Clinical Trial Knowledge Among Adults with Inherited Retinal Dystrophy (IRD)

by

Alexandra Larson

Bachelor of Science, Hope College, 2019

Submitted to the Graduate Faculty of the

School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2024

UNIVERSITY OF PITTSBURGH

SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Alexandra Jeanne Wyeth Larson

It was defended on

April 9, 2024

and approved by

Jodie Vento, MS, LCGC, Department of Human Genetics

Joseph Martel, MD, Department of Ophthalmology

Thesis Advisor: Michelle Alabek, MS, LCGC, Department of Ophthalmology

Clinical Trial Knowledge Among Adults with Inherited Retinal Dystrophy (IRD)

Alexandra Jeanne Wyeth Larson, MS

University of Pittsburgh, 2024

Background: Treatments for inherited retinal dystrophy (IRD) are quickly becoming a reality due to tremendous advances in ocular gene therapy research. Patient misconceptions about clinical trials can act as a barrier to study participation enrollment.

Purpose: This study aims to identify potential clinical trial knowledge gaps among adults with IRD as well as patient preferences for receiving new information. The hope is that this information can be used to develop patient educational intervention and promote timely, informed decision-making.

Methods: The Clinical Trial HEalth Knowledge and Beliefs Scale (CHEKS) was distributed via email to members of the My Retina Tracker registry, an international research database of individuals and families affected by IRD. The study team developed an additional 4 items to assess clinical trial knowledge that is particularly relevant to ocular gene therapies (CHEKS+). In addition to the CHEKS tool, the survey included demographic questions, sources of clinical trial information, and preference for receiving educational material.

Results: For 202 survey responses, the mean CHEKS+ score was 94.5 ±13.6 (out of a possible total 116). Participants who reported that they had a good understanding of clinical trials scored higher (101.4 +11.3) than those who did not self-perceive strong understanding (90.3 +13.2) ($p < 0.001$). CHEKS items that addressed the patient experience during a clinical trial, such as the option to withdrawal from the study, performed worse (mean score of 3.1 out of 4) than items that addressed patient considerations prior to trial consent (mean score of 3.4) ($p < 0.001$).

Participants most often obtained clinical trial information from registries (indicated by 55.9% of participants) and ophthalmology providers (28.2%). Of the participants who preferred to receive written information on clinical trials (89.1%), 85.4% preferred online over hardcopy distribution. Most participants preferred to receive clinical trial information on a recurring basis (84.8%).

Conclusions: There are common clinical trial misconceptions among adults with IRD. The findings from this study support public health efforts to develop educational interventions that enable equitable access to research opportunities for patients with IRD.

Table of Contents

List of Tables

List of Figures

Preface

The successful completion of this project would not have been possible without the support of several individuals. The committee chair, Michelle Alabek, MS, LCGC, generated the initial idea for the project and maintained unfailing enthusiasm throughout its duration. I am incredibly grateful for her guidance and invaluable insight into the subject matter. I would like to express immense gratitude for Jodie Vento, MS, LCGC who acted as a committee member and provided guidance throughout my graduate training. Her instruction strengthened my abilities as a genetic counselor and researcher. Joseph Martel, MD allotted time from his clinical schedule to serve on the committee and share his expertise on the IRD clinical trial space. I am highly appreciative of his input and believe it strengthens the impact of the project.

I would like to thank Joan Fisher, Senior Research Specialist at FFB for her collaboration on this project. Joan was a pleasure to work with and was essential for participant recruitment in this study.

I am grateful for the endless encouragement from my family including my parents, John and Kathleen Wyeth, and siblings, Rebecca and Jessica Wyeth. Thank you for helping me recognize my skills and passions so that I can use them to improve the lives of others. Finally, I cannot express enough appreciation for my husband, John Larson, who witnessed every moment of excitement and frustration that came with this project. Thank you for your constant inspiration, excellent advice, and unfailing patience; I could not have completed this training without you.

Introduction

Inherited retinal dystrophies (IRD) are a group of rare, monogenic conditions that cause degeneration of the retina – the tissue layer at the back of the eye that generates vision by sensing light and sending electric signals to the brain. These diseases cause progressive and potentially severe vision loss, impacting quality of life and inflicting economic burden (Gong et al., 2021). Once fabled treatments for IRD, including gene therapies, are quickly becoming a reality. Voretigene neparvovec-rzyl (Luxturna®) became the first FDA approved ocular gene replacement therapy in 2017, treating patients with biallelic *RPE65*-associated retinal dystrophy (Fischer, 2017). Dozens of other ocular gene therapies for IRD are in development or are undergoing clinical trials (Ghoraba et al., 2022). Relative to other parts of the body, the eye is a reasonable target for gene therapy, as it is small and distinct with a notable "immune privilege". The eye uses an immune deviation response to protect itself from potentially blinding inflammation, making it remarkably receptive to viral gene therapies (Keino et al., 2018). With the great promise of gene therapy treatments for IRDs, patients have increasing opportunities to participate in clinical trials.

At this time, a clinical trial may be the only opportunity a patient with IRD will have to receive a gene therapy. While these treatments are developing rapidly, the drug approval process can take several years, and patients may be limited by the therapeutic window of their disease. While it is ultimately most important that patients make informed decisions about whether to participate in a clinical trial, trial participation in general promotes research and treatment development. Clinical trials that effectively recruit participants are able to advance quickly and potentially offer stronger evidence of intervention safety and efficacy. This could result in earlier availability of an FDA-approved therapy.

Research in oncology has demonstrated that patient misconceptions about the clinical trial process can discourage their enrollment while patients with a good understanding show greater interest in participating (Asher et al., 2022; Cameron et al., 2013). There is no research to date on how well the IRD patient community understands clinical trial terms and fundamental processes. A gap in clinical trial knowledge in these patients could be problematic and diminish equitable trial opportunities as well as research progress. Accordingly, the specific aims of this project are to assess clinical trial knowledge, determine clinical trial misconceptions, and identify preferences for receiving educational material among adults with IRDs.

A collaborative academic team based out of New York University recently developed CHEKS, a 25-item survey, to assess clinical trial health knowledge (Chung et al., 2022). The Clinical Trial HEalth Knowledge and Beliefs Scale (CHEKS) was slightly modified for use in this study. To address this study's specific aims, a small number of items were added to the survey to assess patient preferences for receiving information and to measure knowledge of concepts that are particularly relevant to IRD clinical trials. The survey was broadly distributed via email by the Foundation Fighting Blindness, a US-based non-profit organization, to individuals participating in their My Retina Tracker patient registry. This global registry includes patients and caregivers with IRDs; affected adults were recruited for study participation. Collected data was analyzed to identify overall knowledge levels, common misconceptions about clinical trials, and preferences for receiving informational resources among this patient population.

1.0 Manuscript

1.1 Background

Inherited retinal dystrophies (IRD) are a collection of rare, monogenic conditions that cause cellular breakdown of the retina. The retina is the ocular tissue layer that perceives light and sends electrical signals to the brain to create vision. Features of IRDs can vary with disease type, but common manifestations include color or night blindness, peripheral or central vision disruption, and stationary or progressive vision loss of varying severity. Prevalence also varies with disease type, but estimates confirm IRDs are a group of "rare" diseases as opposed to "ultra-" or "hyper-rare" (Galvin et al., 2020; Gong et al., 2021; Smith et al., 2022). One feature that can differentiate IRDs from other causes of vision loss is a considerably early age of onset. IRDs were determined to be the leading cause of legal blindness in working-age adults in Australia, England, and Wales (Heath et al., 2021; Liew et al., 2014). Finding and maintaining employment that accommodates vision impairment can be challenging and many individuals with IRDs report difficulty in this area ((CADTH), 2020; Chaumet-Riffaud et al., 2017; Watanabe et al., 2023). The annual cost of IRDs in the United States (U.S.) is estimated to be $13.4 billion when considering health systems, loss of patient productivity, loss of wellbeing, aids and modifications, travel, education, and loss of taxation payments (Gong et al., 2021).

Despite the considerable prevalence and notable burden of these rare diseases, treatment options for IRDs have historically focused on symptom management. Fortunately, there has been substantial progress in ocular gene therapy research over the past few decades. Notably, IRDs are a genotypically diverse group of disorders with over 270 causative genes that have been identified

(Chawla H., 2023). One IRD gene currently has an FDA-approved treatment; Luxturna® is a gene therapy available to individuals with *RPE65*-associated retinal dystrophy. Many other therapies for IRDs are currently in pre-clinical and clinical trials. As of March 2023, ocular diseases comprise 1.6% of indications addressed by gene therapy clinical trials, monogenic diseases constitute 13.1% (Journal of Genetic Medicine, 2023).

