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Ocular gene transfer communications: Developing ethical frameworks for phase I choroideremia clinical trials

by

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DEDICATION

To the choroideremia community that, despite its small size, is engaged, empowered, and visible.

ABSTRACT

I investigate how to ethically communicate about a phase I gene transfer trial for choroideremia, a blinding retinopathy, in light of this novel biotechnology's portrayal as a potential 'cure'. I analyzed gene transfer communications in three contexts: (1) interviews with clinicians (n=15), patient advocates (n=6), and patients (n=20) about their perspectives on risks, benefits, and timeframes for clinical implementation of ocular gene transfer; (2) a content analysis of Canadian (n=26), American (n=55), and British (n=77) newspaper articles about ocular gene transfer; and (3) interviews with choroideremia patients (n=20) about their impressions (a) of general media coverage about gene transfer, and (b) in response to a YouTube video about a completed ocular gene transfer clinical trial for a related retinopathy. The thesis provides recommendations for clinicians and patient advocates about how to communicate about the promise of gene transfer in the context of clinical realities for the research and for patients.

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LIST OF ABBREVIATIONS

ADA	Adenosine deaminase
CBER	Center for Biologics Evaluation and Research
CHM	Choroideremia
DNA	Deoxyribonucleic acid
FDA	Food and Drug Administration
IBC	Institutional biosafety committee
IRB	Institutional review board
LCA	Leber congenital amaurosis
NIH	National Institutes of Health
OBA	Office of Biotechnology Activities
OTCD	Ornithine transcarbamylase deficiency
RAC	Recombinant DNA Advisory Committee
REP 1	Rab escourt protein 1
X-SCID	X-linked severe combined immunideficiency

CHAPTER ONE: INTRODUCTION

The field of gene transfer[1] has been subject to high hopes and high profile failures. These failures have sullied the reputation of gene transfer and posed several setbacks for its clinical development. Recently, with emerging successes of ocular gene transfer clinical trials, new hopes have been revived in the field. In light of the checkered history of gene transfer, novel ocular gene transfer clinical trials necessitate the investigation of the communications landscape in the field to ensure that as new trials are developed the biotechnology is represented in a balanced and responsible manner. In this thesis I explore the communications landscape surrounding ocular gene transfer and provide recommendations to clinicians and patient advocates with the aim of establishing balanced messaging about early-phase ocular gene transfer clinical trials. In particular, I focus on multi-stakeholder perspectives associated with a phase I[2] gene transfer clinical trial for choroideremia (CHM), a degenerative retinopathy leading to blindness. In this chapter, I begin by discussing the historical landscape of gene transfer communications, focusing on key events in the field and highlighting patterns of hope and subsequent disappointment. I then continue with an explanation of the objectives of my research, and conclude with a roadmap of this thesis.

1.1 Historical Overview

A Tale of Genohype: Gene Transfer Polarized between Hope and Horror

"Nowhere in biotechnology has the promise been more tantalizing and the failures more devastating than in gene therapy" (Branca, 2005). Indeed, the field of gene transfer, colloquially known as 'gene therapy', has been historically situated within a culture of sensationalism that follows genetic research and

[1] Defined as "the introduction of normal genes into cells in place of missing or defective ones in order to correct genetic disorders" (Gene therapy, 2012).

[2] According to Health Canada: "Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses" (Health Canada, 2008). See Appendix XVVIII for clinical trial phase definitions.

biotechnologies. Such sensationalism, termed “genohype”, describes the exaggerated portrayal of both the benefits and risks associated with genetic research and biotechnologies (Holtzman, 1999). Subject to discourse of promise in a techno-optimistic society “where the human genome is described as "the book of life", research objectives as "holy grail" and dramatic disease reversal as “Lazarus response”” (Kimmelman, 2010, p. 73), gene transfer communications have generated high hopes for the treatment of a myriad of diseases ranging from cystic fibrosis, to metabolic disorders, to cancer. Despite these hopes, however, the biotechnology has yet to live up to its colloquial name, as most genetic diseases remain without a clinically available treatment, evincing that despite the initial hype this biotechnology is developing at a slow and incremental pace (Glassman & Sun, 2004). Beyond the unrealized hopes, the field of gene transfer has been subject to high profile failures and abuses that sullied its reputation and resulted in significant setbacks for its development (Smith & Byers, 2002). In the historical overview to follow I describe key gene transfer trials with an emphasis on the influence of recurrent themes of hopefulness and disappointment on the communications landscape surrounding them.

Initial Aversion and Moratorium

Gene transfer research is conceptually rooted in the contributions of Avery, McLeod and McCarty, who studied DNA-mediated genetic transformation of pneumococci in the 1940s (Avery, McLeod, & McCarty, 1944). In the 1960s early genetic transformation concepts were expanded with the development of mammalian cell lines suitable to test genetic transformation, and it quickly became evident that pursuing stable and efficient gene transfer techniques would be necessary (Friedmann, 1992). This goal was pursued in the 1970s by Paul Berg of Stanford University, who designed an experiment that would combine a tumour virus, SV40, with a bacteriophage that occurs naturally in *Escherichia coli* (*E. coli*), that lives in the human gastrointestinal flora. Despite the promise of this research, Berg was concerned that the integration of SV40 with *E. coli* would pose an oncogenic risk to humans, and indefinitely postponed his study (Swazey, Sorenson, & Wong, 1978). The risks posed by this recombinant experiment were prominently discussed in the scientific community, with scientists expressing perspectives of fear:

> “[no] one could be certain what that combination of genes might do, and the possibilities ranged from nothing at all to some nightmarish version of contagious cancer.” (Rogers, 1977, p. 37).

The delay of Berg’s recombinant experiment was the first self-imposed moratorium in the field of gene transfer, and represents the initial aversion of the scientific community to the biotechnology (Wolf, Gupta, & Kohlhepp, 2009). This moratorium lead to the formation of a stringent regulatory environment for

gene transfer including the National Institutes of Health Research (NIH)-based Recombinant Advisory Board (RAC) that oversees recombinant DNA experiments (Wolf et al., 2009).

The First Gene Transfer Clinical Trial: Deception

In 1980 Martin Cline began the first human gene transfer clinical trials for β-thalassemia. The institutional review board of the University of California, Los Angeles had refused to approve Cline's experiment, and the trials were consequently conducted in Israel and Italy (Thompson, 2000). It was later revealed that Cline had mislead the Israeli and Italian review committees, as it was not disclosed that the study protocol involved the transfer of recombinant DNA to patients (Wade, 1981). Cline was found to violate US federal regulations on human experimentation and was stripped of NIH funding (Sheridan, 2011). This abuse initiated debate about the use of recombinant DNA technologies in human subjects and attention to the social and ethical issues raised by human genetic engineering (Wolf et al., 2009).

Early 1990s: Climate of Hope

With an increased understanding of genetic diseases and developments in DNA manipulation and delivery, high hopes were raised for gene transfer by the media, industry and investigators alike (Sheridan, 2011). For example, leading gene transfer investigator French Anderson asserted that soon "any physician can take a vial off the shelf and inject an appropriate gene into a patient" (Jaroff, 1992). Additionally, the "rosy confidence" (Friedmann, 2005) of researchers promoted optimistic media reporting that projected a 10-year time frame for the therapeutic application of early gene transfer efforts, portraying the biotechnology as a cure-all (Carey, 1993; Condit, 2007). With this backdrop of hope, Michael Blaese and French Anderson began the first approved human gene transfer clinical trial in 1990. This trial aimed to address a rare immune disease called adenosine deaminase (ADA) deficiency. Gene transfer pioneer Theodore Friedmann recalls the early optimism of the scientific community spurred by the ADA deficiency trial:

> Many scientific symposia and other presentations during that time featured teasing initial reports of apparently impressive phenotypic corrections. Some of the scientific and lay media uncritically trumpeted the coming of gene therapy for life-threatening disorders and stoked the hopes and expectations of patients and their families (Friedmann, 2005).

Despite the initial hopes, when the results of the ADA deficiency gene transfer trials were published it became obvious that the expression of the transferred genes was poor and transient (Blaese et al., 1995; Bordignon et al., 1995). These

results disappointed the scientific community and it became widely recognized that gene transfer would be a more complex endeavour than initially envisioned (Friedmann, 2005).

Ornithine Transcarbamylase Deficiency Gene Transfer: Erosion of Public Trust

The year 1999 was marked by a tragic event in the field of gene transfer with the death of a research participant, Jesse Gelsinger, in a gene transfer trial for ornithine transcarbamylase deficiency (OTCD) at the University of Pennsylvania. Gelsinger received the gene transfer intervention, and died within 98 hours, with autopsy results confirming that his death was directly caused by an immune response to the viral vector carrying the OTC gene (Wilson, 2009). Gelsinger's death was immediately reported to the RAC, Food and Drug Administration (FDA), as well as the NIH. Clinical research was halted at the University of Pennsylvania following Gelsinger's death in response to concerns about infrastructure regulating human research, causing a notable delay in the development of gene transfer biotechnologies (Smith & Byers, 2002).

Risk perspectives following serious adverse events are often amplified[3], as publics perceive the magnitude of adverse events with greater salience than the incidence or probability of their occurrence (Deakin, Alexander, & Kerridge, 2009). In the case of Gelsinger's death, the media played a significant role in amplifying risk perspectives. News headlines immediately following Gelsinger's death displayed heightened scrutiny, for example: "Death leads to concerns about future of gene therapy" (Wade, 1999). Media discourse elucidated the disappointment of the OTCD trial in light of the initial high hopes for gene transfer:

> The Sept. 17 death of Jesse Gelsinger of Tucson, Ariz., marks the first fatality in the burgeoning and still highly experimental field of gene therapy, which has promised to bring cures to a wide range of diseases ranging from cancer and heart disease to a multitude of inherited conditions (Collins, 1999)

Scholars argue that that the death of Jesse Gelsinger generated a disproportionate volume of media attention (Deakin et al., 2009). While serious adverse events are not foreign to clinical research, Gelsinger's death was highly publicized and scrutinized. In 1999, twenty-two articles were written about Gelsinger's death in the *New York Times*. In the same year 153,964 serious adverse events in clinical trials were reported to the Center for Drug Evaluation and Research of the US FDA, of which 17,399 resulted

[3] Amplification of risk refers to the increased perceived salience of risk. Term derived from Social Amplification of Risk Theory (Kasperson, Renn et al. 1988).

in patient deaths (Deakin et al., 2009). While Jesse Gelsinger's name is known to many professionals and lay publics, the names of the majority of the research participants who died as a result of serious adverse events in clinical trials remain unfamiliar to most. Not only did media coverage target the tragedy of Gelsinger's death, it also reinforced the failures of the field of gene transfer at large. Media attention to Gelsinger's death presented gene transfer in a negative light, engendering public aversion to the field (Deakin et al., 2009).

