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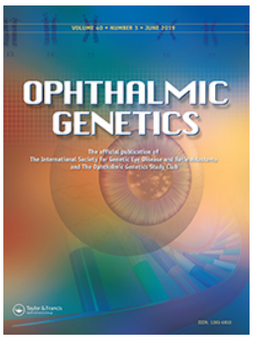

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CASE REPORT

Participant perspectives on a phase I/II ocular gene therapy trial (NCT02077361)

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ABSTRACT

Background: To learn from the experiences of potential clinical trial participants, participants in a Phase 1 ocular gene therapy trial, and their partners to improve communications and trial conduct.

Materials and methods: Primary and secondary qualitative analysis of semi-structured interviews of potential participants (n = 20), clinical trial participants (n = 2) and their partners (n = 2) in a gene therapy clinical trial for choroideremia (NCT02077361). Analysis included: 1) thematic analysis of transcribed entrance and exit semi-structured interviews with trial participants and their partners; and 2) secondary qualitative analysis of interviews with potential trial participants, conducted prior to the initiation of the clinical trial.

Results: Participants and partners who had received information during the consent process had a better understanding of the risks and benefits of participation in a Phase 1 gene therapy clinical trial than potential trial participants. However, participants and partners reported deficiencies in communication throughout the trial. Results highlight additional opportunities for trial staff to reinforce initial information about the trial, communicate logistical information and individual outcome data, and express appreciation for participation.

Conclusions: Our study enabled clinical trial participants to describe their experiences in a clinical trial for a novel gene therapy. We provide practical recommendations to future clinical trial staff on communications and conduct participant perspectives. Communications strategies should address changing information needs over the course of the trial, express appreciation for participation and enable feedback from participants and their supporting family members, friends, or caregivers.

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Gene therapy; clinical trials; informed consent; communication; patient-oriented research; trial conduct

Introduction

Ocular gene therapies for inherited retinopathies are advancing through clinical trials to market authorization. In 2017, the United States Food and Drug Administration (FDA) approved Spark Therapeutics' (Philadelphia, PD) voretigene neparvovec-rzyl (Luxturna™) for Leber congenital amaurosis (LCA) (1). Other retinopathies targeted by gene therapies include choroideremia (CHM), Usher syndrome, and X-linked retinitis pigmentosa, raising patient hopes and expectations for a treatment for previously untreatable conditions. These hopes impact patient decisions to participate in gene therapy clinical trials (2,3).

Clinical trial participation is predicated on voluntary and informed consent. However, concerns persist about communication for informed consent, especially in early phase clinical trials that focus on safety and collect limited data on efficacy. For example, concerns about voluntariness may arise if recruitment communications are coercive or confusing (4). While patients desire information and supporting data (5), complex documentation may leave participants confused about clinical trial characteristics, including goals and therapeutic potential (4,6–8). Alternatively, potential participants without therapeutic options may have a 'nothing-to-lose' mentality (9), making communication about risks more challenging (2). Trial staff may especially struggle to explain the distinction between clinical research and therapy (2), and conflation of these concepts may lead to therapeutic misconception and/or therapeutic misestimation (3,10–12). The former is characterized by patient expectation of direct benefit in early phase, safety-focused trials, the latter by patient misunderstanding of the possible likelihood or magnitude of any risks or benefits. For example, expectations of a cure without a theoretical/biological basis for that expectation may lead participants to accept higher risks (9).

In planning a Phase I clinical trial for CHM (see Dimopoulos et al. (13) for protocol and results of NCT02077361), the clinical staff committed to a concurrent study of patient and partner experiences during the trial, including communications before consent to join the trial. We aim to understand the perspectives of participants and their partners to improve communications about clinical research and logistical supports in future ocular gene therapy clinical trials.

Materials and methods

We used two data sources, both of which received ethics approval from the Health Research Ethics Board at the University of Alberta. Participants gave informed consent for our studies.