Recent success of gene therapies is partially attributed to the eye's immune privilege. The eye, as an organ, is uniquely poised to receive interventions like gene therapy due to its sophisticated ability to soften the local immune system (Streilein et al., 1997; Sugita, 2009). Complimenting this convenient feature, adeno-virus serotype 2 (AAV2) has been established as an effective vector for transducing retina cells (Bennett, 2003; Hu et al., 2021; Miraldi Utz et al., 2018). While researchers are continuing to evaluate vector dose and mode of delivery in clinical trials to improve efficacy and safety, promising trial outcomes show that highly anticipated ocular gene therapies are quickly becoming a reality (Ghoraba et al., 2022; Hu et al., 2021; Miraldi Utz et al., 2018).

With increasing opportunity for patients with IRD to participate in gene therapy clinical trials, it has become imperative to address barriers to trial enrollment including patient knowledge. Patients in the IRD and hemophilia communities have indicated that their perception of trial risks and benefits influences their participation decision (Au et al., 2015; Limjoco et al., 2022; Napier et al., 2022; Turriff et al., 2019). However, research to assess clinical trial knowledge in the general public identified common misconceptions about risks associated with different phases of clinical trials. The public tends to overestimate therapeutic benefits and minimized potential risks (Aiyegbusi et al., 2020). Further research is needed to determine if similar misconceptions are present within the IRD community. Fortunately, educational resources have been seen to improve

attitude towards and knowledge of clinical trials in the general public and oncology (Kruse et al., 2000; Miller et al., 2013). This study aimed to evaluate clinical trial knowledge among patients with IRDs to inform future resource development and promote timely, informed decision-making.

1.2 Methods

The University of Pittsburgh Institutional Review Board (IRB) determined the study design and recruitment materials meet the regulatory requirements for exempt research under 45 CFR 46.104(d). The letter of approval is provided as a supplemental file in Appendix A.

1.2.1 Survey Development

The study team developed a survey to collect relevant participant demographics, identify preferred methods for receiving educational information, and assess clinical trial knowledge. The study team consisted of medical and academic professionals with expertise in ophthalmology, ocular gene therapy clinical trials, and genetic counseling. The complete survey is available as a supplemental file in Appendix A and contained four main sections:

- *Personal Information*
    - Items were developed by the study team to collect demographic information.
- *Sources of Information*
    - "I have obtained information about clinical trials from (select all that apply):" was pulled from the AGT-Eye (McGuinness et al., 2022).

- The series of questions that address preference for receiving new information were developed by the study team.

- *Perceived Knowledge*
  - "I have a good understanding about how clinical trials work" was used in an oncology study that was conducted by Cameron et al. in 2013 (Cameron et al., 2013).

- *Knowledge Assessment*
  - The Clinical Trial Health Knowledge and Beliefs Scale (CHEKS) as developed by Chung et al. was used in the "Knowledge Assessment" portion of the study survey (Chung et al., 2022).
  - Survey items 26-29 in the "Knowledge Assessment" section were specifically developed for use in this study to address unique aspects of IRD-related clinical trials. Knowledge assessment items 1-29 are referred to as "CHEKS+"

The survey was built and published using the Qualtrics^{XM} online platform. This program includes an ExpertReview feature to ensure the survey is WCAG 2.0 AA (and Section 508) compliant for use with third-party screen readers. Survey item type, display theme, and progress display were considered for optimal survey accessibility. By nature of the study design, all collected data, including medical information, is self-reported.

1.2.2 Recruitment

The study team partnered with the Foundation Fighting Blindness (FFB) for survey distribution. The survey was distributed via email by the FFB's research specialist to members of

the My Retina Tracker (MRT) patient registry. This international registry includes individuals and caregivers affected by IRD. FFB emailed approximately 99 registry members per day for nine days for a total of 883 emails. Emails were sent between January 20th and 28th, 2024 and the survey was open January 20th, 2024 through February 25th, 2024. Recipients were organized by Participant ID to randomize alphabetical, geographic, and age factors. To minimize the chance of a participant receiving two recruitment emails, Participant IDs were recorded by the distributor. The MRT technical team also used a one-time test method to email (Eblast) 1,900 registry members; 66 emails returned as undeliverable. The test was halted due to technical issues; it is unclear how many registry members received the announcement through this Eblast. The recruitment material that was included in the distribution email is available as a supplemental file in Appendix A.

The first two survey questions screened for adults (or their support person) with an IRD diagnosis who were fluent in English. Accordingly, the study excluded individuals who were below the age of 17, had limited English proficiency, or did not have an IRD diagnosis.

1.2.3 Analysis

CHEKS and CHEKS+ scores were totaled based on participant response to each item (4 = Definitely True, 3 = Somewhat True, 2 = Uncertain, 1 = Somewhat False, 0 = False) (Chung et al., 2022). A maximum score of 100 could have been achieved on CHEKS, a maximum of 116 on CHEKS+. A higher score is representative of a stronger understanding of how clinical trials work relative to a lower score.

All two-sample *t*-tests assumed equal variances and were completed using the XLMiner Analysis ToolPak. All *z*-tests for proportions were completed using the "Z-test Calculator for 2 Population Proportions" from Social Science Statistics. An α of 0.05 was used to assess

significance. Power and β were calculated using GPower 3.1 software with thresholds 0.90 and 0.20, respectively (Serdar et al., 2021).

1.3 Results

1.3.1 Participant Characteristics

The survey was completed by 202 participants, with characteristics as described in Table 1. The mean age was 52.5 years; 50% of participants were female and 49.5% were male (1 participant reported intersex assignment at birth). The majority of participants identified as white with no Hispanic or Latino ancestry and most participants reported residence in the United States. A bachelor's degree was most commonly reported as the highest level of education a participant had received (31.7%), while 32.1% of participants had received some kind of graduate or professional training.

Table 1. Participant Characteristics.

Respondents self-reported demographic information through multiple choice or multiple select questions. Free-text responses were available for some questions

Characteristic		Value
Participants (n)		202
Mean age (years)		52.5 ±15.1
Sex [n (%)]		
	Male	100 (49.5)
	Female	101 (50.0)
	Intersex	1 (0.4)
Race [n (%)]		
	White	177 (88.5)

	Black or African American	5 (2.5)
	American Indian or Alaska Native	1 (0.5)
	Asian	8 (4.0)
	Native Hawaiian or Pacific Islander	0 (.0)
	More than one race	7 (3.5)
	Unknown	2 (1.0)
Ethnicity [n (%)]		
	Not Hispanic or Latino	174 (87.9)
	Hispanic or Latino	19 (9.6)
	Unknown	5 (2.5)
Country of Residence [n (%)]		
	United States (US)	173 (86.5)
	Non-US*	27 (13.5)
Highest level of education [n (%)]		
	Highschool or equivalent	22 (11.0)
	Associate degree	18 (9.0)
	Some college coursework completed	32 (16.1)
	Professional degree	12 (6.0)
	Bachelor's degree	63 (31.7)
	Master's degree	38 (19.1)
	Doctorate degree	14 (7.0)
Syndromic Retinal Dystrophy [n (%)]		
	Syndromic**	16 (7.9)
	Non-syndromic	141 (69.8)
	Unsure	45 (22.3)
Prior enrollment in a clinical trial [n (%)]		
	Yes***	16 (7.9)
	No	180 (89.1)
	Unsure	6 (3.0)
Legally blind [n (%)]		
	Yes	85 (42.1)
	No	85 (42.1)
	Unsure	32 (15.8)

*Participants with non-US residency reported residency in Argentina (1), Australia (1), Brazil (2), Canada (3), Croatia (1), France (1), Germany (1), India (1), Mexico (2), Peru (1), Poland (1), Russia (1), Saudi Arabia (1), South Africa (2), Taiwan (1), Ukraine (3), United Arab Emirates (1), United Kingdom (3).

**Participants with syndromic retinal dystrophy reported Alstrom disease (1), Usher syndrome (unspecified) (1), Usher syndrome type I (1), and Usher syndrome type II (13) diagnoses.

***For participants with prior enrollment in a clinical trial, the mean amount of time reported since they were last in a trial was 11 years (range 0-41 years).

Retinitis pigmentosa (RP) was the most common self-reported diagnosis among patients (65%), followed by Stargardt disease (13%) (Figure 1). Most participants reported non-syndromic retinal dystrophy, while 7.9% attributed their diagnosis to a syndrome, most commonly Usher syndrome type II. Most participants reported that they had not participated in a clinical trial before (89.1%). Nearly half of participants indicated they met criteria for legal blindness (42.1%) while 15.8% were unsure.

