in the protocol:

- ▶ EQ-5D-5L Questionnaire (a generic health status score)<sup>37</sup> to assess quality of life, and for use in future cost efficacy and utility calculations using published cost data.
- ▶ National Eye Institute Visual Functioning Questionnaire (VFQ-25),<sup>38</sup> a patient-reported outcome instrument widely used in clinical trials to assess vision-related quality of life. Evidence of the burden of disease will be instrumental for regulatory and funding bodies.
- ▶ PACT 22 Clinical Trial Attitudes Scale<sup>39</sup> to assess attitudes towards clinical trial participation, including therapeutic misconceptions. This will assist in differentiating perceptions of experimental and approved therapies.

Copyright owners of the three validated survey tools have each given permission for their use.

### Design of the AGT-Eye Tool

A three-stage strategy was used in order to develop the items which will be included in the surveys. Communication within focus groups at each stage was implemented by internet video-conferencing and email; as in-person meetings and focus groups were discouraged during the COVID-19 pandemic.

#### Stage 1: theme generation

In the first stage an expert working committee consisting of 12 ophthalmologists with expertise in IRD (HM, FKC, JG, TLE, AWH, AK, MH, DM, JR, MS, DAT, JW) followed a Delphi process to identify domains based on their extensive knowledge of IRD gained through involvement with patients in clinical practice and their experience of running a natural history study of IRD. Statements thought to capture the latent traits within these domains were generated in a format to be evaluated against a 5-point Likert scale with responses ranging from *Strongly disagree* to *Strongly agree*. These statements were then reviewed independently by an independent multidisciplinary team expert in genetic disease and treatment (RVJ, AGC, GH, AM, BN, IS). Consensus was sought but, where needed, the senior leaders (HM, FKC and JG) arbitrated and made final decisions.

#### Stage 2: involvement of target population

A patient engagement advisory committee was recruited from patient support groups, and comprised seven people with IRD, and two parents of minors with IRD. They were provided with a link to the online REDCap database<sup>40</sup> containing provisional AGT-Eye statements, along with the survey questions, and asked their opinion on the following topics:

- ▶ The appropriateness of AGT-Eye statements, including any concerns for respondents' psychological health when answering sensitive questions.

- ▶ Additional concepts that they consider relevant which have not been covered in the provisional AGT-Eye statements.
- ▶ The accessibility and clarity of the full battery of questionnaires.
- ▶ The time required to complete the survey.
- ▶ The appropriateness of our proposed recruitment strategies (public and private ophthalmology clinics and patient support organisations).

#### Stage 3: readability and clarity

Throughout the process, draft questions were reviewed for readability, clarity and avoidance of duplication by a multidisciplinary committee consisting of researchers with backgrounds in optometry, orthoptics, biostatistics and data management (FO'H, MM, ACZ, NT, LA), all with expertise in retinal disease and online data collection, in addition to the primary investigator (HM). The final 6 domains and 22 questions are shown in [table 1](#).

Responses will be rated on a 5-point Likert scale from 1 *Strongly disagree* to 5 *Strongly agree*. Items 4, 6, 7, 8, 12, 16 and 22 will be reversed for consistency of score interpretation. Item 2 will be scored as a mean between 1 and 5 of responses to the nine subitems. Total scores for the 22 AGT-Eye items will range between 22 and 110. The six domains will be scored as weighted means of the component individual items in a range between 1 and 5, and totalled to a range from 6 to 30. Interpretation of scores is shown in [table 2](#).

#### Future Stage 4: instrument calibration and item reduction

Item response theory methods will be employed to refine the AGT-Eye tool using responses from the full survey. This step will involve item reduction and reassessment of domains if appropriate, as detailed below. After item reduction and reassessment of domains the final AGT-Eye score will be calculated for each respondent to be used in statistical analysis.

#### Patient and public involvement

As detailed above, input from people with IRD was sought during stage 2 of AGT-Eye development through a second working group, and their feedback was taken into consideration in the final drafting of the protocol. It is possible that the themes discussed during tool development may prompt these nine people to undertake additional independent research into gene therapy. Therefore, the nine people involved in the working group will be excluded from participating in the final survey, in order to remove a potential source of bias. There was no public involvement in protocol design.