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First, we audio-recorded semi-structured entrance and exit interviews with 2 out of 6 male participants recruited into *An Open Label Clinical Trial of Retinal Gene Therapy for Choroideremia* (NCT02077361) and their partners. Entrance interviews were held 2 months post-surgery (2015), and exit interviews were one month after patients received final trial results (2017). The interviews comprised open-ended questions on clinical communications about trial risks and benefits, decision-making processes, and trial experiences. One participant experienced no therapeutic benefit from the gene therapy and one participant experienced a serious adverse event, resulting in vision loss that persisted at the time of the exit interview (13).

We complemented our dyad interviews with a secondary analysis of transcripts of interviews with 20 prospective trial participants (PTPs), conducted in 2011–2012. These interviews explored the perspectives of 20 men with CHM, aged 18 and older, about their beliefs about risks, benefits and research timelines for gene therapy (9). These interviews were conducted prior to the first CHM gene therapy clinical trial publication in 2014 (14).

We inductively coded and analyzed all transcripts to identify recurring themes (15) informed by the constant comparison method (16), using NVivo qualitative data management software. We constructing summary reports for each individual interview and returned these to each participant for comments (Member Checking), which we integrated into our final analysis (17).

Results

Four key findings emerged from this study. First, trial participants and their partners, who had gone through the consent process with clinical trial staff, had a better understanding of gene therapy risks and benefits compared to PTPs, who had not. Participants noted that staff emphasized uncertainty and risks associated with trial participation during pre-trial communications associated with informed consent (Table 1). Second, evidence from ongoing and early-stage published clinical trials influence enrolment decisions. Accordingly, clinical trial staff should be prepared to discuss this evidence, including its limitations, to inform participants' risk-benefit analysis. Third, in addition to risks associated with the gene therapy intervention, participants underestimated the magnitude of side effects from supportive medications, specifically steroidal anti-inflammatories. They also did not adequately understand the opportunity cost of participation; they will likely be excluded from any future or later-phase trials with enhanced protocols and interventions. Finally, trial staff can improve participant and family experiences by: improving communications pre- and post-intervention, over the course of follow-up visits, and when presenting general and individual trial results; minimizing logistical and infrastructure impediments to trial participation; accounting for degree of vision as well as life and family circumstances; and providing supports for study visits, including compensation for travel, childcare, and lost wages.

Discussion

Informed consent and communications processes can influence patient expectations and clarify their understanding of risks, especially when delivered by trained trial staff who understand the perspectives of participants and their families. While PTPs in our study held a 'no risk' attitude about gene therapy clinical trial participation and over-estimated the potential for therapeutic benefit (9), trial participants who went through the consent process were aware of the associated risks and were able to articulate more informed risk-benefit analyses. They were willing to accept trial risks because their stronger eye was left untreated. They recognized the experimental nature of the trial and understood the uncertainty of any therapeutic benefit.

Participants and partners described their hopes, their avoidance of uninformed hope, and were able to differentiate hope from expectation. Stone et al. (18) similarly found that participants in placebo-controlled trials were generally hopeful, but realistic and aware of the possibility that the therapy may not "work". To promote informed hope, communications should center on current clinical realities, namely what assistive technologies and disease prognoses mean for patients, emphasizing that clinical trials are experimental with uncertain outcomes (3,19).

The participants in our study appreciated a balanced communication approach during the informed consent process. However, the use of 6-month safety data from the Oxford University CHM gene therapy trial (NCT01461213) gave the impression that the intervention had already proven safe and efficacious, which influenced participation decisions. Our trial offered the only available six-month safety data on record at the time of enrollment. Its information sheet only presented the lack of adverse events in the Oxford trial, but trial staff discussed the associated preliminary publication, which emphasized early signs of benefit in two patients (14). This preliminary study, published in *The Lancet*, received widespread media coverage, and participants accessed and accounted for these published results in their decisions to enroll in the Canadian trial. The considerable media coverage of the Oxford trial, like other coverage of biomedical research, highlighted benefits and failed to adequately report the risks of clinical research (12,19–22). Such exaggerated or unfounded health claims in the media may impact patient perceptions of the immediacy and magnitude of benefits of investigational products (33,12,22–24). Our study therefore highlights (1) the ethical imperative to publish clinical trial results, because these inform not only the scientific community, but also future clinical trial participation and (2) the need for clinical trial staff to support potential participants in their interpretation of the risks and benefits identified in prior studies.