Beyond Gelsinger's death, the OTCD trial sullied the reputation of gene transfer because of several abuses and protocol infringements. One of the significant charges against the OTCD team was the omission of key information concerning serious adverse events associated with the viral vector used. Omissions included deaths of two rhesus monkeys during the pre-clinical trial due to immunologic responses to the vector delivering the OTC gene, and adverse reactions causing temporary liver stress in two of the human participants. FDA reports concluded that Gelsinger might not have agreed to participate in the gene transfer trial in light of the concealed adverse events to the viral vector (Smith & Byers, 2002), and scholars questioned the integrity of this trial's informed consent as a consequence of these omissions (Liao, Sheehan, & Clarke, 2009; Yarborough & Sharp, 2009). Further allegations of abuse concerned protocol infringements (Smith, 2003), including an unauthorized amendment to the inclusion criteria of the trial to allow Gelsinger's participation, and a change of the injection site of the viral vector (Wilson, 2009). The principle investigator of the OTCD trial, Dr. James Wilson was also accused of holding undisclosed financial conflict-of-interest, including shares in Genovo, a biotechnology company that sponsored the OTCD trial, valued at $28.5- $33.3 million (Wilson, 2010). Although Wilson maintained that the financial stakes he held in the OTCD trial did not motivate him (Wilson, 2009), scholars determined that the involvement of private sector in research ventures decreases public support and engenders public distrust (Critchley, 2008). In the case of the OTCD trial, Genovo's stake in the research might have sparked public scrutiny. Critics argue that the complex web of financial ties in the OTCD trial coupled with Gelsinger's death were corrosive to public trust[4] in gene transfer research (Wilson, 2010).

Despite a strong impetus for restructuring the regulatory infrastructure of gene transfer biotechnologies, critics suggest that the failures and abuses of the OTCD trial continue to "cast a cloud over biomedical research" (Teichler Zallen, 2000; Yarborough & Sharp, 2009). Scholars suggest that the OTCD trial engendered a "culture of distrust" as the result of acts of non-disclosure, and that public trust in gene transfer biotechnologies may still not be restored over a decade after the trial (Liao et al., 2009). Moreover, scholars argue that the research community has not

[4] Trust refers to "the expectation that a trustee is both able and motivated to behave in a way that is valued by the trustor" (Critchley, 2008).

internalized the lessons from the OTCD trial. This is evident as United States federal conflict-of-interest disclosure policies have not been amended since Gelsinger's death (Wilson, 2010). Described as "the most famous conflict-of-interest case in medicine" (Wilson, 2010), the OTCD trial was a seminal failure in the field of gene transfer that highlights the delicate nature of public trust in research (Yarborough & Sharp, 2009). The abuses of the OTCD trial continue to present challenges to the reputation of gene transfer risk today, and elucidate the importance of sustaining public support in the field of gene transfer (Liao et al., 2009; Yarborough & Sharp, 2009).

X-SCID and Insertional Mutagenesis

In 1999, a gene transfer trial for X-linked severe combined immunodeficiency, a rare and fatal immune disease, began in Paris. In 2000, a report announced that two children in the trial displayed improved immune function as a result of gene transfer (Cavazzana-Calvo et al., 2000). The results of this trial, at the time, were regarded as the first unequivocal success in the field of gene transfer (Johnston & Baylis, 2004; Sheridan, 2011). This success, however, was short-lived, as one of the children who derived clinical benefit presented with leukemia-like symptoms in October of 2002. Three months later a second case was reported (Hacein-Bey-Abina et al., 2003). Investigations revealed that the viral vector, which was based on Molony murine leukemia virus, had inserted near LMO-2, a proto-oncogene and activated it (Sheridan, 2011). This instance of "insertional mutagenesis" raised concerns about the safety and feasibility of gene transfer (Hacein-Bey-Abina et al., 2008). The Paris trial as well as similar gene transfer trials in Germany and the United States were halted in response to the incidence of leukemia, and British regulatory agencies increased the scrutiny of gene transfer trials as a result (Johnston & Baylis, 2004). To date, of the twenty children who received the gene transfer, five developed leukemia, and four of these five survived the leukemia (Fischer, Hacein-Bey-Abina, & Cavazzana-Calvo, 2010).

Ocular Gene Transfer: Revival of the Field

On the heels of high profile adverse events such as the death of Jesse Gelsinger and the diagnosis of leukemia in the X-SCID trials, a report in *Nature Genetics* revitalized long-standing hopes in the field of gene transfer. This report outlined the visual improvement afforded by gene transfer to Briard dog models for a rare childhood blindness called Leber congenital amaurosis (LCA) (Acland et al., 2001). A variety of genetic mutations yield this disease, one of which, the RPE65 gene mutation, was addressed through this research. The promising animal data suggested that gene transfer could be applied to humans with LCA to improve vision. The report fueled great excitement among the scientific community, the media, as well as patients. Gustavo Aguirre, an investigator of the study, publicly

displayed his enthusiasm, “This is the promise of gene therapy—making the lame walk and the blind see” (Giresi, 2005).

Human LCA gene transfer clinical trials began in 2007 in three study centers. Three subjects were enrolled in each of these phase I clinical trials, and subjects displayed improved visual function with no serious safety concerns arising (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). The improvement of vision in these phase I trials aimed at establishing indexes of safety generated excitement among the scientific community. Clinicians even began to assert that these nascent trials were going to change the landscape of clinical care:

> These findings and new insights present a paradigm shift in our management of retinal dystrophies of all types, previously thought to be an untreatable group of human diseases (Koenekoop, 2008).

The enthusiasm of the scientific community was reflected in the media (Kaplan, 2008). Media headlines highlighting hope for an imminent cure emerged, for example: “Gene holds hope for a blindness cure” (Winstein, 2008). Lay literature even asserted that the successes of this trial saved the field of gene transfer (Lewis, 2012). The promise highlighted in the media soon reached hopeful patients, eager to participate in gene transfer clinical trials. A common misconception emerged among patients, as they expected that RPE65 gene transfer would offer a cure to various forms of LCA, leaving patients confused and frustrated with their lack of access to the intervention (Héon, 2009). The RPE65 mutation, however, is only responsible for 5% of LCA cases, leaving 95% of LCA patients ineligible to participate in further trials, and many patients with an RPE65 mutation unable to access gene transfer, as it is currently experimental and not standard-of-care.

Since the initial LCA gene transfer trials, further studies continued to display consistent safety and efficacy data for small subject pools (Simonelli et al., 2010), with phase III clinical trials currently underway (NCT00999609) (National Institutes of Health & Children’s Hospital of Philadelphia, 2012). LCA gene transfer successes have served as an impetus for the development of clinical trials for a diversity of ocular genetic diseases (Smith, Bainbridge, & Ali, 2009), including Stargardt disease (NCT01367444) (National Institutes of Health & Oxford Biomedica, 2011), retinitis pigmentosa (NCT01482195) (National Institutes of Health & Fowzan Alkuraya, 2011), and choroideremia (NCT01461213) (National Institutes of Health & University of Oxford, 2011).

1.2 My Research

Sensationalized high profile failures have historically sullied the reputation of gene transfer, resulting in setbacks on its clinical development. Currently, promising ocular gene transfer clinical trials are revitalizing the field and raising the hopes of stakeholders including clinicians, patient advocacy organizations, patients, and the media. In light of recurring themes of hopefulness and subsequent disappointment in the history of gene transfer, it is essential to ensure that as contemporary gene transfer clinical trials are developed the communications surrounding them are balanced. Responsible communications will promote public trust, an essential constituent to the sustainable translation of this biotechnology (Chalmers & Nicol, 2004).

At this junction of cutting-edge gene transfer research, communications are prominently centered on the theoretical promise of the biotechnology (Kimmelman, 2010), despite a clinical reality in which most genetic diseases do not have available treatments. While some scholars maintain that promotional discourse is necessary to facilitate an acceptance of novel biotechnologies as a natural element of the construction of technological futures (Hedgecoe, 2004), others critique promotional discourse as "hype" (Holtzman, 1999). In the case of ocular gene transfer, hype is often associated with media communications, likely because the media is the most accessible source of information about health technologies for many members of the public (Caulfield & Condit, 2012). However, many stakeholders engage in building social expectations surrounding gene transfer trials through promotional messaging. As such, several actors, including clinical investigators, clinicians, and patient advocacy organizations engage in "expectation management" to promote gene transfer efforts in the public sphere (Kimmelman, 2010). The dynamics between all of these stakeholders shape the public representations of the biotechnology (Stockdale, 1999). Discourse of promise may influence the emotional stakes or disease management strategies of the most vulnerable[5] stakeholders: the patients who may be future beneficiaries of gene transfer endeavours. According to Reimer et al. (2010), "meaningful therapy will only be realized when it is responsive to individual values and priorities and situated in the context of hope that is fully informed" (Reimer, Borgelt, & Illes, 2010). It is therefore important to consider the views of key stakeholders when pursuing novel ocular gene transfer clinical trials, and to cultivate a communications landscape surrounding gene transfer

[5] Patients closely follow promotional communications about gene transfer (Kimmelman, 2010). These communications may raise patient hopes (Petersen, 2009) for a mediation of their own prognoses. Hope carries with it an inherent vulnerability (Simpson, 2004)—that is, that once hopes are raised the possibility of future disappointment makes patients prone to emotional or practical harms.

efforts that is responsive to stakeholder concerns and values, and approaches vulnerable patients with ethical messaging.

In this thesis, I investigate a key research question:

> How can stakeholders of novel ocular gene transfer clinical trials ethically communicate about the risks and benefits associated with the research in light of a perceived 'cure', while avoiding the hype that has historically undermined this field of translational medicine?

As a case study of novel ocular gene transfer efforts, I explore the communications landscape surrounding a phase I gene transfer clinical trial for CHM (NCT01461213) (National Institutes of Health & University of Oxford, 2011). CHM is a sex-linked disease, with an incidence that varies between 1:50 000 and 1:100 000 (Coussa & Traboulsi, 2012; van den Hurk et al., 1997). CHM is characterized by a mutation in the gene encoding Rab Escort Protein 1 (REP 1), a protein involved in vesicular trafficking (Cremers, Van De Pol, Van Kerkhoff, Wieringa, & Ropers, 1990; Jacobson et al., 2006). In the absence of functional REP 1, the choriocapillaris, retinal pigment epithelium, and photoreceptors progressively degenerate (Roberts et al., 2002). CHM begins to affect males in the first or second decade of life, first through night blindness, then typically through peripheral visual field restrictions, and progressively leads to legal blindness by middle age (MacDonald, Russell, & Chan, 2009). The first gene transfer clinical trial to address choroideremia was began phase I studies in 2011 (NCT01461213) (National Institutes of Health & University of Oxford, 2011), with additional phase I studies projected to begin at the University of Alberta and the University of Pennsylvania in 2013. Early-phase gene transfer efforts for CHM present an opportunity to establish responsible communications about the biotechnology as it is developed, and to consider the needs of key stakeholders such as clinical investigators, clinicians, patient advocates, and patients. Exploring the context of communications surrounding CHM clinical trials, including the discourse of media outlets, will aid in establishing guidelines for clinical communications that balance the hope engendered by the theoretical promise behind research efforts and the current clinical reality.