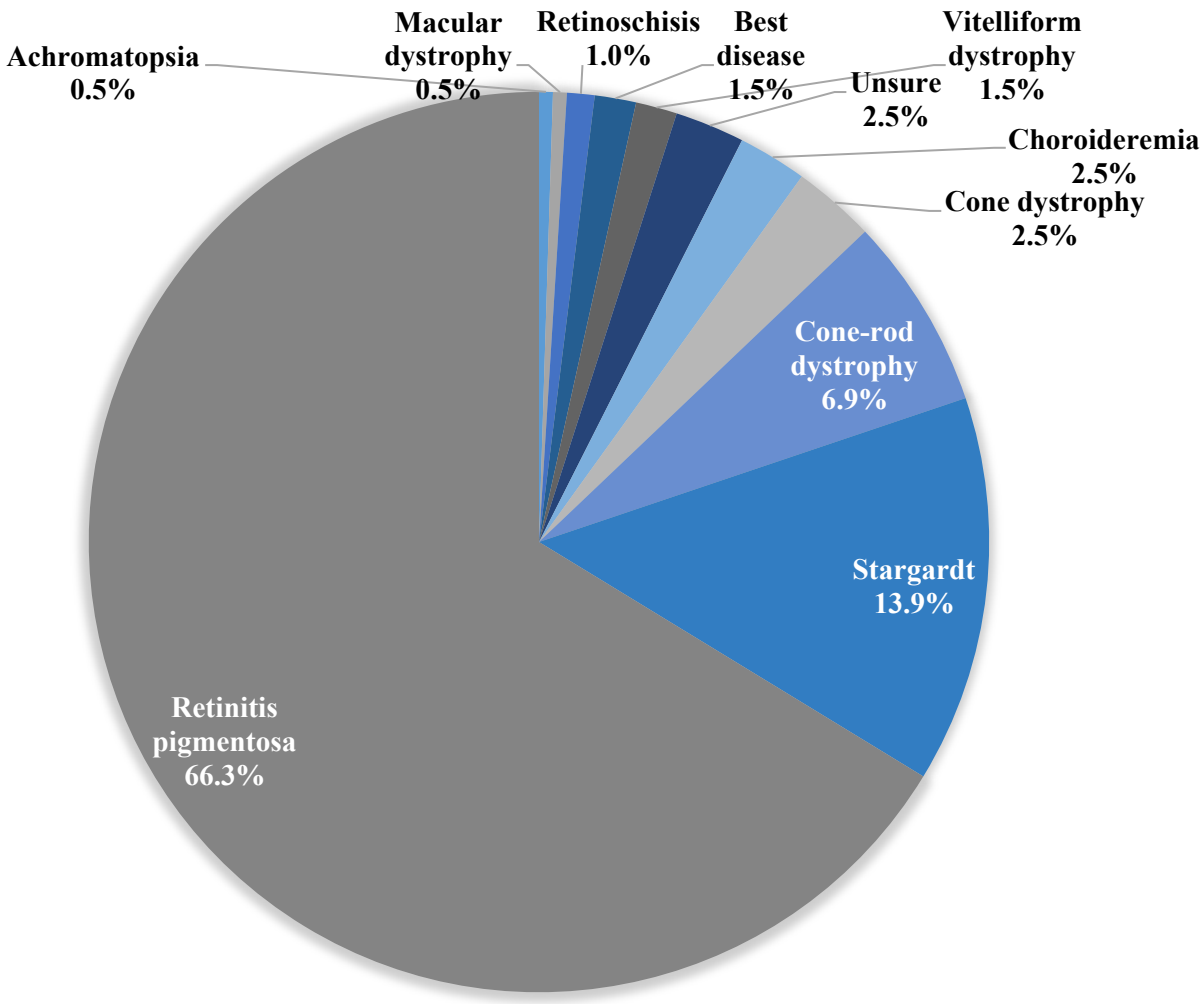


Figure 1. Participant Self-Reported Inherited Retinal Dystrophy (IRD) Diagnoses.

Respondents provided IRD diagnosis through a multiple choice survey item. A free-text response option was provided for participants who answered, "Unsure". Written answers that applied to a listed disease category were appropriately recoded for data analysis.

1.3.2 Sources of Information and Preferences

A patient registry, such as MRT, was the most frequently selected source of information about clinical trials, followed by ophthalmologists, the internet, and genetic counselors (Figure 2). A significantly greater proportion of participants under the age of 65 selected registries as a source information (61.1%) compared to participants 65 or older (15.3%) ($p < 0.001$) (Table 2). A significantly greater proportion of participants who reported non-US residency selected the internet as a source of information (55.6%) compared to participants who reside in the US (20.2%) ($p < 0.001$).

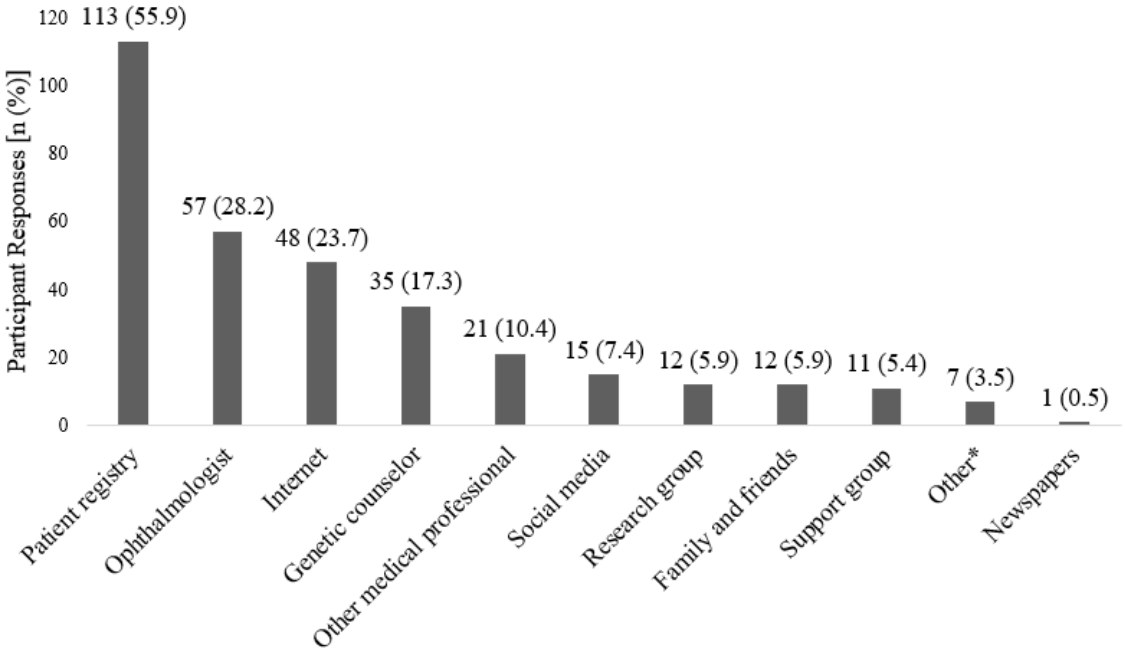


Figure 2. Participant Sources of Clinical Trial Information.

Respondents indicated what source types they had previously obtained information on clinical trials from through a multiple select question. A free-text response option was provided for participants who selected "Other".

Table 2. Participant Characteristics and Sources of Clinical Trial Information.

Characteristic	Participants who obtained information from each source type (%)										*p*- value*	*z* -statistic*
	Patient Registry	Ophthalmologist	Internet	Genetic Counselor	Other medical professional	Social Media	Research Group	Family and Friends	Support Group	Newspapers		
Age											<0.001	5.606
< 65 y/o	61.1	27.1	27.1	16.0	10.4	9.0	5.6	6.3	6.9	0.0		
≥ 65 y/o	15.3	36.0	22.0	22.0	14.0	4.0	8.0	6.0	2.0	2.0		
Country of Residence											<0.001	3.942
United States (US)	56.1	30.1	20.2	19.1	12.1	6.9	6.4	5.2	4.0	0.6		
Non-US	59.3	22.2	55.6	7.4	7.4	11.1	3.7	11.1	14.8	0.0		
Highest level of education												
Highschool/Associate/Professional	61.9	28.6	21.4	13.1	0.6	4.8	6.0	7.1	4.8	1.2		
Four-Year College/Graduate	53.9	28.7	27.0	20.0	15.7	9.6	6.1	6.1	6.1	0.0		
Prior clinical trial participation												
Yes	58.3	28.3	25.6	17.2	9.4	7.2	5.0	6.2	4.4	0.1		
No	37.5	37.5	18.8	6.3	25.0	12.5	6.3	6.3	12.5	0.0		

Significant difference between proportions

*All tests are z-tests for proportions with power >0.90 or β <0.20

The proportions of respondents who selected different information source types were compared between participant characteristics. While all listed characteristics are of interest to the study team, only comparisons of statistical significance are listed in red bold. All other comparisons would benefit from a larger sample size to increase sensitivity and reduce the type I error rate.