Participants and partners also expressed communication needs about surgical and drug side-effects. Side effects and discomfort are common reasons for declining to enroll in trials (25). Improved communications aid in preparing patients and their families, as well as preventing potential harms as participants reach out to informal information sources.

Participants and partners further called for enhanced information on what to expect during appointment so that they could better manage time and make logistical arrangements, including transportation, child care, and nutrition. Adequate communications on these subjects increase patient satisfaction (26). In circumstances where participants feel that testing is prioritized over trial experience, clinical trials risk alienating patients, making them feel like 'lab rats' or 'guinea pigs' (27,28). Communication deficits may exacerbate these sentiments,

Table 1. Illustrative quotes on participation in an ocular gene therapy clinical trial.

Finding 1: The Consent Process Improved Understanding of Risks and Benefits	
Potential Trial Participant Perspectives (not consented for trial)	
Benefit: Therapeutic Potential	If there was a therapy … that would be a dream come true, that would be unbelievable having full sight … I would feel like an X-man if I could see at night! (PTP 19)
Benefit: Therapeutic Window	The treatment is not available fast enough … There's a real sense of urgency … I know everybody wants to … do it … in a careful way; but for me, I'd rather take the chance and save my eyes. (PTP 20)
Risk: Vision Loss	If I lose my sight, it's going anyway. (PTP 2)
No-Risk	For me, there are no risks. The only thing that could happen is to get some vision back. (PTP 7)
Participant and Partner Perspectives (consented for trial)	
Modulating Hope	When I was 19, … [my clinician] told me at the time that like a cure is like three to five years away. I'm [in my 30 s]. I was all excited. Then I did some research into it, found these forums … I found out that this is pretty common to get your hopes up for this kind of things … I still try not to get my hopes up about [the trial outcome] … I just think I'll take the victory if it comes but if it doesn't I'm ready for it. (Participant 2 – Entrance Interview)
Therapeutic Benefit	[I wanted] to watch my kid play catch and sports and stuff so if I can stop it from getting worse and keep doing those things I would it for sure. (Participant 1- Entrance Interview) I don't think they were short on volunteers … So it was more for personal reasons that I joined. (Participant 2- Entrance Interview) Losing his eyesight just really holds him back. I think he would be a lot happier. … Even if he could walk around without having every single light blasting. Even something that simple would be great. (Partner 2 – Entrance Interview)
Altruism	I don't feel like society can get ahead and medicine can get ahead unless people are willing to do this … Even if it didn't have a positive outcome, this information could help going forward. (Partner 2 – Entrance Interview) We knew going into it that regardless of the outcome to be able to be contributing towards doing something like this was something that a lot of people might not get a chance to do. So we were really on board with that. (Partner 2 – Entrance Interview)
Risk	If this were a business decision, I would not be doing it because I'm not getting enough facts, there's too much risk involved but because I'm a patient, I don't have that information but I don't want to miss out on this opportunity so I think I just need to try it. (Participant 2 – Exit Interview) [The trial staff] were very clear about like we don't really know what's going to happen. There were no promises, which was good. They definitely presented it as a really unique opportunity … (Partner 2 – Entrance Interview)
Opportunity	I knew that after considering all the facts I knew that there was no choice … That there was good science behind this process working. And the benefits to it were quite great. And the consequences to it were given the probability is quite small. So I knew that it was a real no brainer to do this process. (Participant 2 – Exit Interview) The day after [the surgery] my sight was already worse which they said was normal. So I didn't think anything of it. And then it just stayed like that. Each of the follow-ups, it was still like that, so I never contacted them. (Participant 1 – Exit Interview)
Finding 2: Evidence from early-stage published trials influence enrolment decisions.	
When considering enrollment	Well, just hoping that it maybe stopped the eye from, you know, getting worse and worse or at least – that was my hope. The doctors were clear at the beginning like, "We don't know. It could. It could not." So they didn't know, so I was kind of hoping it would. Some other people I read about in the UK, some of them were getting better or not getting worse too. So I thought [the chances for benefit] were pretty good. (Participant 1 – Entrance Interview)
Post-trial reflections	There was very little information when I asked about [the UK] studies … Depending on the information available, maybe I'd change my answer … I probably would've declined to enroll … But it was presented already in the positive light that at six months [in the UK trial], three out of six have seen positive reactions. If we're using that information, let's get the complete information. (Participant 2 – Exit Interview)
Finding 3: Participants underestimated potential side effects.	
Side Effects	[The prednisone] was the hardest part for me. I was angry and upset and after my husband had to start a second round of it. I was kind of thinking, "was this the right thing to do?" (Partner 1 – Entrance Interview). There were a couple negative surprises like the effects of the steroids … had I had more information, I would've been able to prepare and react a little bit to the weight gain and moodiness … I suppose the other thing to consider and communicate for risks that may not be considered is how this may exclude you from other trials for the future. That wasn't clear. (Participant 2 – Exit Interview)
Finding 4: Suggestions for improving the experiences of participants.	
Respectful treatment	[The contracted vision clinic] was tough. Dealing with the trial surgeons, they are great but the patient care [at the contracted vision clinic] … bedside manner is not important there. (Participant 2 – Entrance Interview). I didn't go to the appointments at [the contracted vision clinic] because we thought that because he's legally blind they would be more hands on, they totally weren't though. Things like, waving at him from across the room and saying, "oh mister, this way" like he can see them. Then asking him to sit in a chair in a pitch-black room. He can do that if they take him to the chair but he can't see the chair if you leave him in the hallway. (Partner 2 – Entrance Interview)
Post-surgery recovery	Not having any vision there are a lot of mixed facts on how quickly your vision would return. There are mixed facts on how long the stitches would take to dissolve. I think I asked three or four different doctors and literally I got three or four different answers … some said 2 weeks and after I asked about it at my 3 week post-surgery appointment the surgeon said 6 to 8 more weeks. (Participant 2 – Entrance Interview)