1.3 Thesis Outline

I follow this introduction to my paper-based thesis with an overview of the methods (chapter two) and the research design. I begin with a disclosure of my perspectives, drawing on the epistemological and ontological propensities that shape my research. I continue with an explanation of ethical considerations for research, particularly those raised by the involvement of human participants. Finally, I detail both the qualitative and quantitative inquires employed. Specific methods are further elaborated within chapters three and four. Each of these

chapters has been prepared as a stand-alone paper for submission to a peer-reviewed publication.

In the third chapter of this thesis, I address the perspectives of various stakeholders involved in communicating about CHM gene transfer, with an emphasis on the concerns of the most vulnerable potential beneficiaries: CHM patients. In this chapter I explore the dynamics of communications between clinicians, patient advocates and patients that shape the priorities of CHM gene transfer. I explore challenges to communicating a balance between the hope for therapeutic benefit and the current clinical reality that does not offer a treatment for CHM. In this chapter I highlight stakeholder perspectives about (1) the risks (2) benefits and (3) the time frames associated with the clinical implementation of CHM gene transfer. More specifically, I address the following research questions:

- What are the benefit perspectives of stakeholders with respect to CHM gene transfer?
- What are the risk perspectives of patients associated with phase I CHM gene transfer clinical trials?
- In what manner can discrepancies in communications between stakeholder groups be addressed through discussions in the context of clinical care?
- What considerations do stakeholders' risk/benefit perspectives pose for the informed consent process in the context of clinical trial enrollment?
- How can time frame estimates be communicated to address the concerns of patients and patient advocates?

In the fourth chapter of this thesis I explore media communications about gene transfer through an investigation of Canadian, American and British newspaper communications about ocular gene transfer. Additionally, I explore the perspectives of CHM patients about (1) general media communications about gene transfer, and (2) a YouTube video clip featuring the views of researchers, patient advocates and patient families about the LCA gene transfer clinical trial. In this chapter I address the following questions:

- Are errors of omission that past studies associated with hype (Bubela & Caulfield, 2004; Holtzman et al., 2005) present in newspaper coverage about gene transfer?
- How do the media represent the risks and benefits associated with ocular gene transfer?
- Do CHM patients trust media coverage about ocular gene transfer?
- How do CHM patients view ocular gene transfer in light of its media coverage?
- Does ocular gene transfer media coverage pose challenges to CHM patients in managing their disease?
- What considerations for informed consent in the context of clinical trial enrollment does ocular gene transfer media coverage pose?

Finally, in the fifth chapter, I conclude this thesis and provide recommendations for ethical communications about CHM gene transfer, highlighting that the onus of responsible messaging lies with clinical investigators, clinicians, and patient advocates. I conclude with ideas for future research.

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CHAPTER TWO: RESEARCH METHODS

This chapter gives a general overview of the methods used in this study, as well as the theoretical justifications for their use. Specific methods are elaborated in each results chapter, one representing participants' views on ocular gene transfer about an upcoming gene transfer clinical trial for choroideremia (CHM), and the second analyzing media coverage of ocular gene therapy and the views of patients about such media coverage.

2.1 Statement of Personal Perspectives

> Not everything that counts can be counted, and not everything that can be counted counts.
>
> –Albert Einstein

This thesis was shaped by my ontological, epistemological and methodological propensities. My background in molecular genetics has grounded my understanding of science in a post-positivist paradigm that aims to capture an objective truth among bias-laden research. The exploratory research questions that I investigate in this thesis, however, lend themselves in a social constructivist realm that embraces a subjective reality and seeks to illuminate bias. Throughout the analysis phase of this research, I found great difficulty accepting that personal accounts can be subjectively analyzed to yield empirical research.

In this thesis I incorporate a triangulation of qualitative and quantitative methods to explore the communications landscape surrounding CHM gene transfer. With my struggle to find a position at the intersection of two epistemologies, I surrendered to an approach of "eclectic pragmatism" that borrowed methodological designs from diverse disciplines and traditions to explore different research questions.

As I embrace my newly cultivated constructivist approach, I reflect upon how my biases shape my research. One prominent bias in my research is shaped by my optimistic worldview. In this thesis I make critical remarks about the incremental nature of progress in the field of gene transfer in contrast with the high hopes surrounding this biotechnology. Despite these critical arguments, I am optimistic about the promise of gene transfer. My background in molecular genetics may dispose me towards a techno-optimistic worldview. Beyond this disciplinary inclination, I believe that my interactions with vulnerable populations affected by genetic disease have shaped my personal hopes for the development of gene transfer. Having spoken with many patients and their families, I am aware of the

emotional stakes associated with the development of a successful gene transfer intervention. While I give recommendations to avoid the therapeutic misconception, I find myself not only understanding of those who hope for a treatment in the context of a phase I clinical trial, but also, with the stories that patients shared with me in mind, hopeful for the same outcome.

2.2 Ethics Review and Participant Recruitment

Researchers working with human participants must ensure that research practices adhere to the *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Canadian Institutes of Health Research, Natural Sciences & Engineering Research Council of Canada, & Social Sciences & Humanities Research Council of Canada, 2010). To ensure that these ethical standards were met, I sought ethics review from the Health Panel of the Review Ethics Board at the University of Alberta, which assesses non-invasive health research (refer to Appendix I for University of Alberta Health Research Ethics Board approval letter). Additionally, as patients were recruited using Alberta Health Services resources Alberta Health Services Operational Approval was granted (refer to Appendix II for Alberta Health Services operational approval letter).

I recruited participants through a purposeful sampling of clinicians and CHM patients (see Appendices III-VI for recruitment materials). I conducted interviews at the Royal Alexandra Hospital Eye Clinic, ophthalmology research offices at the Katz Building at the University of Alberta, at private locations in conferences, as well as over the phone. Each participant was provided with an information sheet (see Appendices VII-IX) explaining the purpose and procedures of the study, as well as the confidentiality and withdrawal provisions. Participants were given the chance to review this document and to ask questions of the investigator. The investigator highlighted to each patient that participating in this study is separate from his clinical care and will not promote access to therapeutic interventions or to the upcoming CHM clinical trial. I obtained informed consent from each participant prior to each interview (refer to Appendix X for consent form). In cases where participants were not able to read and sign the consent form (e.g., due to severe visual impairment), a study researcher, with the permission of the participant, read the information sheet and audio recorded an oral consent. Interview questions were based on the interview guides (Appendices XI-XIII). Any personnel hired for this research (i.e., transcriptionist) signed a confidentiality agreement (Appendix XIV).

Concerns in the ethics review process included data storage, confidentiality, and risk/benefit analysis. I de-identified the data collected at the transcription verification stage by the use of codes instead of names to protect the confidentiality of participants. The collected data, including audio recordings, transcripts of recordings, and any notes, will be stored in a secure manner (locked

in a cabinet in a locked room) by the principal investigators and kept for 5 years, after which the data will be destroyed. The benefits of participating in this research included a chance for participants to express their views, concerns, hopes and expectations about gene transfer, as well as contributing to ethics research on gene transfer, which will result in concrete recommendations about communications strategies in this context. Risks applicable to all research participants included being upset by some of the interview questions or fatigued by the interview process. In cases where I identified participant distress during interviews, I reminded participants that they could take a break or choose to terminate the interview at any point. Since the ocular genetics research community is small, well-known clinicians who have expressed distinct attitudes in the media may be identified even though their names will not appear in publications. I explained this risk to clinicians during the informed consent process.

2.3 Interviews

Number of Participants

I conducted 41 interviews: 20 with CHM patients, 15 with clinicians, and 6 with patient advocacy group representatives. Experts expect that with the use of a qualitative framework, 20 interviews will likely reach saturation (Saumure and Given, 2008). Saturation is defined as "the point in data collection when no new or relevant information emerges" (Saumure and Given, 2008). I determined saturation using the constant comparative method (Charmaz, 2006). Clinicians represented a unique sample, as this group depicted more homogenous perspectives, perhaps due to commonalities engendered by a shared discipline. Data from this group reached saturation at 15 interviews. CHM is a rare disease, and as such has few patient advocacy organizations. I interviewed a representative from each CHM patient advocacy organization worldwide.

Participant Inclusion

Patients

The patient group was comprised of males that self-identified to be affected by CHM. These patients were chosen as potential participants in an upcoming CHM gene transfer clinical trial to commence at the University of Alberta in 2013. These patients were therefore personally engaged in communications, as recipients, active seekers of information, and some as disseminators of information through patient advocacy organizations or patient support groups. The gene transfer effort might affect these patients' hopes, life goals or disease management strategies (Héon, 2009).

I did not include individuals impacted by CHM who would not be eligible to participate in the clinical trial, namely female carriers and patients under the age of 18. I excluded CHM female carriers from participating in this study because they are generally not visually impaired as severely as males due to the X-linked pattern of inheritance of CHM (MacDonald, Russell, & Chan, 2009) and may have unique considerations (e.g., reproductive concerns about passing disease gene to offspring) with the potential to confound the data. I also excluded patients under the age of 18 because participation in this study required mature reflection about one's experiences of living with CHM, managing vision loss, and about how the possibility of participating in a gene transfer clinical trial might affect one's life. Finally, the questions in the interview guide elicited painful emotional responses in several patients, and in an effort to protect participants who may be more vulnerable than others, only adult patients were included.

Clinicians

The clinician group of participants was comprised of clinicians who care for CHM patients and communicate with them about gene transfer clinical trials. Clinicians included ophthalmologists and genetic counselors. All clinicians were experts in ocular genetics and had a comprehensive understanding about the challenges of communicating about the promise of gene transfer with CHM patients.

Patient Advocacy Representatives

In North America the four patient advocacy organizations dedicated to serve CHM patients and raise research funds are: Foundation Fighting Blindness, USA, Foundation Fighting Blindness, Canada, Choroideremia Research Foundation, USA, and Choroideremia Research Foundation, Canada. In Europe there are two CHM patient groups: France Choroïdérémie and Coroideremia Asociacion de Afectados. I interviewed one representative in a leadership position from each patient advocacy group organization.

Recruitment

Participants were recruited through purposeful sampling with respect to the study's inclusion and exclusion criteria.