#### Survey eligibility

Eligibility criteria includes males and females aged 18 years and above with an IRD, including syndromic forms, or the adult guardian of a person with an IRD who is aged below 18 years. IRDs are defined as retinal disorders caused by an inherited gene mutation resulting in loss of photoreceptor function accompanied by visual

**Table 1** AGT-Eye domains and items

<b>Awareness of treatment</b>	
1	I have good knowledge about gene therapy for inherited retinal diseases.
<b>Sources of information</b>	
2	I have obtained information about gene therapy treatment from My ophthalmologist Other medical or health professional Registry for example, Australian Inherited Retinal Disease Register Research group Newspapers Internet Social media Patient support group Family/friends
<b>Knowledge of clinical trials vs approved treatment</b>	
3	I understand the difference between an experimental treatment provided by a clinical trial and a treatment that has already been approved by the Australian government.
<b>Timing and method of treatment</b>	
4	<i>Gene therapy for the eye is suitable at any stage of a person's life.</i>
5	Generally, gene therapy for inherited retinal disease is delivered to both eyes.
6	<i>Gene therapy for the eye is injected into the blood stream through the arm.</i>
7	<i>Gene therapy and stem cell therapy are the same treatment.</i>
<b>Understanding of outcomes</b>	
8	Gene therapy for the eye can restore vision back to normal.
9	Gene therapy for the eye is a treatment that may slow down the disease.
10	Treatment complications to my eyes, such as permanent blindness, are possible with an approved gene therapy.
11	Gene therapy in my eye may have side effects elsewhere in my body.
12	<i>Having gene therapy for their eye condition means a person will not pass on an eye condition to any children they may have in the future.</i>
13	I may not be eligible for financial or other government benefits if my gene therapy for my eye condition is successful.
14	Gene therapy for inherited retinal diseases will require many years of follow-up with my eyecare practitioner.
15	Receiving gene therapy for my inherited retinal disease means I won't be eligible for future genetic treatments.

Continued

**Table 1** Continued

<b>Awareness of treatment</b>	
16	<i>I will lose my privacy if I undergo gene therapy, and my data will be in the public domain.</i>
17	If I undergo gene therapy, it will affect my eligibility or terms of conditions in life, disability or health insurance in the future.
<b>Understanding the cost and opportunity cost of treatment</b>	
18	The government should pay all costs of my gene therapy.
19	Government subsidy of my treatment would be an effective use of taxpayer money.
20	If gene therapy for my condition was not available in my state I would consider travelling interstate to access it.
21	My private health insurance should pay all out of pocket costs for my gene therapy.
22	<i>I would consider a payment plan for my gene therapy.</i>

Domains (bold) and items designed to measure the attitudes of people with inherited retinal disease towards gene therapy. These domains and items will be revised using item response theory after responses to the survey have been received. *Italised* items will be reversed in score calculations for consistency of interpretation. AGT-Eye, Attitudes to Gene Therapy for the Eye.

loss,<sup>41</sup> and should have been previously diagnosed by an ophthalmologist. No prior confirmation of genotype is required. People who are carriers of IRD mutations but do not display an ocular phenotype will be excluded. People with other retinal conditions with known genetic risk factors (such as age-related macular degeneration) will be excluded in the absence of an ophthalmologist-diagnosed IRD as defined above.

### Survey recruitment

Australian paediatric and adult patients with IRD will be recruited from the Australian Inherited Retinal Disease Registry and DNA Bank (a registry of 4164 IRD-affected participants from 2911 families),<sup>42 43</sup> Australia's specialist ophthalmic hospitals (Royal Victorian Eye and Ear Hospital and Sydney Eye Hospital), the ophthalmology and clinical genetics departments of the major metropolitan teaching hospitals and the private practices of the authors who are specialists in IRD. All Australian ophthalmologists will be notified through the Royal Australian and New Zealand College of Ophthalmologists and asked to forward an invitation to their eligible patients. Participants will also be recruited through four patient support groups which have given in-principal support: Retina Australia, Vision Australia, Cure Blindness Australia and UsherKids Australia.