(*Continued*)

Table 1. (Continued).

Logistics and support for study visits	There was one time I grabbed a cab home. I made it to the sidewalk but couldn't see the cab. I was just trying to figure out which one the cab was … And I have to work and being on my phone is a critical part of that. So it was not knowing that I was going to be dilated and then having the vision get worse and it just adds unexpected issues with these appointments. (Participant 2 – Exit Interview) That's your whole day. He's missing work and then I'm taking him there so we're missing whatever is going on with kids. It was a lot. We're lucky because both of our moms live [where we live 40–45 minutes from different clinical trial sites] so we can work it out like that. If we didn't have those supports in place and I didn't have anybody to consistently watch my children, I'm not sure how honestly how that would have worked for us. (Partner 1 – Entrance Interview)
Feedback and information	And the follow-up doctors at the university had absolutely no information for him … They just take pictures, take down their information. They don't have any way to like reassure him, to say "this looks okay, this doesn't look okay," Those were people who really could have given him proper feedback. (Partner 2 – Entrance Interview) One thing they could work on is providing more information and keeping us in the loop. We go in and they did the test, but they don't really tell you anything unless you specifically asked … [the research staff is] just very nonchalant which is fine, which is good for a doctor to be. They don't get you all worried and stuff like that. But it would be nice to know how my eyes are compared to normal people or what rate they're getting worse. (Participant 1 – Exit Interview)
Results	[The investigator] went and kind of showed how I was at the beginning and how my eye is now and just how it's got a little worse … I think it would have been nice if there was something there that I can understand more … it was kind of just generic. (Participant 1 – Exit Interview) When I got the official sit down, in my memory, how the situation played out was like a minute long. "Here it is, here's the information, okay? Okay, all right." I was pretty unemotional about it. I was trying not to have any expectations. I would've been quite disappointed if I had some negative side effects. (Participant 2 – Exit Interview)
Post-trial reflections	For this trial, I would say you should do it. Like if you're in my situation, I would say definitely do it. … there will be really tough moments with the steroids and the stitches and some of the poking and prodding you had to do but it's worth it. (Patient 2 – Exit Interview) "[The adverse event] was a surprise of course … They didn't expect that at all, it was new to them … It sucks because there were issues with me that they're still trying to figure out, but it was still a good experience. (Patient 1 – Exit Interview)