Patients

Investigator Dr. Ian MacDonald identified appropriate patients in his clinical practice (Alberta Health Services administrative approval granted see Appendix II), and these patients were invited to participate in the study through a recruitment letter (Appendix IV). Other patients were recruited through notices on

the websites of three patient advocacy group: Foundation Fighting Blindness US, Canada and Choroideremia Research Foundation US, Canada (Appendix V).

Clinicians

I identified top clinicians in the field of ocular genetics through publication contributions or conference presentations. Clinicians were contacted via e-mail (Appendix III), or in-person at conferences.

Patient Advocacy Representatives

I contacted patient advocacy group representatives via email (Appendix III) or in-person at conferences. Advocacy group representatives were identified in organizational personnel listings on their respective web sites.

Data Collection

I used semi-structured interviews, approximately forty-five minutes to one hour in length. The flexible nature of semi-structured interviews allowed participants' attitudes and views to emerge and to be further explored by the interviewer using follow-up probes and prompts. Additionally, semi-structured interviews allowed for a balance of structure in the conversation and space for the emergence of themes that were relevant to individual participants (Charmaz, 2006).

The interview guides were based on concerns raised by previous studies about issues related to genetic communications (Henderson et al., 2004; Henderson et al., 2006; McAllister et al., 2007; Petersen, 2006). Additionally, experts in the fields of ocular genetics, risk communication, bioethics, and health law reviewed the interview guides.

The interview guides were designed to explore participants' expected therapeutic benefits, perceived risks, and time frame estimates for clinical implementation of gene transfer. The interview guides were structured to elicit emotional responses such as fear, hope and concern, as well as common issues such as comprehension of communications surrounding gene therapies and sources of information (McAllister et al., 2007). It is understood that genetic risk perspectives are not isolated to the influence of clinical communications, and are also influenced by popular discourse in the media and other venues (Nelkin & Lindee, 1995). Because the media are an important and accessible (Caulfield & Condit, 2012; Geller, Bernhardt, & Holtzman, 2002) source of health information and information about new technologies for patients and the public, I examined patient perspectives on these sources. I asked patients questions about their exposure to and opinions of media coverage about gene transfer. I also showed participants the most viewed video clip on YouTube depicting a Leber congenital amaurosis gene transfer clinical trial. The video clip showed the perspectives of

study investigators, patient advocates and affected families (BIOchannel, 2010). I asked participants questions about how the video made them feel in general and about participating in a gene transfer clinical trial. For additional details about the interview guides, refer to Appendix XI.

Data Analysis

I audio recorded all interviews, which were then transcribed by a professional. Following transcription, I verified each transcript by comparing the transcribed output with the original audio to ensure accuracy. I analyzed the interview transcripts using NVivo 9.1 software (QSR international, 2010), a qualitative data management program that provides assistance with data organization and coding. I initially coded the transcripts "line by line", where each line of the data was given a preliminary code using gerunds. Gerunds promote a sense of action and help identify processes in the data (Glaser, 1978). Initial coding followed the data closely, as the codes used the participants' language. Charmaz explains that "staying close to the data and, when possible, starting from the words and actions of your respondents, preserves the fluidity of their experience and gives you new ways of looking at it" (Charmaz, 2010 p.49). I analyzed for distinction and similarity within and between transcripts using the "constant comparison method" (Glaser and Strauss, 1967). Through an iterative process of transcript comparison and arrangement of codes into emerging sub-themes and themes I eventually developed a codebook. The principle investigator reviewed thematic codes to ensure comprehensiveness and accuracy. I reviewed selected quotes in the context of the original transcripts to ascertain precision of interpretation. In addition to coding, I wrote reflexive field memos following each interview and developed analytic memos to document the theme development process.

Member Checking

To make sure that the interpretation of study results remained true to the views of study participants, I prepared summaries of study results and sent these to participants for feedback (see appendices XVI- XIX). I prepared stakeholder-specific reports to ensure that participants viewed only the perspectives of their own stakeholder group and were not influenced by the comments of other groups that may have contradicted, or influenced their responses. Finally, participants were encouraged to respond to the reports with any comments or questions. Responses from participants were overall supportive of the results.

Data Management

Data management followed the *Tri-Council Policy Statement: Ethical Conduct for*

Research Involving Humans (Canadian Institutes of Health Research, Natural Sciences & Engineering Research Council of Canada, & Social Sciences & Humanities Research Council of Canada, 2010). Interviews were audio recorded and subsequently transcribed verbatim. To protect the confidentiality of participants, names were replaced with participant codes. The data will be stored in a locked cabinet for five years, after which it will be destroyed. I used NVivo 9.1 software (QSR International, 2010) to organize and code data.

Trustworthiness

Four measures of trustworthiness are used to describe rigour in qualitative research terms: *credibility, confirmability, dependability,* and *transferability* (Lincoln and Guba, 1985). Credibility (parallel to the quantitative construct of internal validity) is a measure of how accurately and completely the researchers have described the phenomenon studied (Given and Saumure, 2008). In this study credibility was maintained through the construction of interview guides based on a comprehensive survey of research in the field. The codebook used to analyze interview data was reviewed by my thesis supervisor (Tania Bubela) and a independent expert in qualitative methods (Elaine Hyshka) for comprehensiveness of codes and distinction between codes. The use of NVivo data management software increased the credibility of the research because this tool facilitated data coding and organization and created an audit trail of analysis procedures (Seale 2002). Additionally, as per Lincoln and Guba's recommendation (Lincoln and Guba, 1985), to ensure that the data accurately represents participant views and to avoid misrepresentations, I employed a member checking exercise by re-contacting every interviewed participant with a summary of results. Participant responses were largely supportive of my analyses. Indeed, the responses from patients additionally highlighted my analysis of their sense of urgency to access gene transfer clinical trials. In one instance, I integrated a participant response, who requested that I clarify the primary role of advocacy organizations as fundraising.

Confirmability (parallel to objectivity) is a measure of how well the claims of research are supported by the data (Given and Saumure, 2008). We ensured confirmability in our study by providing direct quotations of research participants, which bolstered our analysis. All quotations were reviewed in their original context prior to their integration in the study results.

Dependability, unlike its analogous quantitative concept, reliability, does not call for the ability to replicate study findings perfectly. Instead, the concept of dependability suggests that if the study should be repeated with similar participants, the results would be similar or have traceable differences (Jensen, 2008). The dependability of this study was achieved by ensuring that the themes were saturated. We interviewed clinicians and participants until recurring themes

consistently emerged and new interviews did not elicit new theoretical concepts. This saturation increases the likelihood that future studies conducted with similar populations will elicit similar themes.

Transferability (analogous to generalizability) refers to the description of the scope of the study (Given and Saumure, 2008; Jensen 2008). Transferability depends on similarities and differences between original and subsequent research studies. As such, transferability relies on an in-depth understanding of commonalities and differences in study contexts (Carlson, 2010). To facilitate this understanding, I provided a detailed description of research context, study participants, data collection and data interpretation. The results of these interviews detailing communications concerns surrounding ocular gene transfer clinical trials are expected to apply to populations affected by genetic disorders under the investigation of gene transfer clinical trials beyond those in the realm of ocular genetics. In this manner, the proposed project may be transferrable to a variety of genetic diseases for which a therapeutic intervention is under investigation.

2.4 Media Analysis

Data Collection

I searched for newspaper articles about ocular gene transfer using the top 50 newspapers identified by circulation statistics (Audit Bureau of Circulation, 2011) in the US, UK and Canada. These countries are the top three English-speaking countries that have generated the most human gene transfer clinical trials (National Institutes of Health, 2011; The Journal of Gene Medicine, 2011). With the help of expert library information science specialists, I developed a search strategy using algorithms that captured colloquial synonyms for gene transfer (Table 2-1). I retrieved newspaper articles appearing between the dates of January 1, 1990 to June 30, 2012 from both Factiva (for US and UK newspaper search) and Canadian Newsstand databases (for Canada newspaper search) to ensure completeness of newspaper article inclusion. Initially the search produced 2070 articles (84 Canadian, 647 UK, and 1339 US). After reading each article, I narrowed down article inclusion criteria to only include articles about gene transfer for genetic retinopathies. Final numbers of articles are displayed in Table 2-1.

Table 2-1: Newspaper search for articles about ocular gene transfer

Country	Search Strategy	n
US	At least one of these words: blind* ocular ophtha* vision sight retin* eye This exact phrase: gene therapy	55
Canada	TITLE(blind* OR ocular OR ophtha* OR vision OR sight OR retin* OR eye) AND (gene therap*)	26
UK	At least one of these words: blind* ocular ophtha* vision sight retin* eye This exact phrase: gene therapy	77

Data Analysis

I explored newspaper communications about ocular gene transfer using a deductive content analysis and an *a priori* coding frame. I developed the coding frame (Appendix XV) to address the concerns arising from interviews with clinicians, patients and patient advocacy group representatives. Additionally, the coding frame was informed by other studies about media communications or gene transfer communications (Bates, 2005; Bubela & Caulfield, 2004; Condit, 2001; Condit, 2007; Holtzman et al., 2005).

I trained a research assistant to use the coding frame, bringing her attention to the subtleties of methods depictions, research terminology, visual benefit representations and other areas of interest addressed in the coding frame. The research assistant had no post-secondary education, and this was advantageous in ensuring that the coding captured a lay perspective. To ensure reliability in coding, I coded 30 articles (19% of the total article count). I then performed a Cohen's Kappa test. The test yielded a kappa range of 0.71-1.0, indicating acceptable inter-coder reliability (Neuendorf, 2002).

Further statistical analysis was necessary to detect statistically significant differences for the constructs coded between countries. I used STATA 11 (StataCorp, 2009) to perform Fischer's exact chi squared tests. This test detects statistically significant differences using a contingency table analysis even among data sets with small sample sizes that does not satisfy the assumptions of a Pearson chi squared test (Daniel, 2009 p.629). To test the null hypothesis that no differences in the median number of benefit and risk representations existed between countries, I performed a Kruskal-Wallis analysis of variance. This non-

parametric alternative to a one-way analysis of variance is appropriate for the data set because the small number of Canadian articles does not allow for the assumption of a normal distribution (Daniel, 2009).