Potential participants will be invited to participate by the partners listed above via email or letter, and a social media campaign is planned. Interested people will be

**Table 2** Interpretation of scores on the domains of the questionnaire

Dimension	Low score	High score
Awareness of treatment	Respondents have low awareness of gene therapy treatment	Respondents perceive they have high awareness of gene therapy treatment
Sources of information	Respondents require information	Respondents do not require information
Knowledge of clinical trials and approved treatments	Respondents do not understand the difference between a clinical trial and approved treatments	Respondents believe they understand the difference between a clinical trial and approved treatments
Timing and method of treatment	Respondents have low understanding of gene therapy process	Respondents have good understanding of gene therapy process
Understanding of outcomes	Respondents have low understanding of gene therapy outcomes	Respondents have good understanding of gene therapy outcomes
Understanding the cost and opportunity cost of treatment	Respondents expect to contribute personally to the cost of treatment	Respondents expect governments and insurers to pay for treatment and disability support services
Overall score	Respondents have high information need regarding gene therapy for IRD	Respondents have sufficient knowledge and awareness to sign informed consent if they are offered gene therapy for IRD

IRD, inherited retinal disease.

directed to the survey webpage to register. Participants will not be compensated for their participation.

### Survey sample size

The number of participants recruited will be limited by the recruitment period (4 months) rather than the number required to statistically evaluate a hypothesis. Based on a population frequency of 1 in 2000 individuals,<sup>1</sup> Australia's population of patients with IRD is estimated at 16 000. However, many of these people will still be undiagnosed, or may have withdrawn themselves from medical care or patient support organisations (our recruitment streams). Given that responses to internet surveys are typically low,<sup>44</sup> although unknown in our target population, we estimate gathering responses from 500 participants. It is anticipated that these participants will represent a range of Australians with IRD in terms of age, type and severity of condition, visual function, location of residence and socioeconomic status and comprise approximately 3% of Australians with IRD. Given this is the first instrument of its kind, the overall and subgroup scores that are required to estimate the statistical power achievable with this sample size are difficult to predict. The primary purpose of this study is to describe the distribution of responses within the population.

### Consent

The consent process will be self-administered via mixed-mode approach suitable for visually impaired participants.<sup>45</sup> Participants completing the online version of the study will read the online plain language statement and an online consent form. Participants will be asked to indicate consent by selecting a YES button. They will then proceed to the survey. Participants who self-complete the paper-based survey will read a plain language statement,

sign one consent form and return it by mail, and keep one consent form for their records.

### Survey procedure

We envisage that the majority of participants will enter data directly into the REDCap<sup>40</sup> platform, which has accessibility functionality (font enlargement and text-to-speech facilities). Participants will have the option of providing identifiers (name and email address or telephone number) or remaining anonymous. A small number of older participants who do not have internet availability and/or skills (estimated to be less than 10%) will complete a paper-based survey and return it with the signed consent form to the researchers by pre-paid mail for entry into the database by study staff.<sup>46</sup>

Email reminders to participate will be sent at 4 weeks by the organisations facilitating recruitment. Participants who have registered and partially completed the survey will receive automated REDCap email reminders at 2 and 4 weeks. Participants who have been mailed a paper-based survey will have a reminder letter mailed at 4 weeks.

### Survey

The paper version of our survey (online supplemental files 1 and 2) shows explanatory wording and the context provided. However, most participants will complete the survey online via REDCap database software. Basic demographic data including age, gender and information relating to socioeconomic status will be collected. Participants will record if they are an affected individual or the parent of an affected child. Self-reported clinical data, such as information about symptoms, history of treatment and perceived barriers to receiving gene therapy will be recorded. Participants will complete the 22 AGT-Eye items, followed by the three previously validated questionnaires.

The time taken to complete the full survey is estimated up to 1 hour for individuals with low vision.

### Participant timeline

Enrollment will begin early in 2021. The recruitment period will be 4 months. The project is time critical given that Voretigene neparvovec-rzyl was approved in Australia 4 August 2020, and we intend to assess knowledge prior to treatment of the first Australian patient.