Most participants indicated that they would like to receive more information about clinical trials (92.1%), with the majority preferring written information (89.1%) over verbal (10.4%) (Table 3). Of the participants who indicated they would prefer to receive written information, most preferred that this information be available online. In a free-text survey item, several participants indicated that they would prefer to receive clinical trial information via email. One individual indicated, “Email is fine as long as it is in a voiceover friendly format.” Of the participants who preferred verbal information, most preferred one-on-one communication, and most indicated

preference for a phone call. Most participants also indicated that they would prefer to receive information on a recurring basis (84.8%).

Table 3. Participant Preferences for Receiving Information About Clinical Trials.

Information distribution method	Participants who selected method as most preferred
Written [n (%)]	164 (89.1)
Online (n)	140
Hardcopy (n)	24
Verbal [n (%)]	19 (10.4)
One-on-one (n)	18
Group (n)	1
Phone call (n)	13
Video call (n)	5
In-person (n)	1
One-time [n (%)]	28 (15.2)
Recurring [n (%)]	156 (84.8)

Respondents who expressed that they were interested in receiving more information about clinical trials subsequently indicated their preference for information type through a series of multiple choice questions.

1.3.3 Perceived Knowledge

Participant perception of their clinical trial knowledge varied, with most participants indicating that they neither agreed nor disagreed with the statement, "I have a good understanding of how clinical trials work". 16 participants reported that they had previously participated in a clinical trial, most of whom agreed or strongly agreed (75.0%) that they had a good understanding of how clinical trials work.

1.3.4 Knowledge Assessment Outcome

The mean CHEKS score among all participants was 80.6 ±12.0 (range 50-100). The mean CHEKS+ score was 94.5 ±13.6 (range 58-116). There was not a significant difference in mean CHEKS+ scores between participants who had participated in a clinical trial before and those who had not ($p = 0.113$) (Table 3). Participants who reported a good understanding of clinical trials also scored significantly higher than those who did not indicate a strong understanding ($p < 0.001$).

Table 4. Participant Characteristics and Mean CHEKS+ Score.

Characteristic	Participants (n)	Mean CHEKS+ Score	*p*-value*	(df)*t*-statistic*
Highest level of education				
Highschool/Associate/Professional	84	91.8 ±15.1		
Four-Year College/Graduate	114	96.2 ±12.0		
Country of Residence				
United States (US)	173	94.7 ±13.9		
Non-US	27	93.6 ±11.6		
Prior clinical trial participation			0.113	(194) 1.592
Yes	16	99.7 ±10.2		
No	180	94.1 ±13.7		
Good understanding of clinical trials			<0.001	(202) 6.161
Responded Agree/Strongly	77	101.4 ±11.3		
Other response	125	90.3 ±13.2		

*All tests are *t*-tests with power >0.90 or β <0.20

Mean CHEKS+ scores were compared between participant characteristics. While all listed characteristics are of interest to the study team, comparative statistics are only provided for comparisons with statistical value (power >0.90 or β <0.20). All other comparisons would benefit from a larger sample size to increase sensitivity and reduce the type I error rate.

Participant performance on each knowledge assessment survey item is reported in Figure 3. Participants scored significantly higher on items that were tailored to ophthalmology clinical trials (mean score of 3.5) compared to the standard CHEKS items (mean score of 3.2) ($p < 0.001$) (Figure 4).

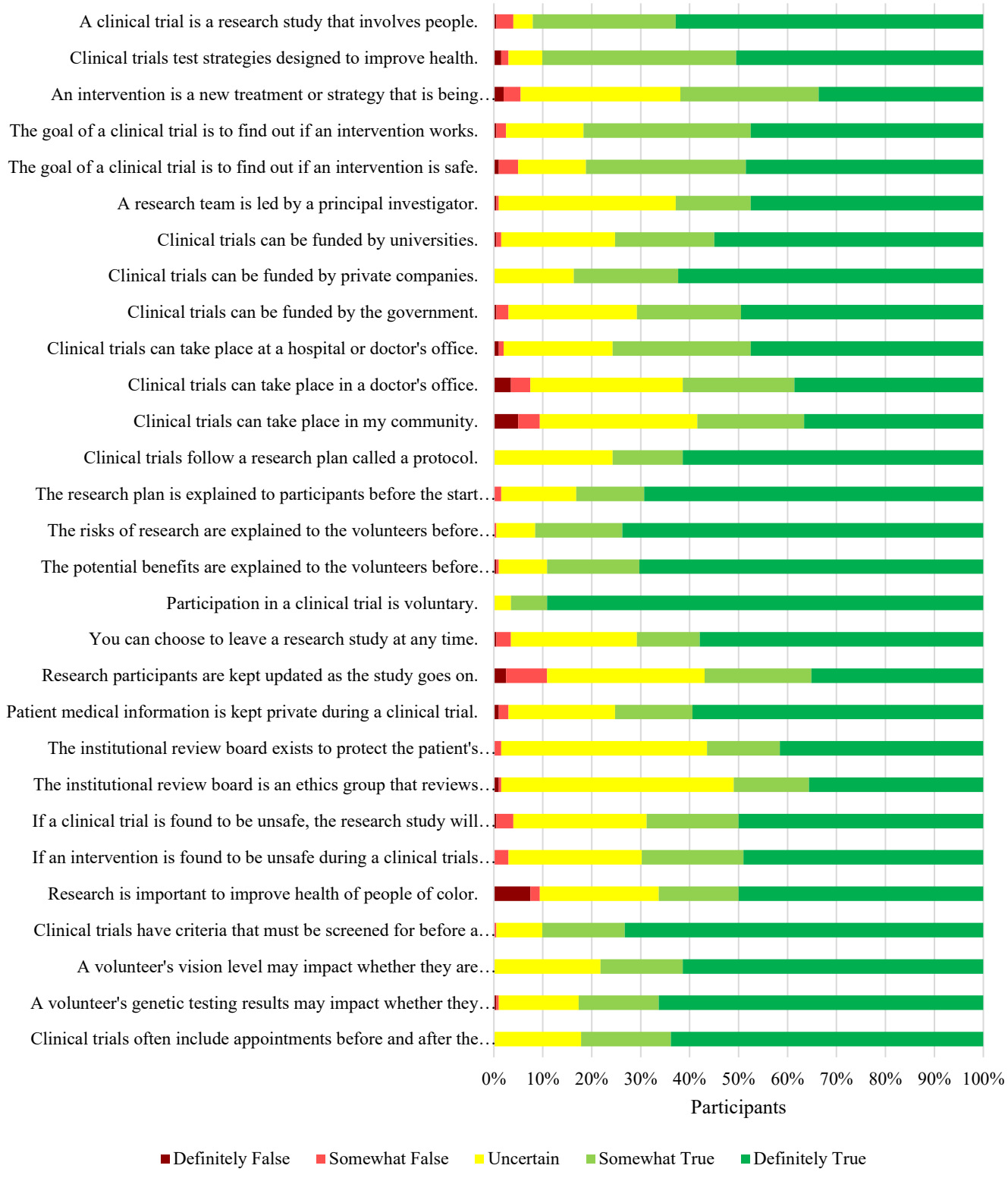
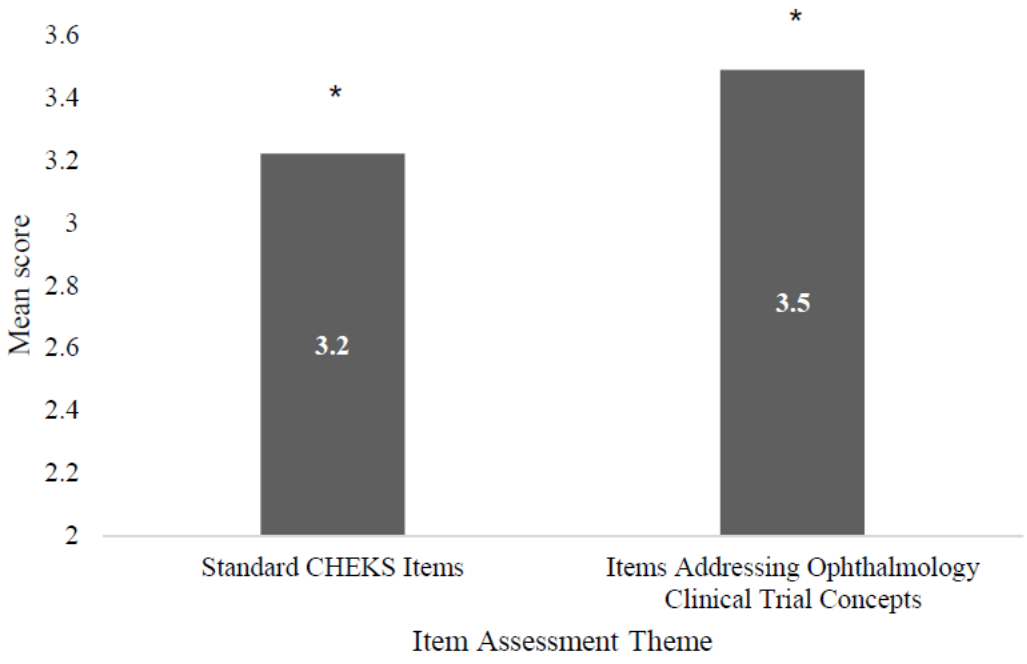


Figure 3. Participant Knowledge Assessment Survey Responses.