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CHAPTER THREE: IS A CURE IN MY SIGHT? STAKEHOLDER PERSPECTIVES ON CHOROIDEREMIA GENE TRANSFER

3.1 Introduction

Despite many advances in genomics research since the sequencing of the human genome, effective treatments have not become available as standard-of-care for most genetic diseases (Evans, Meslin, Marteau, & Caulfield, 2011), including choroideremia (CHM), a sex-linked retinal dystrophy, affecting approximately one in 50 000 males. In the absence of a therapeutic intervention, CHM causes progressive vision loss beginning in childhood and often leads to legal blindness by middle age (MacDonald, Russell, & Chan, 2009). In the face of this prognosis, gene transfer (colloquially known as 'gene therapy'), a novel experimental intervention for CHM, is now in early-stage clinical trials. In October 2011, researchers in the United Kingdom initiated a phase I[6] gene transfer clinical trial for CHM (NCT01461213) (National Institutes of Health & University of Oxford, 2011), igniting the hopes of patients, patient advocacy groups, and clinicians for a future treatment. CHM gene transfer holds great promise, but its merits and risks remain uncertain (Thalman, 2006).

Gene transfer has fueled high expectations as a "miracle technology" (Stockdale, 1999) for a variety of conditions. But despite high hopes, the field has faced significant setbacks as a result of serious adverse events, including two deaths and the development of leukemia in children, as well as abuses including failures to report adverse events to regulatory bodies (Wolf, Gupta, & Kohlhepp, 2009). These abuses and high profile failures resulted in significant public scrutiny (Deakin, Alexander, & Kerridge, 2009) and sullied the reputation of gene transfer (Branca, 2005; Pattee, 2008).

Recent successes in gene transfer clinical trials for ocular applications have revived long-standing hopes for the field. In 2007 clinical trials for Leber congenital amaurosis (LCA)—a severe infant-onset retinal dystrophy—began. Phase I trials displayed both safety and improved measures of visual function (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). Following

[6] According to Health Canada: "Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses" (Health Canada, 2008). See Appendix XVVIII for clinical trial phase definitions.

the publication of these trials, clinicians emphasized the ground breaking contribution of LCA gene transfer clinical research:

> These findings and new insights present a paradigm shift in our management of retinal dystrophies of all types, previously thought to be an untreatable group of human diseases (Koenekoop, 2008 p.91).

This enthusiasm was echoed in the international media, fueling public and patient expectations for the treatment of previously untreatable ocular conditions (Kaplan, 2008). The controversial inclusion of children in later LCA trials demonstrated that early application of gene transfer produces optimal visual outcomes, suggesting that there is a limited therapeutic window[7] of opportunity for visual gain (Maguire et al., 2009). These results introduced not only great promise for application of gene transfer to other retinopathies, but also a notion of haste to develop treatments for patients within their limited therapeutic window. Patients have adopted this sense of urgency (Héon, 2009), especially since LCA trials have continued to demonstrate both safety and efficacy (Simonelli et al., 2010) and are now entering phase III studies (NCT00999609) (National Institutes of Health & Children's Hospital of Philadelphia, 2012). Early positive outcomes from the LCA trials have served as an impetus for the development of CHM gene transfer (Kalatzis, Hamel et al., 2012). This development was enthusiastically supported by a patient community frustrated by a lack of clinically available treatments and eagerly seeking opportunities for inclusion in similar clinical trials (Héon, 2009).

Patient advocacy organizations and clinical investigators likewise promote gene transfer for CHM and other ocular conditions while raising funds and public support for such trials. However, while these stakeholders drive innovative and novel research into clinical care, they are also responsible for communicating with patients about associated benefits, risks, and time frames. In this domain, clinicians and patient advocates temper their communications of progress and promise, taking into account the current reality of patients facing a prognosis of increasing visual impairment.

The enthusiastic response to LCA gene transfer successes may present challenges for communicating with patients about the risks and benefits of a first-in-human gene transfer trial for CHM. Significant challenges arise in communicating about risks and time frames with patients when the current landscape of hope focuses on visual benefits. This empirical study of multi-stakeholder communications (patients, patient advocacy organizations and clinicians) surrounding a gene transfer clinical trial for CHM addresses: (1) How can clinicians and patient advocates involved balance communications with patients about both benefits and

[7] In this context, refers to the range of time in which GT could alter the outcome for a patient with a progressive disease.

the risks?; and (2) Whether patient hopes, particularly those concerning time frames for clinical application, align with those of other stakeholders, such as clinicians and patient advocates? The paper concludes with recommendations for responsible communication strategies about benefits, risks, and therapeutic time frame estimates necessary for avoiding the hype that has historically been associated with this field of translational medicine (Branca, 2005; Glassman & Sun, 2004).

3.2 Methods

Study Participants

I interviewed 15 clinicians (C); 20 CHM patients (P); and 6 representatives of patient advocacy organizations involved in research fundraising (PA, or patient advocates) between June 2011 and June 2012. Clinicians included ophthalmologists and genetic counselors. Five clinicians were directly involved in ocular gene transfer clinical trials, and 10 were practicing clinicians specialized in ocular genetics. Patient advocates represented organizations focused specifically on CHM or genetic retinal dystrophies. I recruited clinicians and patient advocates via email and at conferences, and patients from an eye clinic using recruitment letters and through notices on patient advocacy group websites.

Data Collection

I conducted semi-structured interviews, approximately forty-five minutes to one hour in length. The interviews had a flexible structure combining formal questions with follow-up-prompts to enable the views of participants and key themes to emerge (Charmaz, 2006). The interview guides were informed by previous studies about communication in genetics (Henderson et al., 2004; Henderson et al., 2006; McAllister et al., 2007) and were reviewed for depth and breadth of coverage by experts in ocular genetics, genetic risk communication, and bioethics. The interview guides probed about the risks, benefits, and hopes for the time frame of clinical implementation of gene transfer. They were designed to prompt conversation about emotional responses such as fear, hope, and concern, as well as views on communications about gene transfer (McAllister et al., 2007). The Health Panel of the Ethics Review Board at the University of Alberta approved the study.

Data Analysis

I analyzed verbatim transcripts of the recorded interviews using NVivo 9.1 qualitative analytic software (QSR international 2010). I coded a subset of

interview transcripts "line by line", and analyzed these codes for similarities and differences between transcripts using the "constant comparison method" (Charmaz, 2006). Starting with this initial close examination of the transcripts, I developed a codebook, which I further cultivated through an iterative process of continual comparison between transcripts. I then organized the codes into themes and sub-themes. A second investigator reviewed the codes to ensure that they comprehensively captured the key themes. In addition, I reviewed the illustrative quotes used below in the context of the original transcripts to ensure they retained their original meaning. Finally, I constructed stakeholder-specific reports of study results, explaining the main themes that emerged from the interviews for each stakeholder group (Appendices XVI, XVIII, and XIX). I sent these reports to participants, inviting them to ask additional questions or share their views about the results. I integrated participant comments into the final analysis.

3.3 Results

Benefits of Gene Transfer for CHM

The discussion of benefits arose in two contexts: (1) the benefits of participation in a gene transfer clinical trial for CHM; and (2) the visual outcomes expected from CHM gene transfer. While the three stakeholder groups agreed on many aspects of the benefits of participating in a gene transfer trial for CHM, key differences arose between their outcome expectations and in their understanding of each other's expectations.

Patients described many benefits that would arise from participating in a CHM gene transfer clinical trial: for society at large, their families and themselves. Altruistic benefits included contributing to research, being involved in disease advocacy, and feeling a sense of social responsibility in light of the small size of the CHM community:

> It would be very positive… contributing to research. It would be pushing it forward for others that have choroideremia with vision not as bad as me. And would definitely have something to look forward to [as] part of the initial research. –P3

Since CHM is an X-linked disease, many patients expressed a desire to help future generations and to assist their carrier daughters in future reproductive decisions by helping to advance a potential treatment. Other patients wanted to participate in a gene transfer trial in an effort to facilitate a treatment for their affected grandchildren, acknowledging the time limitations before their grandchildren become significantly visually impaired.

> [GT would be beneficial] for my own extended family because…my mother had the disease, all three boys got the disease and then those three boys each start having kids. –P16

Additionally, patients described how gene transfer might alleviate some of their own anxieties associated with future vision loss.

> If they could stop it [vision loss] here, I'd feel like I won the lottery, because that's the fear. I know where I am. I want to know where I am. And every time your eyes adjust… it's like changing a new world, going into a new surrounding. –P17

Most participants perceived visual benefit as a salient motivator for participating in a CHM gene transfer clinical trial. Patients, clinicians, and patient advocates discussed their expected visual benefits from CHM gene transfer. Figure 3-1 illustrates these visual benefit perspectives along a continuum, ranging from a conservative perspective of slowing down vision loss to a cure. All stakeholder groups recognized the possibility that gene transfer clinical trials might not produce visual benefit.

> They are experiments. There is no guarantee that it will work. It is nothing more than trying to see if it will work, and expectations have to be kept in line with reality. –PA3

Despite the global understanding that gene transfer clinical trials might not deliver visual benefit, some patient advocates, whose children are affected by CHM, did not accept the potential for failure and described their stakes in the development of a therapeutic intervention for the disease.

> For sure there will be something [a therapeutic intervention]. It cannot be another way. –PA5

Clinicians and patient advocates, however, believed that visual benefit outcomes of a CHM gene transfer trial would range between slowing down vision loss to a partial reversal of lost vision. These perspectives were mediated and informed by the outcomes of analogous LCA gene transfer trials (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). Many clinicians and patient advocates emphasized that gene transfer could provide a treatment for CHM but not a complete cure; it is unlikely to provide regenerative benefits to retinal cells that have already degenerated.

> We hope that gene therapy would be able to stop the degeneration of the cells. We know that it will not completely cure the disease because for all the cells that have been destroyed already it's too late, but at least it will stop the disease. –PA5

Many clinicians believed that it is difficult for patients to conceptualize what a treatment for CHM could mean in light of their understanding of "treatment" in the context of other diseases.

> People say therapy like, "Oh, we can treat the pneumonia, therefore my lungs are normal again. I'm going to have gene therapy all my vision is going to be restored." You know, there's only one person that I know of who ever laid on hands and made the blind see. And unfortunately, he is not around anymore. –C11

Clinicians also believed that patients lack the tools to understand detailed nuances that distinguish between the potential visual outcomes.