### Follow-Up

No specific follow-up is organised for the participants of the study. However, respondents will be asked if they wish to be contacted with further information on IRDs and upcoming gene therapy options in Australia and if they consent to their deidentified survey data being retained for possible future longitudinal studies (subject to future ethical approval). Respondents will also be provided with contact details for organisations that offer resources for mental health, in case the questions used in the study raise psychological concerns.

### Analyses

The psychometric properties (such as targeting, reliability, consistency, discrimination, dimensionality and differential item functioning) of AGT-Eye will be investigated using item response theory methodology. Item reduction will be performed if appropriate. Participant scores for this instrument will be generated as both a single index value, and according to any identified subscales. Following analysis of the survey responses, items may be reworded or removed before a final version will be recommended for future use. Each of the existing instruments will be scored according to published methods.<sup>36–38</sup>

Descriptive and inferential statistics will be used to investigate the associations between demographics and self-reported clinical data and the scores in the various instruments and the correlation between instruments. Because the AGT-Eye will provide novel data, the distribution of responses will need to be assessed prior to deciding which statistical tests will provide valid inference. Subgroup comparison may be conducted via analysis of variance (>2 groups), Welch's t test or linear regression (2 groups) in the presence of approximately normally distributed AGT-Eye scores. Otherwise, the Kruskal-Wallis test (>2 groups) or the Wilcoxon rank-sum test (2 groups) will be used. Correlation between instruments will be quantified using Spearman's correlation coefficient. Subanalyses will be made of data submitted by persons with IRD compared with parents and guardians of people under the age of 18 years.

A narrative comparison between responses in this cohort and published findings from gene therapy clinical trial participants with eye conditions and other systemic and neurological conditions, such as Huntington's disease, will be made. Huntington's disease has been chosen as a comparator with IRD as both are untreatable neurodegenerative conditions. However, it should be noted that

the former is a fatal condition, whereas IRDs lead to an isolated sensory loss, with no risk to life. As such, we will consider the different risk/benefit ratios that patients will need to consider, and the underlying psychological aspects to the two diagnoses. To our knowledge, there is no better comparator—we have not seen studies investigating recently approved non-gene therapies for IRD, for example.

### Data collection, management and privacy

Deidentified data for this study will be collected using REDCap, a secure web application for building and managing online surveys and databases.<sup>39</sup> REDCap includes a full audit trail and specified user-based privileges. Access to study data in REDCap will be restricted to the members of the study team by username and password and two-factor authentication. User access rights will enforce restricted viewing of Protected Health Information. Data will be accessible to administrators only as deidentified read-only data. Only deidentified data will be permitted to be exported for the purposes of analysis and reporting.

The REDCap platform consists of a MariaDB relational database and a web server. These servers are in a physically secure location on premise at the Centre for Eye Research Australia and managed by the CERA Information Technology team. Both REDCap and MariaDB are widely used, reliable and well-supported systems.

Participants will have the option to choose to provide their name and contact details, and allow their survey results to be identifiable (for future follow-up). This identifiable data will only be available to a limited number of researchers (as specified in our ethics approval).

Storage and destruction of data are compliant with the Australian Privacy Principles<sup>47</sup> and the Australian National Statement on Ethical Conduct in Human Research.<sup>48</sup> Intermittent random audit of data quality will be performed by the principal investigator, and governance procedures will be carried out by the Centre for Eye Research Australia.

## ETHICS AND DISSEMINATION

### Ethical review

Formal ethical approval has been granted by the Human Research Ethics Committee of the University of Melbourne (#2057534). All procedures are in accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 2014<sup>49</sup> and with Australian National Statement on Ethical Conduct in Human Research.<sup>47</sup> All participants will provide consent after being informed of the nature of the study, regardless of survey administration method.

### Dissemination

The study results will be disseminated through scientific publications in peer-reviewed journals and presentations in relevant national and international conferences.

In addition, deidentified reports of aggregate data and findings will be provided to participants, and presentations at meetings will be provided to Retina Australia, Vision Australia, Cure Blindness Australia and UsherKids Australia. The patient engagement advisory committee will also assist in result dissemination. The standardised checklists such as those from the Strengthening the Reporting of Observational Studies in Epidemiology<sup>50</sup> guidelines and relevant items from the Consolidated criteria for Reporting Qualitative studies<sup>51</sup> checklist will be used to ensure that all relevant aspects of study design and data collection are addressed.