reducing participant willingness to continue engaging with the study team and undermining their trust in research staff (28) and in clinical trials (27). Finally, provision of logistical support indicates appreciation for participants and reduces selection bias, making trials accessible to a wider range of participants (25,29).

Follow-up appointments present opportunities to remind participants of the aim and key features of the trial, express appreciation for participants' ongoing contributions, and listen to participants' experiences to improve further trial experiences, including communications (4). Indeed empathetic engagement during trials acknowledges participants' valued contributions to science (30). This is especially important because confidentiality prevents participants' contributions from being publicly recognized. Finally, ongoing communication can be a useful mechanism to keep patient hopes and expectations informed (19).

Limitations

All six clinical trial participants were invited to participate in this study. While only two trial participants and their partners agreed to share their experiences, their reflections highlight successes and limitations of the communication strategies employed. Nevertheless, the small sample size does not represent a complete understanding of how various communication strategies will be received by trial participants and their family members. While our study contributes important considerations for clinical communication design in the rare ocular disease context, future research is required to add to our findings about how to communicate about

Box 1. Clinical trial communication recommendations.

On Communications

- Prepare clinical trial staff to discuss risks and benefits of the clinical trial, logistic and practical expectations for trial participation, and evidence of potential therapeutic outcomes, including their likelihood and magnitude.
- Provide balanced risk-benefit information to inform trial enrollment decisions in the context of individual and family circumstances.
- Provide participants with information sheets on the possible duration of discomfort and adverse effects associated with drugs and surgical interventions. Provide contact information for trial staff in case of adverse effects.
- Prepare staff to assist participants and their support persons in interpreting evidence from published clinical trial reports, including limitations in study design and sample size, and associated media coverage.
- Encourage participants and their support persons to maintain a running list of questions throughout the trial. Ensure that staff answer such questions based on current evidence and acknowledge limitations in evidence/knowledge.
- At all trial appointments, ask participants and their support persons about concerns and questions. Take the opportunity to clarify any misunderstandings.
- Express appreciation for participants and their support persons.
- Share individual outcome data.
- Respect participant contributions by publishing clinical trial results and engaging in other knowledge translation activities, including with patients.

On Logistics

- Offer logistical support, including transportation, meals, and child care. Attempt to accommodate participant work and travel schedules.
- Clearly lay out appointment expectations, including appointment schedule, duration, location, and tests to be performed, including whether tests will limit participants' ability to undertake daily activities. Advise of any special arrangements that may need to be made.
- Scheduling appointments via a shared online calendar system enables greater flexibility.

trial risks and inform reasonable hope and expectations of trial patients and their partners.

Conclusion

While our study is limited to a small number of participants in one trial, its results are consistent with the literature on the importance of communications throughout a clinical trial. We provided a platform for clinical trial participants to express their experiences in a clinical trial for a novel gene therapy and to provide practical recommendations to future clinical trial staff, which we summarize in Box 1.

In summary, communication strategies should promote informed hope for participants and family members about the potential risks and benefits of the experimental intervention and provide information on the practical and logistic challenges of participation. Communication strategies should be dynamic to address both emerging evidence and be respectful of the information needs of participants and their families.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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