> I don't know if people are…all that sophisticated in the nuances of really what treatment means…that's already a level of understanding of what all of the options of treatments are out there. That is pretty advanced. –C3

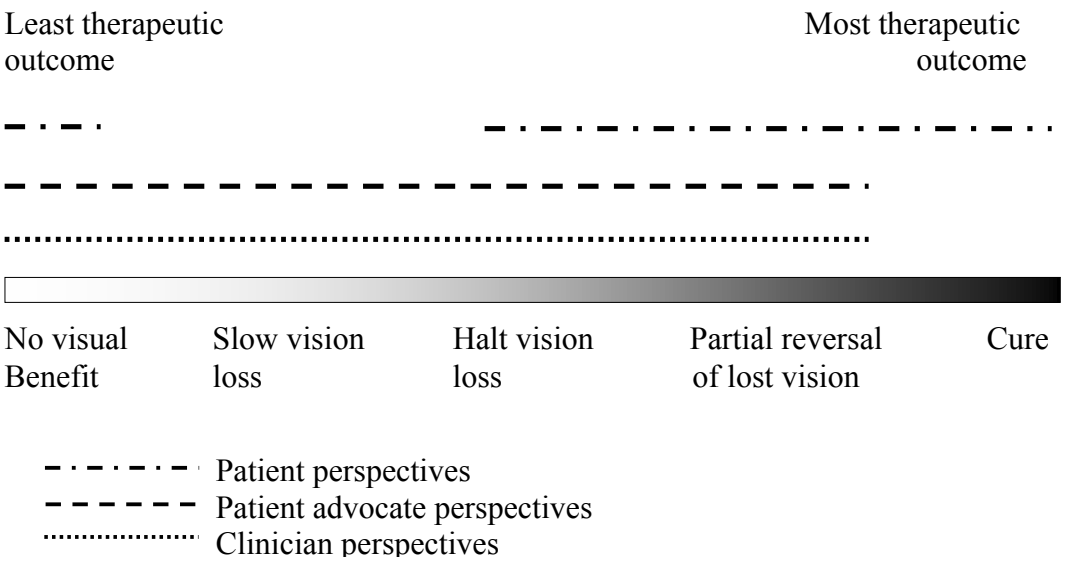
Despite clinician concerns about patient understanding of what a CHM treatment might offer, most patients articulated their visual outcome hopes in a nuanced manner. Much like clinicians, many patients hoped for a treatment rather than a cure.

> It [gene transfer] gives me hope that there is a treatment, not a cure obviously, but treatment. –P2

Patient visual outcome perspectives ranged from halting vision loss to a cure. The majority of patients expected gene transfer to halt vision loss, and only a single patient hoped for a cure. Despite patient expectations focused on halting disease progression through CHM gene transfer, patients expressed hopes that somatic cell transfer combined with gene transfer would provide a regenerative effect in the future.

> Well ideally, if gene therapy can halt the degeneration, I do hope one day that stem cell therapy will get to the point where we actually could re-grow retinal tissue and actually restore the retina to its pre-choroideremia state. –P10

Figure 3-1: Multi-stakeholder visual outcome perspectives for choroideremia gene transfer clinical trials



Risks of Gene Transfer for CHM

As high hopes for therapeutic benefit were discussed and reinforced by patient trust in the researchers and the infrastructure of science bolstering gene transfer trials, discussions were focused on gaining access to gene transfer rather than its' risks.

Clinicians and patient advocates worried that patients do not express much concern about the risks associated with participating in novel CHM gene transfer clinical trials. For example, clinicians described that patients ask many questions about research efforts aimed at developing therapeutic interventions, but do not inquire about the safety of gene transfer trials. Clinicians concluded that the salience of patient hope for a treatment diverts their attention away from the risks.

> Deep down in the heart of any patient for whom there is no effective treatment or cure, clinical trials mean "this might be the thing that's going to help me"…so safety is…not their first concern. –C10

Consistent with the observations of clinicians and patient advocates, patients questioned the interviewer about gaining access to the trial rather than on risks.

> How would I better my chances to get involved in any of these trials? Whether it be in the States or with you or even in the UK?…because I would easily go there. —P17

In addition to this focus on access, five of the twenty patients adopted a "no risk" attitude, articulating no perceived risks associated with CHM gene transfer trials.

> [gene transfer] makes me feel good…I would definitely want to do it…For me there's no risks. The only thing that could happen is to get some [vision] back. –P7

Despite the "no risk" perspectives of some, all patients acknowledged accelerated vision loss as a risk associated with CHM gene transfer. Patient perspectives diverged, however, with respect to the personal relevance of this risk. Some patients explained that the functional vision they have left is precious to them, and they would be hesitant to risk losing it.

> I've been pretty tentative…if there was any risk to making my vision worse, at this point in time it's pretty good... I wouldn't want to risk that. —P6

Other patients, particularly those who described their visual field as significantly deteriorated, expressed a willingness to accept the risk of accelerated vision loss.

> If I lose my sight, it's going anyway. –P2

The discussion of other known risks associated with CHM gene transfer is outlined in Table 3-1.

Table 3-1: Patient descriptions of risks associated with participation in a phase I choroideremia gene transfer clinical trial

Risk category[8]	**Described by patients?**
Financial burdens	Yes
Psychological stress	Yes
Surgical risks	Yes
Germline gene transfer	No
Loss of vision	Yes
Loss of an eye	No
Insertional mutagenesis/ oncogenesis	No
Brain toxicity[9]	No
Immune response to viral vector	Yes
Death	No

Patients also described factors that attenuated their risk perspectives. Some patients normalized the nature of risk as inherent to all clinical trials.

> Accepting the risk would go with it [gene transfer clinical trial] and moving the scientific project forward, because you need people to do that obviously. Human beings to step forward and say I'm willing to do that.—P13

Other patients indicated trust in the researchers, physicians, or scientific traditions bolstering CHM gene transfer trials.

> I have faith in our medical system, that they do make sure that things are safe.—P8

Urgency: I know it's in Sight, but Will it be in My Sight?

Patients and several patient advocates affected by CHM highlighted their urgency to access gene transfer. Clinicians recognized this concern and worried that this sense of urgency might lead patients to overlook the risks of participating in a clinical trial.

Many patients expressed pressing interest to participate in a CHM gene transfer clinical trial.

[8] Risk categories derived from those outlined in a CHM gene transfer phase I clinical trial consent form (MacDonald, 2012)
[9] Due to viral vector access to optic nerve

> If the treatment [referring to a gene transfer clinical trial] came out tomorrow I'd have that procedure done, absolutely. —P2

Patients understood that young men affected by CHM would likely gain the most therapeutic benefit from gene transfer prior to significant vision loss. Additionally, many patients expressed worries that the time frame for clinical implementation of CHM gene transfer may not meet their own therapeutic window.

> For me personally, I think that the sooner the better. My eyes are degenerating. I can tell every month that there's less vision there. So, I think there's urgency. And it [gene transfer] would allow me to keep more of my vision the sooner I get it. –P8

Some patients described their frustration with the slow process of gene transfer safety trials.

> The treatment is not available fast enough…There's a real sense of urgency…I know everybody wants to…do it…in careful way and not hurt anybody or make them unhealthy in some way; but for me, I'd rather take the chance and save my eyes. –P20

Clinicians and patient advocates also commented about the patient sense of urgency to gain access to therapeutic interventions.

> I think they [patients] want the treatment tomorrow because they've lived with this disease for their whole life and they're desperate and they're upset. –C14

These stakeholders also noted that the patients' sense of urgency caused them to overlook safety concerns.

> Our patients, they want to be treated as quickly as possible… we tell them we wanted their safety first. No, they said they don't care. –C12

Many patients explained that they would do anything it took to access CHM gene transfer. Patients explained that they would incur a financial burden, take time off of work, or travel to participate in a gene transfer trial.

> I would in a minute [participate in a gene transfer trial]. I'd go anywhere I had to, do whatever I had to do. If I had to fly out there, or fly out west to you, or I'd fly to Pennsylvania or to the UK, I would. —P17

Affected patient advocates echoed this perspective, revealing their personal stake in gene transfer clinical trials.

> I will go for the second mortgage on my home if that's what it takes [to participate in a gene transfer clinical trial]. –PA1

Clinicians displayed an awareness of the stakes of their patients and the lengths to which they would go to access a clinical trial.

> I think anybody…faced with the prospect of blindness [would] say that "I would do anything within reason to undertake clinical trial that would be a potential benefit"…patients have said to me "I'd rather have a heart attack than lose my vision". –C9

Gene Transfer Time Frames

With an awareness of their limited therapeutic window and an urgency to access gene transfer within it, patients wanted to understand the projected time frame associated with the clinical application of gene transfer. Clinicians, however, did not communicate effectively about time frames, frustrating patients and patient advocates alike.

Uncertainty about time frames for the clinical implementation of CHM gene transfer was a major patient concern, leading to confusion and frustration.

> I don't even know the average time for any given clinical trial to go through the phases...Let's assume for example that the CHM [gene transfer clinical trial] phases are all successful, is it the best case scenario for something like that within a two-year time frame, five years, ten years, twenty years?—P10

Such uncertainty was most concerning for patients caught between the current reality of their prognosis and the possibility of an intervention within a therapeutically meaningful window. This uncertainty was unsettling for patients who were limited in their ability to plan for the future without clear idea of treatment potential and its impact on their progressive visual disability.

> The reason that I ask these questions [about gene transfer time frames]... [is] for my own future planning…because having that knowledge…will help me to…make arrangements with my family.—P10

Both clinicians and patient advocates were aware of patient concerns surrounding time frames.

> Every…affected individual with a progressive disorder…[asks] "Is [gene transfer] going to happen in my lifetime?"—C11

> [Patients ask] "When is [gene transfer] going to be in the clinic? When can we get it?...How soon is something going to be available for my child? For my wife? For me? For my father-in-law?"… So their main question is when are we going to see something that is the fruit of all of the research that has been done over the years that's going to–and they're very blunt about it–*cure* the disease. –PA3

Nevertheless, clinicians did not communicate effectively about time frames, frustrating patients with vague or dismissive responses to their concerns. Patient advocates were similarly frustrated with the vague time frames articulated by clinicians. Moreover, patient advocates noted that clinicians presented vague time frames not only to patients in a clinical context, but also to potential donors at fundraising venues.

> It's difficult for [clinicians] to speak sometimes because they're there to say what they've done and to generate optimism, because I think their goal is to generate some funds. Like it's, "Yes, we're doing good works so donate". And at the same time they probably have to be cautious about not raising hopes too high, and so you get the vague answer. Like, when will a certain thing be standard of care? You know, it will become the five to eight year time frame. –PA2

Patient advocates were not only frustrated with vague time frame estimates, but were also disappointed and confused when projected time frames were not met.

> It would be nice if things went faster. That, I think, is a common concern…Time frames in research never seem to be accurate…there's a lot of slippage in the time frames that are given. That's disappointing, I think. It's difficult to understand. [Referring to interviewer] You're in the university, can you explain why there are those sorts of time frames are not very firm? –PA2

Left to interpret vague time frames for gene transfer, patients shared their expectations and understanding of time frames for clinical application. The majority of patients indicated hope that CHM gene transfer will be available in time to provide them with visual benefit. Two patients did not believe that gene

transfer would likely be available to them within their therapeutic window for visual benefit. Both of these patients already had significantly deteriorated visual fields, and had understood that their therapeutic window for gene transfer had therefore passed. These patients were nevertheless hopeful for visual benefits through gene transfer for future generations of their families.