*Items added to the CHEKS for specific assessment related to ophthalmic clinical trials

Figure 3. Participant Knowledge Assessment Survey Responses (cont.)

Respondents answered Likert questions to assess their knowledge of clinical trial concepts.



*t-test completed demonstrated a significant difference in mean score (p <0.001, t > 1.96, power > 0.90)

Figure 4. Survey Item Assessment Theme (Standard CHEKS vs Ophthalmology-Specific) and Mean Score.

The mean score of the original CHEKS survey items was compared to the the mean score of survey items that were developed for this study to be specific to clinical trials in ophthalmology.

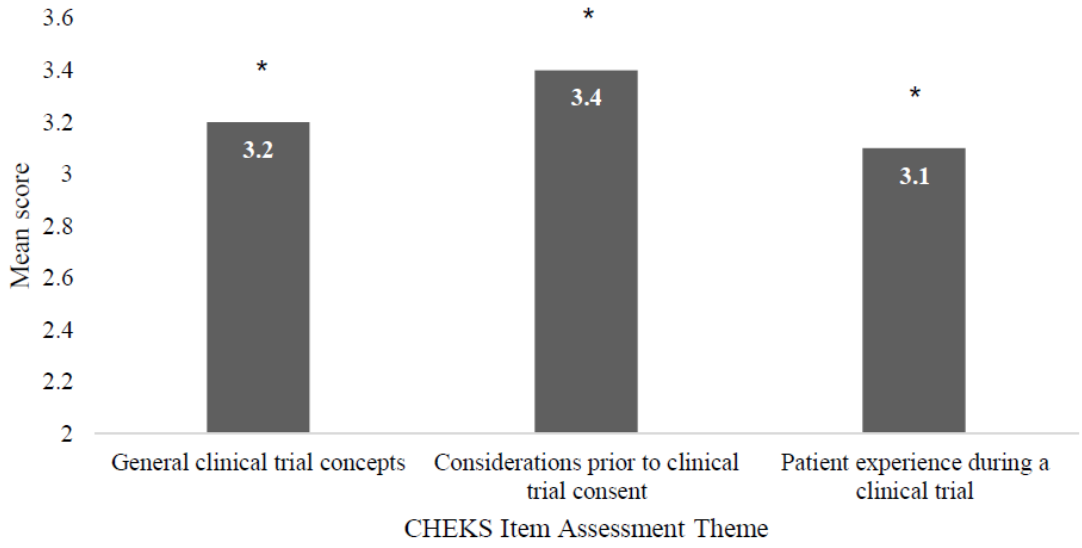
The study team noted the five highest scoring CHEKS items addressed concepts that a patient would consider at the time of consent (Table 5). Subsequent analysis revealed that CHEKS survey items related to considerations prior to a clinical trial performed significantly better (mean

score of 3.4) than items that assessed understanding of general clinical trials concepts (3.2) and the patient experience during a clinical trial (3.1) (p <0.001) (Figure 5). The categorical grouping of survey items was determined by the primary investigator and committee chair and is available as a supplemental file in Appendix A.

Table 5. Lowest and Highest Scoring CHEKS Items.

Lowest scoring CHEKS items	Highest scoring CHEKS items
An intervention is a new treatment or strategy that is being tested by the research team.	A clinical trial is a research study that involves people.
Clinical trials can take place in a doctor's office.	The research plan is explained to participants before the start of the study.
Clinical trials can take place in my community.	The risks of research are explained to the volunteers before they agree to take part in the research study.
Research participants are kept updated as the study goes on.	The potential benefits are explained to the volunteers before they agree to take part in the research study.
The institutional review board is an ethics group that reviews the research plan prior to the start of a clinical trial.	Participation in a clinical trial is voluntary.

The five lowest scoring and five highest scoring CHEKS survey items were recorded based on mean score.



*t-tests completed between each group demonstrated a significant difference in mean score (p <0.001, t > 1.96, power > 0.90)

Figure 5. CHEKS Item Assessment Theme and Mean Score.

The mean score was compared between three categorical groups of CHEKS items: Questions that assess understanding of 1. General clinical trial concepts, 2. Considerations prior to clinical trial consent, and 3. Patient experience during a clinical trial.

1.4 Discussion

While prior studies have assessed patient perspectives, influences on decision-making, and knowledge of gene therapy, this is the first study to focus on clinical trial knowledge in adults with IRD (Au et al., 2015; Mack et al., 2023; Napier et al., 2022; Turriff et al., 2019). Ideally, this information can be combined with previous research to close patient knowledge gaps and thereby improve clinical trial recruitment as well as the patient experience.

1.4.1 Participant Clinical Trial Knowledge Gaps

Overall, the results of this study suggest that adults with IRD have a reasonable knowledge base of clinical trial processes and, perhaps more importantly, a desire for more information. With an average score equal to about an 80% correct response rate, participants scored slightly higher than the study sample used to validate the CHEKS tool. While the CHEKS has not been used in other published studies at this time, the initial validation of the survey reported a mean score of 75 ±15 (out of a possible 100) when tested in a group of 409 participants recruited through Amazon Mechanical Turk (MTurk) (Chung et al., 2022). Since IRD treatments have become a popular research focus, patients with these rare diseases, especially those enrolled in MRT, may have more familiarity with clinical trials than the general public.

However, there were several concepts assessed in this survey that participants appeared to have a limited understanding of. The lowest performing survey items revealed that patients may have limited knowledge of terms related to clinical trials including "intervention" and the "institutional review board". While understanding the intricacies of IRB responsibilities may not necessarily benefit patients, a general understanding of their rights may empower patients to make better-informed decisions. Familiarity with clinical trial terms may also improve patient literacy regarding clinical trial information.

Additionally, survey items related to the patient experience during a clinical trial had the lowest mean score. This suggests that patients may not have a well-developed understanding of what clinical trials look like after enrollment and initial intervention. While most participants correctly understood that clinical trial participation is voluntary, nearly a third of the participants disagreed with or felt unsure about survey item, "You can choose to leave a research study at any time." A study conducted in adults with IRD who had recently completed a clinical trial found that

14% of patients thought they were not able to withdrawal from the study (Au et al., 2015). Similar misconceptions about study withdrawal have been identified among patients with cancer (Asher et al., 2022; Bergenmar et al., 2011; Cameron et al., 2013).

Also reported in the Au et al. study, 24% of patients with IRD expressed that the clinical trial was too time-consuming, suggesting that they had not appropriately understood the time commitment when enrolling. About 18% of participants in this study were unsure about clinical appointment requirements before and after a trial intervention. About a third of participants also did not understand that a clinical trial will stop if it is found to be unsafe for participants. Overall, clarification of what clinical trial participation looks like after initial intervention may improve recruitment as previous IRD research suggests that patient perception of trial risks and benefits influences their enrollment decision (Napier et al., 2022; Turriff et al., 2019).

The survey items with the highest average scores suggest participants better understood the consenting and enrollment process for clinical trials. Nearly all the highest-scoring items refer to steps that occur *before* trial enrollment. For example, about 90% of participants understood that the risks and benefits of a study are explained to volunteers before enrollment. Similarly, a little over 90% of participants recognized that volunteers must meet screening criteria prior to enrollment. The nuances of eligibility are particularly relevant to ophthalmic clinical trials where, often, both genetic and clinical criteria must be met. Notably, while participants generally performed well on the ophthalmology-specific questions, about 20% of participants were still unsure about whether genetic testing results and vision level would affect one's ability to participate in a trial.