### Data sharing, access and release

The deidentified dataset that supports the findings of this study will be made available on reasonable request, to appropriate researchers, subject to approval of an ethics amendment by the relevant Human Ethics Research committee. Requests for data access should be directed to the corresponding author, HGM. Data will be available beginning at 6 months after and ending 7 years following article publication.

## DISCUSSION

IRD is now the most common cause of blindness in working age adults in Australia<sup>5</sup> and the UK,<sup>6</sup> and likely in other developed countries. Aside from the limited evidence that some nutritional supplements can delay progression, for example, Vitamin A supplementation for RP,<sup>52</sup> there have been no treatments until 2017 when voretigene neparovec-rzyl (Luxturna) became the first USA Food and Drug Administration-approved treatment for the very rare *RPE65* mutations causing congenital and adult-onset IRD. Previous studies have demonstrated that potential gene therapy recipients lack information and have misconceptions regarding the value of trial participation and the risks of treatment.<sup>31–36</sup> There is no information on the perspectives of persons with *RPE65* gene mutations who may be eligible for this approved treatment (as distinct from participating in a clinical trial), or from other persons with IRD who may be eligible for future treatments. This study aims to fill this evidence-gap.

The project is significant in that it will:

1. Validate the first questionnaire regarding participant understanding of approved gene therapy (as distinct from clinical trials) for any indication.
2. By recruiting participants from multiple sources across Australia, including patient support groups, this project will allow a comprehensive analysis of participants' understanding of and interest in both currently approved gene therapy and future clinical trials of new gene therapies for IRDs and a comparison between how approved gene therapy and clinical trials are viewed.
3. Collect quality of life data (EQ-5D-5L, VFQ-25)<sup>37 38</sup> which will assist health economic calculations for government and insurers who pay for gene therapy.

4. Provide the opportunity to undertake future follow-up surveys, including stratification of data from those who undertake gene therapy and those who decline gene therapy (subject to patient consent for data retention, and future ethics approval), and
5. Allow further collaboration with patient support groups and the patient community, necessary in planning research in rare conditions.<sup>53</sup>

Potential limitations include lack of pilot data, uncertainty around sample size planning, selection bias, self-reporting of data with regard to IRD diagnosis and symptoms and misdiagnoses by ophthalmologists. Discrepancy in quality of life reporting between children and their parents/guardians is well recognised.<sup>54</sup> To address this, we will perform subanalyses separately on people with an IRD, and the parents/guardians of children. Although genetic testing in IRD is now regarded as the standard of care in Australia,<sup>41</sup> the majority of patients may not have a genetic diagnosis of their condition. Data capture via an internet-survey, as compared with focus groups for example, may limit the study by low response rate<sup>44</sup> and reliance on information technology to survey a group of participants who may have low vision. We have sought to overcome low vision limitation by the option of hard copies of the survey to those who request it. The conventional utility measurements (EQ-5D-5L<sup>37</sup> and VFQ-25<sup>38</sup>) used may have limitations in this patient group.

In summary, the results of this study will delineate the perspectives of potential ocular gene therapy patients in Australia, critically timed to coincide with approval of the first gene therapy for IRD in Australia, provide a foundation methodology for future studies and generate data for future cost utility measures for this new and exciting treatment option.

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**Contributors** HM is the Principal Investigator and conceived the project, drafted the first draft of the AGT-Eye survey and was primary author of this manuscript. She is a guarantor. FKC and JG assisted in protocol development and editing of the manuscript. JDR assisted in protocol development and editing of the manuscript, and also helped with the recruitment strategy (as Lead of the AIRDR). RJ assisted in coordinating multidisciplinary team input and in protocol development. NT, FO'H and ACZ assisted in protocol development, REDCap database construction and editing of the manuscript. MM assisted in protocol development, REDCap database construction and statistical expertise. LA assisted in protocol development, ethics applications, project management and editing of the manuscript. The members of the Australian Ocular Gene Therapy Group all assisted in AGT-Eye protocol development.

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