> I'm hopeful for what's happening with science…and I don't know how much it will help me I guess, but the one thing I'm hopeful for is for when my daughters pass the disease on to sons…I hope that science is there and it can possibly cure them or help them out at least. –P6

Clinicians and patient advocates also expressed varying opinions on the time frame for clinical implementation of CHM gene transfer. Many clinicians believed that treatment would be available for children diagnosed with CHM.

> For young kids, I think [CHM gene transfer] will come in their lifetime. –C4

Patient advocates also believed that gene transfer would be available to children, some displaying a great deal of certainty in this prospect, and others simply hoping that this would be the case.

> If a baby is born today I have absolute full confidence that that baby is going to have a treatment before their eyes get so bad that there's going to be a noticeable difference in their sight. –PA1

Clinicians did not believe adults would have access to CHM gene transfer as a standard-of-care treatment within a reasonable time for therapeutic benefit.

> It depends on how old the patient is, if they're an adult then I say I'm not sure if there will be [a therapeutic intervention] in their lifetime. –C5

In contrast to clinician views, some patient advocates expressed that the hope for adults, including themselves, to gain visual benefit from CHM gene transfer was ignited by the recent successes of the LCA clinical trials.

> When we formed…this organization, older guys…knew…research takes time. So we were into this with the full knowledge that by the time anything is found it's probably going to be too late for us. But we at least are going to get the ball rolling and maybe the next generation will see that cure…Then in the blink of an eye [after the results of phase I LCA gene transfer trials were reported]…that whole mindset did a complete 180. Now there's a chance for my sight to be saved by a genetic therapy. –PA1

Further ambiguities in time frame predictions of some clinicians and patient advocates were apparent as they quantified the length of time for CHM gene transfer to become a standard-of-care treatment. Predictions ranged between 3 and 10 years for both stakeholder groups. While some clinicians quantified their expectations of time frames for clinical implementation, others made general remarks about the progress in the field of ocular gene transfer.

> I only have to answer that I don't have an answer to that [question about time frames for the clinical implementation of CHM gene transfer]. Because I don't know but to say that there are advances, and…it's going to depend on concurrent trials that are underway. –C2

Other clinicians indicated their uncertainty about time frames for clinical implementation without providing an approximate timeline.

> I can't answer that [question about time frames for the clinical implementation of CHM gene transfer], I can't predict the future.—C4

Communication Strategies About CHM Gene Transfer

Clinicians recognized the difficulties of communicating with patients about the promise of CHM gene transfer in light of its nascent nature and uncertain outcomes. Clinicians identified three main strategies to promote responsible communications about CHM gene transfer: (1) collaboration in communications; (2) patient education; and (3) a "two-pronged approach".

(1) Collaboration in Communications

Clinicians identified many sources of communication about CHM gene transfer. Within the clinic, key communicators are ophthalmologists and genetic counselors; outside the clinic, communicators include patient advocacy organizations, the media, and unofficial sources on the Internet. Clinicians believed researchers involved in CHM gene transfer trials are well positioned to communicate about these efforts. Clinicians also identified genetic counselors as specifically trained to communicate about translational research to lay audiences.

> I definitely think that genetic counselors are right there, like that's part of their role to help translate scientific knowledge to knowledge that a lay person can understand. –C1

Clinicians also felt patient advocacy organizations could position communications about CHM gene transfer in the context of managing daily challenges with CHM

and that they provided credible information, given their close collaboration with scientific experts.

> Other patients are invaluable in talking to newly diagnosed patients... There's nothing better than having a patient with the disease tell another patient about the disease. I cannot tell a choroideremia patient what it's like to walk around with their vision…so to meet other patients, to get involved in support groups, is probably one of the best treatments that you can give especially with chronic conditions. –C7

> The [patient advocacy groups] are going to get pretty reliable information, because they will usually ask physicians, professionals that are actually doing the research or working with families. –C5

Clinicians noted the importance of media communications about CHM gene transfer in informing the general public and patients. To facilitate responsible representation of the goals of CHM gene transfer clinical trials, clinicians explained the need for clinical investigators to convey information to the media in a deliberate and thoughtful manner.

> The specialist in the choroideremia gene replacement therapy trial should be very cautious to say that the expectations are maintenance [meaning halting vision loss] if that's the expectation, or a treatment. That we're not quite at the stage of actually curing and providing 20:20 [vision] and 180 degree visual field but you know, what we are expecting for being very careful to have bulletin notes that we make sure that are addressed and then you can give the bulletin notes to the reporters so they don't either. Do your best to make sure you're not misquoted. –C4

Clinicians highlighted that communication is a collective effort, which requires engagement with a variety of stakeholders to facilitate responsible knowledge exchange.

(2) Patient Education

Clinicians noted a discrepancy between expert communications and patient understanding and attributed these to deficits in patient education. To address this discrepancy, clinicians emphasized the importance of explaining the natural history of the disease and research efforts in lay language. To address a major gap in understanding of time frames, clinicians noted that an educational strategy that clearly explains the different phases of clinical trials might provide the necessary context.

> The one thing that I think would help persons in general when they think about research [is]…just explaining those different phases of a clinical trial… [Patients] don't have a sense of the time that it takes to complete a trial and those phases. –C2

(3) "Two-Pronged Approach"

Communications about CHM gene transfer must balance patient hopes with the uncertainties inherent in the investigational nature of early-stage clinical trials. They need to be grounded in the current reality of limited clinical care, and recognize that having no available treatment raises the emotional stakes of patients for a future therapy. In light of these circumstances, clinicians identified a "two-pronged approach" to promote balanced communications about gene transfer. This approach encourages clinicians to share in patient hope for a future treatment, while emphasizing the caveats of CHM gene transfer clinical trials. Common caveats emphasized by clinicians were unknown risks and safety concerns, particularly those that arose as serious adverse events in past gene transfer clinical trials. Additionally, clinicians agreed that it is important to highlight that CHM gene transfer remains in early-stage clinical research and not as standard-of-care at this point.

> I want people to realize that all of it is research that it's not like they're going to get an injection and get better overnight. –C3

Using the two-pronged approach, clinicians recognized the importance of affirming patient hopes, but articulated the necessity of avoiding giving patients 'false hope' and avoiding sensationalism.

> I think that [CHM gene transfer] has to be followed in a realistic manner: that you do want [patients] to get excited…but I think to be fair to the patient you have to also be as honest as possible... So keep the hope up high, but not so excessive that it's really to the point where you're not believing... You have to be honest within yourself as to where you think [gene transfer] really is, at what stage it really is. –C4

Finally, clinicians noted that the two-pronged approach could also ensure that while patients remain hopeful for therapeutic interventions, they concentrate on managing life with CHM and preparing for a prognosis of continued visual impairment in the case that a treatment will not be available in time for visual benefit.

> We cannot assume really what it [CHM gene transfer] will look like in five years. So we can only talk about what we know. We can say where we hope to go, but be very clear that that's a wish that is not reality right now. –C3

Stakeholders were optimistic about the benefits of CHM gene transfer clinical trials; particularly those of direct visual gain. Such hopes, coupled with an urgency to access a therapeutic intervention attenuated the risk perspectives of patients and left them wondering how long it will take before a treatment will be available.

3.4 Discussion

CHM gene transfer fueled high hopes for therapeutic benefit and urgency for its application. I begin by discussing the stakes of clinicians, patient advocates, and patients surrounding the development of CHM gene transfer clinical trials, and how these affect communications. I continue to explore risk and benefit perspectives by discussing the therapeutic misestimation as well as the therapeutic misconception. Finally, I address patient urgency and time frame concerns by recommending strategies for communicating about the time frame for application of CHM gene transfer to clinical care.

Mapping stakes

Scholars suggest that gene transfer, much like other areas of translational research necessitates the utility of a "public theatre" (Kimmelman, 2010, p. 154) in which communicators generate and manage expectations of key stakeholders, including patient advocates and patients. However, important communicators such as clinical investigators are not impartial and have significant stakes in promoting their research or its clinical applications, resulting in a variety of conflicts of interest (Ransohoff & Ransohoff, 2001). Such conflicts range from direct financial gains to simply investing time and intellectual resources into a research question.

Scholars explain that: "translational researchers must create the future out of nothing: decisions to pursue the development of novel interventions are propelled by beliefs about promise rather than current realities" (Kimmelman, 2010, p. 155). As such, clinical investigators must promote the promise of their research to funding bodies, including patient advocacy organizations, to attain support for their research by emphasizing a currency of hope and progress. For instance, clinicians often frame their research as a series of steps towards a cure or therapeutic outcome, thereby bridging the gap between reality and promise

(Evans, Kotchetkova, & Langer, 2009). Such communications often enter the public realm via the media, which is often closely monitored by stakeholders such as patients and patient advocates (Kimmelman, 2010). Generally, positive media coverage of biomedical research adds to an environment of heightened expectations and optimism (Caulfield, 2004). Because the media is a major source of medical information (Geller, Bernhardt, & Holtzman, 2002) sensationalistic discourse in this venue may mediate patient expectations, setting them up for disappointment (Petersen, 2009). In this indirect manner, clinical investigators may introduce promotional communications to patients and patient advocates.

Clinical investigators also influence direct communications with patients, because it may be difficult for clinical investigators to divorce the promotion necessary to secure research support (Caulfield, 2004) from communications with patients that must be grounded in current clinical realities. This difficulty may also be exacerbated as clinical investigators stake hopes in the success of their own trials. Beyond the direct stakes of clinical investigators, many clinicians—including those not involved in clinical research—hope for the success of gene transfer clinical trials because they are concerned for the welfare of their patients. It is therefore important that clinicians recognize their partisan stakes in gene transfer efforts, whether through a direct or indirect manner, and reflect on their personal biases before communicating with their patients. In keeping with the "two-pronged approach" identified by clinicians in this study, clinicians must highlight hope brought about by gene transfer trials, but must ensure that this sentiment does not overshadow a necessary and pragmatic discussion about planning for or managing life with progressive visual impairment.

Traditionally, patient advocacy organizations served to complement medical care by providing support to patients (Rabeharisoa, 2003; Rapp, Taussig, & Heath, 2002). Patient advocacy organizations provide invaluable support because they not only help patients learn how to manage daily life with their condition; they also help patients construct new identities in light of their abilities and limitations (Charmaz, 2000; Petersen, 2006). These organizations are now increasingly concentrating their efforts on facilitating research by actively engaging in the development of new therapies though working alongside researchers, engaging in political activism, and providing funding (Novas, 2006). In this study, patient advocates emphasized that their main goal is to raise funds for research. At the same time, patient advocates were also concerned with providing patient support. Tension exists between these goals, because it is inherently difficult to balance promotional communications needed to generate funds with the subdued messaging necessary to avoid misleading patients. This tension was exacerbated by the personal claim of many patient advocates who are affected or have family members affected by CHM. In this case, deeply personal and emotional stakes might mediate hopes of patient advocates and influence their projections for gene transfer. Personal hopes, in combination with the goal of promoting research to raise funds create an infrastructure of communications vulnerable to

sensationalism. While raising funds for research is vital for the development of future therapeutics, it is important for patient advocates to ensure that patient support (e.g. peer support about strategies for disease management, access to accurate information sources etc.) remains a primary concern even in the face of an overwhelming hope for a therapeutic intervention (Stockdale, 1999).