When considering patient receptivity to educational aids, participants were, in general, able to adequately self-assess their level of understanding. Participants who were more confident in

their clinical trial knowledge achieved higher CHEKS+ scores; a similar finding was reported in a study that distributed knowledge assessments to patients with cancer (Cameron et al., 2013). Conversely, participants who felt they had a poor understanding of clinical trials had lower CHEKS+ scores. Interestingly, prior participation in a clinical trial was not associated with a higher average score. This is contrary to what has been seen in other disease areas (Cameron et al., 2013). A possible explanation for this could be participant misunderstanding of what a clinical trial is in the first place. In the interest of accurately assessing knowledge, the term "clinical trial" was not defined in the survey. Participants may have considered past involvement with other types of research as trial experience. Prior research on patient and public clinical trial awareness and knowledge has also found that higher education correlates with stronger knowledge (Cameron et al., 2013; Leiter et al., 2015). While a larger sample size would allow stronger conclusions to be drawn from this study, the results generally support this trend.

1.4.2 Participant Information Sources and Preferences

Nearly all study participants indicated they would like to receive more information about clinical trials. This result aligns with what has been seen in retinal dystrophy, the general public, and other disease communities including oncology and hemophilia (Aiyegbusi et al., 2020; Cameron et al., 2013; Limjoco et al., 2022; Napier et al., 2022). Patient engagement in research is critical for the advancement of the field; patient resource development and provider education may improve and maintain patient engagement.

Regarding currently available information on clinical trials, the results of this study will be helpful for evaluating existing patient resources, as well as generating new ones. Patient registries and the internet were identified as two of the most reported sources of information. This is

encouraging for organizations like the FFB and brings awareness to the value of their mission. Notably, a much smaller proportion of participants over the age of 65 reported registries as a source of information. This discrepancy between age demographics should be taken into consideration when developing information distribution methods. The internet was also commonly reported as a source of information about gene therapy in a survey conducted among adults with IRD in Australia (Mack et al., 2023). While the internet offers opportunities to easily dispense information, this distribution method requires further consideration to ensure accessibility for the IRD community (i.e. websites and search engines that are compatible with assistive technologies).

Ophthalmologists and genetic counselors were also reported as two of the most common sources of information. This is consistent with results of a study conducted in adults with IRDs who had recently participated in a clinical trial, which found that the main source of clinical trial information for participants was medical staff (Au et al., 2015). The top three information sources reported in the Mack et al. study out of Australia were the internet, followed by ophthalmologists and only about a quarter reported receiving information from a patient registry (Mack et al., 2023). Genetic counselors were not included as an option in the Mack et al. survey (Mack et al., 2023). It is important that these providers stay updated on trial opportunities and are equipped to answer patient questions on the topic. Notably, genetic counselors are not routinely employed in retinal dystrophy clinics or the broader ophthalmology practice; only 1% of patient-facing genetic counselors reported working in ophthalmology in the 2023 Professional Status Survey (National Society of Genetic Counselors, 2023). Considering their expertise in genetics as well as psychosocial intervention and informed decision-making, there may be an opportunity for genetic counselors to be better utilized as impactful resources for patients seeking information about clinical trials.

Similar to what was reported in a survey of hemophilia patients, most study participants prefer to receive recurring information about clinical trials (Limjoco et al., 2022). The results from this 2022 hemophilia survey and prior research informed the development of a written tool to help patients and providers navigate conversations about gene therapy (Wang et al., 2022). Most participants in this survey of adults with IRDs indicated they would prefer written, online resources. Based on the results of this study in adults with IRDs, efforts devoted to educational aid development may be best focused on recurring, online resources. Again, accessibility will be a key component in the success of such material in the IRD community.

1.4.3 Limitations

Notably, this study has several limitations. A larger sample size would enable completion of comparative statistical analysis on participant characteristics relative to clinical trial knowledge. For example, it would be interesting to analyze IRD diagnosis or age relative to the achieved CHEKS score. A more diverse sample in terms of race and ethnicity would also improve the applicability of the study. Most participants were white with no Hispanic or Latino ancestry which is not appropriately representative of the IRD community.

The proportion of retinitis pigmentosa diagnoses relative to other photoreceptor disorders or macular dystrophy was somewhat higher than what has been seen in IRD descriptive studies (Coco-Martin et al., 2021; Stone et al., 2017). Anecdotally, the members of the study team recall several past referrals to ophthalmology for patients with retinitis pigmentosa who are later given a different IRD diagnosis upon clinical exam and/or genetic testing. It is possible that retinitis pigmentosa may have been incorrectly given as a “catch-all” diagnosis to some of the participants in this study. A smaller proportion of participants reported syndromic IRD relative to what has

been seen in other international cohorts (Coco-Martin et al., 2021; Karali et al., 2022; Stone et al., 2017). However, nearly a quarter of respondents were unsure about whether they had a syndrome. It's possible that some of these individuals do indeed have IRD associated with a syndrome but did understand the question because syndrome was not defined. A larger sample may be more representative of true IRD diagnosis proportions. All collected medical information was also self-reported which can limit the accuracy of these data points.

Additionally, by nature of distributing the survey through an email, the study is biased towards individuals who prefer online communication. As the survey was distributed to members of a patient research registry, respondents may accordingly be more familiar with clinical trials than the target population. Patients enrolled with the registry may also have a more optimistic outlook towards research and clinical trials in general which is not necessarily the experience of all individuals with IRD.

1.5 Conclusion

This study assessed the overall understanding of major clinical trial concepts among adults with IRD and revealed specific knowledge gaps. While patients are generally familiar with the first steps towards enrolling in a clinical trial, their perception of the reality of trial participation may be inaccurate. Clarifying this understanding is necessary to manage patient expectations and allow for proper informed decision-making. The clinical trial space, let alone ophthalmic genetics, is advancing at a rapid pace. Regardless of a patient's level of understanding, it will be important to maintain engagement with the IRD patient community as the field continues to move forward.

The results from this study not only highlight opportunities to bridge patient knowledge gaps, but also suggest strategies for how to best connect the IRD community with helpful information.

A few key findings offer direction for patient educational aid development. Patient registries appear to be an effective way to regularly distribute new information to this disease community. However, online resources should be created with careful attention to compatibility with assistive technology. Additionally, ophthalmology providers play an important role in introducing patients to clinical trial information. It may be worthwhile to assemble a provider resource that can be used to guide conversations around common misconceptions.

While the present study serves as a starting point for educational intervention, the research team hopes to continue to collect survey data for deeper analysis on a larger sample size. Ideally, this study will be used to support patients in their understanding of clinical trials to improve informed decision-making and foster a positive patient experience.

2.0 Research Significance to Genetic Counseling and Public Health

Several aspects of this study support public health efforts to assure equitable care for patients with IRDs. Namely, the study achieved the aim of assessing patient knowledge gaps regarding clinical trials. In addition to sharpening the focus on knowledge discrepancies, the study also highlights strategies for educational intervention to promote patient access to information and research opportunities. Looking forward to a quickly approaching reality where patients with IRDs may have several treatment options available, it is important to address knowledge barriers now before they impact access to care.

The results of this study suggest that a few common misconceptions about clinical trials may be held by the IRD patient community. First, some terms that are generally used to describe clinical trials, such as "intervention", may be unfamiliar to patients, directly affecting their literacy on the topic. Participants in this study also demonstrated misunderstanding around different outcomes of a clinical trial (i.e. the option to withdrawal or the potential for an intervention to be stopped) as well as patient protections in place. Prior surveys in the general public have identified misunderstanding regarding the purpose, risks, and benefits of clinical trials and different clinical trial phases (Aiyegbusi et al., 2020). Regardless of where the understanding falls short, prior research has also shown that greater patient self-efficacy and knowledge reduce decisional conflict as it pertains to clinical trials (Miller et al., 2013). Accordingly, stronger patient knowledge has been associated with increased clinical trial enrollment (Cameron et al., 2013).

With the goal of promoting informed decision-making, this study suggests several approaches to bolster patient clinical trial knowledge. Importantly, medical providers including ophthalmologists and genetic counselors were identified as common sources of information about

clinical trials. Similar findings have been reported previously (Aiyegbusi et al., 2020; Au et al., 2015; Yadav et al., 2022). It is encouraging that patient trust in clinical providers has been demonstrated; this emphasizes the opportunity for providers to educate their patients. Initial, brief and ongoing conversations in clinic may generate greater familiarity with clinical trial terms among patients and improve literacy.

Genetic counselors may be particularly impactful in the clinical trial space since they are uniquely trained to educate and guide patients through complex decisions. Several of the genetic counseling practice-based competencies can be effective beyond the scope of genetic testing. For example, genetic counselors are prepared to, "Communicate genetics and genomics information to clients, colleagues, and other community partners." (Accredidation Council for Genetic Counseling, 2023). While genetics and genomics are certainly relevant topics when clinical trials involving gene therapy, the argument could be made that genetic counselors are skilled at distilling medical and scientific information in general. Additionally, genetic counselors are experts at, "Promot[ing] integration of psychosocial needs and client-centered decision-making into genetic counseling interactions" (Accredidation Council for Genetic Counseling, 2023). This proficiency is well-suited to nuanced conversations with patients about the decision to enroll in a clinical trial. Such decisions can be affected by personal values and the conversation may be emotionally charged.

Genetic counselors are becoming more involved with roles that involve research coordination (Cho & Guy, 2020; Zierhut & Austin, 2011). A recent survey of genetic counselors reported that 9.7% of participants help patients enroll in clinical trials and 33.3% are asked about clinical gene therapies by their patients (Geiselman et al., 2024). However, this study also identified knowledge gaps among genetic counselors regarding clinical gene therapy trials

(Geiselman et al., 2024). Understandably, genetic counselors who work in rare disease specialties were more likely to feel comfortable in their knowledge as they encounter gene therapies more often in practice. As the field of genetics continues to expand at an exciting rate, genetic counselors must be equipped to grow with it. The majority of participants in the recent survey did not feel that their education on gene therapies was adequate (Geiselman et al., 2024). While further research is needed in this area, provider resources such as CME/CEU credits on clinical trials and gene therapy may help counselors prepare for conversations with patients about such opportunities.

The present study also identified patient registries as the most common source from which patients learn information about clinical trials. Notably, a significantly smaller proportion of participants 65 and older indicated that they obtain information from registries. There could be several reasons for this disparity. The survey was distributed through MRT, a patient registry, so it is apparent that this age demographic is successfully engaging with at least one registry. It is possible that participants misunderstood the definition of a registry and did not recognize the function of MRT. It is also possible that information provided to registry members is less accessible to older patients. Genetic knowledge and health literacy has been reported to be lower in older age groups (Ashida et al., 2011). As this study is biased toward individuals who utilize email, further research may be helpful in identifying the most effective means of information distribution to older demographics. Regardless, efforts should be made to improve clinical trial resource accessibility for patients with low health literacy.

Regarding patient educational aid development, the study team was thrilled to see that patients are willing to engage with new information about clinical trials. Maintaining this relationship will be key to assuring equitable care in a quickly developing field. Participants preferred to receive recurring information on clinical trials. This is ideal since clinical trial

information and opportunities change rapidly. Additionally, more frequent exposure to clinical trial terms and content is likely to improve patient familiarity with the topic. Participants also preferred to receive written information. While medical providers may be a good starting point for conversations about clinical trials, patients often forgot information provided during clinical appointments (Laws et al., 2018). Fortunately, written information on clinical trials has been shown to improve knowledge in the general public (Kruse et al., 2000).

Beyond ophthalmology, the number of registered clinical trials in the US has increased from 100,205 in 2010 to 486,753 in 2024 (Clinicaltrials.gov, 2024). It is important to develop and evaluate educational interventions now so that patients can be prepared to make safe and well-informed decisions about clinical trial enrollment. In this way, equitable research and treatment opportunities can be assured and potential health hazards, such as participation in unregulated studies, can be avoided. This study provides data to guide clinical trial resource preparation and distribution, starting with the IRD community.

Appendix A Appendices and Supplemental Content

The following supplemental files are linked through this D-scholarship upload:

Appendix A Figure 1. University of Pittsburgh IRB Letter of Approval. The University of Pittsburgh Institutional Review Board (IRB) determined the study design and recruitment materials meet the regulatory requirements for exempt research under 45 CFR 46.104(d).

Appendix A Figure 2. Complete Study Survey. The research team collaborated to develop the survey used in the study. The survey features sections to collect "Personal Information", "Sources of Information", and "Perceived Knowledge" as well as a "Knowledge Assessment".

Appendix A Figure 3. Study Recruitment Email. The Foundation Fighting Blindness sent an email to members of the My Retina Tracker registry for study recruitment.

Appendix A Figure 4. Study recruitment announcement. A study recruitment announcement was attached to the email sent by the Foundation Fighting Blindness that included a the survey URL and QR code.

Appendix A Figure 5. Categorical Grouping of CHEKS Items for Comparative Analysis. The primary investigator and committee chair categorical grouped CHEKS items to assess participant knowledge level regarding different clinical trial themes and concepts.

Bibliography

(CADTH), C. A. f. D. a. T. i. H. (2020). The Impact of Inherited Retinal Diseases on Canadian Patients: Patient Input on Luxturna.

Aiyegbusi, O. L., Macpherson, K., Elston, L., Myles, S., Washington, J., Sungum, N., . . . Calvert, M. J. (2020). Patient and public perspectives on cell and gene therapies: a systematic review. *Nature Communications, 11*(1), 6265. doi:10.1038/s41467-020-20096-1

Asher, N., Raphael, A., Wolf, I., Pelles, S., & Geva, R. (2022). Oncologic patients' misconceptions may impede enrollment into clinical trials: a cross-sectional study. *BMC Medical Research Methodology, 22*(1), 5. doi:10.1186/s12874-021-01478-5

Ashida, S., Goodman, M., Pandya, C., Koehly, L. M., Lachance, C., Stafford, J., & Kaphingst, K. A. (2011). Age differences in genetic knowledge, health literacy and causal beliefs for health conditions. *Public Health Genomics, 14*(4-5), 307-316. doi:10.1159/000316234

Au, C. P.-Y., Fardell, N., Williams, M., Fraser-Bell, S., Campain, A., & Gillies, M. (2015). Patient experiences in retinal trials: a cross-sectional study. *BMC Ophthalmology, 15*(1), 80. doi:10.1186/s12886-015-0071-6

Bennett, J. (2003). Immune response following intraocular delivery of recombinant viral vectors. *Gene Therapy, 10*(11), 977-982. doi:10.1038/sj.gt.3302030

Bergenmar, M., Johansson, H., & Wilking, N. (2011). Levels of knowledge and perceived understanding among participants in cancer clinical trials - factors related to the informed consent procedure. *Clin Trials, 8*(1), 77-84. doi:10.1177/1740774510384516

Cameron, P., Pond, G. R., Xu, R. Y., Ellis, P. M., & Goffin, J. R. (2013). A comparison of patient knowledge of clinical trials and trialist priorities. *Curr Oncol, 20*(3), e193-205. doi:10.3747/co.20.1323

Chaumet-Riffaud, A. E., Chaumet-Riffaud, P., Cariou, A., Devisme, C., Audo, I., Sahel, J. A., & Mohand-Said, S. (2017). Impact of Retinitis Pigmentosa on Quality of Life, Mental Health, and Employment Among Young Adults. *Am J Ophthalmol, 177*, 169-174. doi:10.1016/j.ajo.2017.02.016

Chawla H., V. V. (2023). Retinal Dystrophies. *StatPearls*. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK564379/

Cho, M. T., & Guy, C. (2020). Evolving Roles of Genetic Counselors in the Clinical Laboratory. *Cold Spring Harb Perspect Med, 10*(10). doi:10.1101/cshperspect.a036574

Chung, A., Donley, T., Hays, R. D., Robbins, R., Seixas, A., & Jean-Louis, G. (2022). Development and Evaluation of the Clinical Trial HEalth Knowledge and Beliefs Scale (CHEKS). *Int J Environ Res Public Health, 19*(14). doi:10.3390/ijerph19148660

Clinicaltrials.gov. (2024). Number of Registered Studies Over Time and Some Significant Events (as of March 13, 2024). In. https://Clinicaltrials.gov.

Coco-Martin, R. M., Diego-Alonso, M., Orduz-Montaña, W. A., Sanabria, M. R., & Sanchez-Tocino, H. (2021). Descriptive Study of a Cohort of 488 Patients with Inherited Retinal Dystrophies. *Clin Ophthalmol, 15*, 1075-1084. doi:10.2147/opth.S293381

Counseling, A. C. f. G. (2023). Practice-Based Competencies for Genetic Counselors. In.
Counselors, N. S. o. G. (2023). Professional Status Survey 2023. In.

Fischer, A. (2017). FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss [Press release]

Galvin, O., Chi, G., Brady, L., Hippert, C., Del Valle Rubido, M., Daly, A., & Michaelides, M. (2020). The Impact of Inherited Retinal Diseases in the Republic of Ireland (ROI) and the United Kingdom (UK) from a Cost-of-Illness Perspective. *Clin Ophthalmol, 14*, 707-719. doi:10.2147/opth.S241928

Geiselman, L. A., Wetherill, L., Graham, B. H., Payne, K., & Hopewell, E. L. (2024). Survey of genetic counselors identifies a knowledge gap discerning properly regulated cell and gene therapy trials. *Cytotherapy, 26*(1), 88-95. doi:https://doi.org/10.1016/j.jcyt.2023.08.012

Ghoraba, H. H., Akhavanrezayat, A., Karaca, I., Yavari, N., Lajevardi, S., Hwang, J., . . . Nguyen, Q. D. (2022). Ocular Gene Therapy: A Literature Review with Special Focus on Immune and Inflammatory Responses. *Clin Ophthalmol, 16*, 1753-1771. doi:10.2147/opth.S364200

Gong, J., Cheung, S., Fasso-Opie, A., Galvin, O., Moniz, L. S., Earle, D., . . . Daly, A. (2021). The Impact of Inherited Retinal Diseases in the United States of America (US) and Canada from a Cost-of-Illness Perspective. *Clin Ophthalmol, 15*, 2855-2866. doi:10.2147/opth.S313719

Heath Jeffery, R. C., Mukhtar, S. A., McAllister, I. L., Morgan, W. H., Mackey, D. A., & Chen, F. K. (2021). Inherited retinal diseases are the most common cause of blindness in the working-age population in Australia. *Ophthalmic Genet, 42*(4), 431-439. doi:10.1080/13816810.2021.1913610

Hu, M. L., Edwards, T. L., O'Hare, F., Hickey, D. G., Wang, J.-H., Liu, Z., & Ayton, L. N. (2021). Gene therapy for inherited retinal diseases: progress and possibilities. *Clinical and Experimental Optometry, 104*(4), 444-454. doi:10.1080/08164622.2021.1880863

Karali, M., Testa, F., Di Iorio, V., Torella, A., Zeuli, R., Scarpato, M., . . . Banfi, S. (2022). Genetic epidemiology of inherited retinal diseases in a large patient cohort followed at a single center in Italy. *Scientific Reports, 12*(1), 20815. doi:10.1038/s41598-022-24636-1

Keino, H., Horie, S., & Sugita, S. (2018). Immune Privilege and Eye-Derived T-Regulatory Cells. *Journal of Immunology Research, 2018*, 1679197. doi:10.1155/2018/1679197

Kruse, A. Y., Kjaergard, L. L., Krogsgaard, K., Gluud, C., Mortensen, E. L., Gottschau, A., & Bjerg, A. M. (2000). A Randomized Trial Assessing the Impact of Written Information on Outpatients' Knowledge About and Attitude Toward Randomized Clinical Trials. *Controlled Clinical Trials, 21*(3), 223-240. doi:https://doi.org/10.1016/S0197-2456(00)00048-9

Laws, M. B., Lee, Y., Taubin, T., Rogers, W. H., & Wilson, I. B. (2018). Factors associated with patient recall of key information in ambulatory specialty care visits: Results of an innovative methodology. *PLoS One, 13*(2), e0191940. doi:10.1371/journal.pone.0191940

Leiter, A., Diefenbach, M. A., Doucette, J., Oh, W. K., & Galsky, M. D. (2015). Clinical trial awareness: Changes over time and sociodemographic disparities. *Clin Trials, 12*(3), 215-223. doi:10.1177/1740774515571917

Liew, G., Michaelides, M., & Bunce, C. (2014). A comparison of the causes of blindness certifications in England and Wales in working age adults (16–64 years), 1999–2000 with 2009–2010. *BMJ Open, 4*(2), e004015. doi:10.1136/bmjopen-2013-004015

Limjoco, J., Calatroni, A., Aristizabal, P., & Thornburg, C. D. (2022). Gene therapy preferences and informed decision-making: Results from a National Hemophilia Foundation Community Voices in research survey. *Haemophilia*. doi:10.1111/hae.14706

Mack, H. G., Britten-Jones, A. C., McGuinness, M. B., Chen, F. K., Grigg, J. R., Jamieson, R. V., . . . Ayton, L. N. (2023). Survey of perspectives of people with inherited retinal diseases on ocular gene therapy in Australia. *Gene Ther, 30*(3-4), 336-346. doi:10.1038/s41434-022-00364-z

McGuinness, M. B., Britten-Jones, A. C., Ayton, L. N., Finger, R. P., Chen, F. K., Grigg, J., & Mack, H. G. (2022). Measurement Properties of the Attitudes to Gene Therapy for the Eye (AGT-Eye) Instrument for People With Inherited Retinal Diseases. *Transl Vis Sci Technol, 11*(2), 14. doi:10.1167/tvst.11.2.14

Medicine, J. o. G. (2023). Indications Addressed by Gene Therapy Clinical Trials. In. Gene Therapy Clinical Trials Worldwide: John Wileys and Sons LTD.

Miller, S. M., Hudson, S. V., Egleston, B. L., Manne, S., Buzaglo, J. S., Devarajan, K., . . . Meropol, N. J. (2013). The relationships among knowledge, self-efficacy, preparedness, decisional conflict, and decisions to participate in a cancer clinical trial. *Psychooncology, 22*(3), 481-489. doi:10.1002/pon.3043

Miraldi Utz, V., Coussa, R. G., Antaki, F., & Traboulsi, E. I. (2018). Gene therapy for RPE65-related retinal disease. *Ophthalmic Genetics, 39*(6), 671-677. doi:10.1080/13816810.2018.1533027

Napier, M. P., Selvan, K., Hayeems, R. Z., Shuman, C., Chitayat, D., Sutherland, J. E., . . . Héon, E. (2022). Gene therapy: perspectives from young adults with Leber's congenital amaurosis. *Eye, 36*(11), 2088-2093. doi:10.1038/s41433-021-01763-z

Serdar, C. C., Cihan, M., Yücel, D., & Serdar, M. A. (2021). Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. *Biochem Med (Zagreb), 31*(1), 010502. doi:10.11613/bm.2021.010502

Smith, C. I. E., Bergman, P., & Hagey, D. W. (2022). Estimating the number of diseases - the concept of rare, ultra-rare, and hyper-rare. *iScience, 25*(8), 104698. doi:10.1016/j.isci.2022.104698

Stone, E. M., Andorf, J. L., Whitmore, S. S., DeLuca, A. P., Giacalone, J. C., Streb, L. M., . . . Tucker, B. A. (2017). Clinically Focused Molecular Investigation of 1000 Consecutive Families with Inherited Retinal Disease. *Ophthalmology, 124*(9), 1314-1331. doi:10.1016/j.ophtha.2017.04.008

Streilein, J. W., Ksander, B. R., & Taylor, A. W. (1997). Immune deviation in relation to ocular immune privilege. *J Immunol, 158*(8), 3557-3560.

Sugita, S. (2009). Role of ocular pigment epithelial cells in immune privilege. *Arch Immunol Ther Exp (Warsz), 57*(4), 263-268. doi:10.1007/s00005-009-0030-0

Turriff, A., Blain, D., Similuk, M., Biesecker, B., Wiley, H., Cukras, C., & Sieving, P. A. (2019). Motivations and Decision Making Processes of Men With X-linked Retinoschisis Considering Participation in an Ocular Gene Therapy Trial. *Am J Ophthalmol, 204*, 90-96. doi:10.1016/j.ajo.2019.03.009

Wang, M., Negrier, C., Driessler, F., Goodman, C., & Skinner, M. W. (2022). The Hemophilia Gene Therapy Patient Journey: Questions and Answers for Shared Decision-Making. *Patient Prefer Adherence, 16*, 1439-1447. doi:10.2147/ppa.S355627

Watanabe, K., Aouadj, C., Hiratsuka, Y., Yamamoto, S., & Murakami, A. (2023). Quality of Life and Economic Impacts of Retinitis Pigmentosa on Japanese Patients: A Non-interventional Cross-sectional Study. *Adv Ther, 40*(5), 2375-2393. doi:10.1007/s12325-023-02446-9

Yadav, S., Todd, A., Patel, K., Tabriz, A. A., Nguyen, O., Turner, K., & Hong, Y. R. (2022). Public knowledge and information sources for clinical trials among adults in the USA: evidence from a Health Information National Trends Survey in 2020. *Clin Med (Lond), 22*(5), 416-422. doi:10.7861/clinmed.2022-0107

Zierhut, H., & Austin, J. (2011). How inclusion of genetic counselors on the research team can benefit translational science. *Sci Transl Med, 3*(74), 74cm77. doi:10.1126/scitranslmed.3001898