Patients positioned between the sensationalized messaging about the promise of gene transfer and the sober reality of their current prognosis must balance their hopes for a future treatment with a focus on disease management (for further reading on patient perspectives about management of genetic disease see Petersen 2006; McAllister et al 2007). This requires patients to navigate through a complex network of partisan communications (e.g. communications generated by clinicians, patient advocacy organizations, media etc…) and uncertainty to form a personally relevant worldview about gene transfer. For many patients struggling to make practical life choices based on a current prognosis of increased visual disability in light of the possibility of a treatment, finding this balance might be challenging. Despite the prominence of sensationalism surrounding gene transfer, patients in this study critically evaluated communications to mediate their perspectives about the biotechnology's promise. This is evinced by conservative visual outcome hopes, most prominently centering on a treatment rather than a cure. Uncertainty inherent to an early-phase clinical trial, however, leaves room for hope, a construct that introduces an inherent vulnerability (Simpson, 2004) and may have a bearing on patient risk perspectives (Kim, Holloway, Frank, Wilson, & Kieburtz, 2008). It is important for other stakeholder groups involved in communications about gene transfer to recognize patients as critically thinking experts (Petersen, 2006), but also acknowledge patient vulnerabilities. With this understanding, other stakeholders should focus on establishing balance in their messaging rather than managing patient expectations.

Clinicians, patient advocates and patients all have stakes in a common goal: developing a treatment for CHM. As per clinician recommendations, communications about gene transfer must be seen as a collaborative effort. A meaningful therapy will only be established as the concerns and values of all stakeholders are integrated into its development (Reimer, Borgelt, & Illes, 2010). Open communications, where communicators both reflect upon and disclose their conflicts of interest or biases are key to collaboration. Additionally, the deleterious effects of excessive promotion must be internalized not only by clinicians and patient advocates, but by the societal infrastructure that de-values sustainable incremental scientific progress at the expense of sensationalized translational research (Caulfield, 2000).

It is important for clinicians to recognize that their patients are not "uncritical and passive receptacles" (Kimmelman, 2010, p. 168) influenced by various sources of sensationalistic communication or "emotional attitudes" stemming from personal stakes (Simpson, 2004). Indeed, despite clinician beliefs that patients do not understand the potential outcomes of CHM gene transfer, patients had a nuanced understanding of the spectrum of possible visual outcomes, clearly differentiating between treatment and cure. Additionally, in alignment with clinician and patient advocate perspectives, patients most commonly expected gene transfer to halt vision loss.

Nevertheless, there was a small discrepancy between the views of patients, clinicians and patient advocates about visual outcome. While the visual benefit expectations of clinicians and patient advocates ranged from slowing vision loss to partial visual restoration, patient perspectives ranged from halting vision loss to a cure (see Figure 3-1). Clinician and patient advocate perspectives were therefore more conservative than those of patients. These discrepancies in visual benefit expectations are indicative of "therapeutic misestimation" (Horng & Grady, 2003), whereby patients overestimate the visual benefits that could be afforded by CHM gene transfer. Therapeutic misestimation was particularly evident in the expression of curative expectations. Gene transfer does not offer regenerative benefits and thus could not revive photoreceptor cells that have already degenerated, necessitating the prerequisite of viable photoreceptors to prevent future vision loss (Jacobson et al., 2005).

Other studies corroborate this patient tendency to overestimate benefits. For example in phase I oncology clinical trials, patients expressed significantly higher estimates that the experimental intervention would control their cancer compared to study physicians and nurses (Cheng et al., 2000). In another study, advanced cancer patients who agreed or declined to participate in phase I trials showed higher benefit expectancies than their attending physicians, indicating that even patients who do not enroll in clinical trials have high expectations for benefit (Weinfurt et al., 2003). Another study surveying institutional review board members and patients with Parkinson disease about a fictional protocol for a phase I gene transfer trial showed that the median patient estimate of personal benefit was significantly higher than that which institutional review board members would allow an investigator to convey to patients (Kim et al., 2008). Studies also capture a range of estimates for the likelihood of benefit among patients and suggest that a possible reason for these discrepancies could be attributed to the heterogeneous interpretation of the term "benefit", where some patients might interpret the term as amelioration of disease symptoms while others may interpret it as a cure (Weinfurt et al., 2003). This suggestion is confirmed by

this study, showing that not only patients but also clinicians and patient advocates expressed nuanced and heterogeneous perspectives about what a treatment for CHM might provide.

Therapeutic misestimation engages not only an overestimation of benefit, but also underestimation risk (Horng & Grady, 2003). Therapeutic misestimation stemming from underestimation of risk was evident with the "no risk" perspective of some patients. Similar results emerged from a recent study of patients enrolled in phase I trials where 27% claimed that there is no risk involved in trial participation and 59% explained that they are not concerned by the risks (Pentz et al., 2012). The concern here is that as patient attention is diverted away from risks, risk perspectives become attenuated[10] (Kasperson & Kasperson, 1996; Kasperson et al., 1988) and the pressing interest becomes gaining access to gene transfer. Another factor mediating the risk perspectives of patients was trust[11]. Other studies also found that patients in the context of early-phase clinical trials express sentiments of trust in the research infrastructure, scientific traditions (Pentz et al., 2012), or in their physicians (Sulmasy et al., 2010), and that that this trust helps patients reconcile uncertainties in phase I clinical trials as opportunities for benefit rather than as risks (Kim et al., 2008). Risk is an inherent disadvantage of trust (Mechanic, 1996), and patient trust promotes an acceptance of risk (Hupcey, Penrod, Morse, & Mitcham, 2001), thereby attenuating the risk perspectives of patients in this study.

In light of the nuanced understanding of patients, it might be helpful for clinicians to display (or explain depending on vision) the full spectrum of potential visual outcomes to patients. This would enable clinicians to clarify both the likely range of potential visual benefits, in general, and in light of a specific patient's therapeutic window. This would also promote patient awareness to visual outcomes that might have not been apparent (e.g. slowing down vision loss) and would ameliorate the therapeutic misestimation.

Such comprehensive representation could counter the curative public discourse that is common with respect to ocular gene transfer. Curative representations in the media are prevalent with headlines such as: "Gene therapy cures congenital form of blindness in children, study claims" (Anonymous, 2009). While patient advocates in this study did not believe that gene transfer would provide a cure for CHM, curative messaging is often employed by patient advocacy organizations. For example, the Choroideremia Research Foundation claims:

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[10] Attenuation of risk refers to the reduced perceived salience of risk. Term derived from Social Amplification of Risk Theory (Kasperson, Renn et al. 1988).
[11] Trust is defined as "the optimistic acceptance of a vulnerable situation in which the truster believes the trustee will care for the truster's best interests" (Hall, Dugan, Zheng, & Mishra, 2001).

> In our short history, we have already seen incredible advances made in CHM research. Now, it is no longer a question of *if* a cure will be developed; it is a question of *when*!" (Choroideremia Research Foundation, 2012).

The Foundation Fighting Blindness also employs curative language, as their slogan reads: "A Cure is in Sight" (Foundation Fighting Blindness). Outlining the potential visual benefit outcomes would highlight that expert opinion unanimously does not believe gene transfer will offer a 'cure' for CHM. Emphasizing this idea will help patients to critically process curative messages in media or patient advocacy group venues and mediate their perspectives. With this education effort as well as others recommended by clinicians, communicators must be careful to assume that patient attitudes are solely formed by a deficit in knowledge (Nisbet & Goidel, 2007). Often, people rely on values or emotions to make sense of science, and choose to accept information that confirms their beliefs (Bubela et al., 2009). While it is important to convey accurate and nuanced information to patients, communicators must not expect that this strategy will eliminate discordance between views; rather, this strategy should aim to ameliorate discrepancies between stakeholder perspectives.

Therapeutic Misconception

Patients in this study described both indirect and direct benefits associated with participation in a gene transfer clinical trial. Ethicists categorize indirect benefit for research participants into two groups, both of which were expressed by patients: (1) *collateral benefits*, or benefits arising from research participation, including increased clinical surveillance or psychological benefits; and, (2) *aspirational benefits*, or benefits to society and future generations (King, 2000). In this study patients described indirect benefits for participating in a gene transfer trial, including a feeling of empowerment in advocating for CHM research through clinical trial participation and helping family members and future generations. Other studies have similarly found indirect benefits to be significant motivators in clinical trial participation (Sulmasy et al., 2010). Nevertheless, the hope for direct visual benefit was the most prominent among patients in this study and in other studies (Daugherty, Banik, Janish, & Ratain, 2000; Wendler, Krohmal, Emanuel, & Grady, 2008).

Extending beyond the benefit perspectives of patients is controversy surrounding the discussion of therapeutic benefit in early-phase clinical trials. The main aim of phase I clinical trials is to establish indexes of safety (Health Canada 2008). Despite this goal, many patients enroll in early-phase clinical trials because they hope to gain personal benefit, thereby conflating the goals of clinical trials with clinical care (Daugherty et al., 2000; Wendler et al., 2008). This conflation has

been termed “therapeutic misconception”, and is a major barrier to informed consent (Appelbaum, Roth, & Lidz, 1982; Appelbaum, Roth, Lidz, Benson, & Winslade, 1987). Studies show that many patients, researchers, and clinicians view clinical trials as an opportunity for patient care (Henderson et al., 2004; Joffe & Weeks, 2002), unveiling a tacit expectation for these trials to exist as both “science and a source of succor” (Evans et al., 2009). This view, however, is problematic because of the few historical instances of therapeutic gain in early-phase clinical trials. Cumulative evidence in phase I gene transfer clinical trials points to a less than 1% chance for clinical improvement (Kimmelman, 2009).

Despite the rarity of therapeutic outcomes in early-phase clinical trials, Lazarus-like occurrences have been seen in phase I clinical trials, spawning debate about the appropriateness of discussing direct medical benefit in this context. This debate is prominent in the oncology clinical trial literature, where a few investigational agents have produced therapeutic benefits to study participants in phase I trials (Markman, 2006). Critics raise concern about the use of surrogate measures, such as tumour response and stable disease as indicators of end-point measures such as increased survival or improved quality of life. Surrogate measures are not conclusively indicative of clinically meaningful efficacy, and thus, can only serve to suggest the prospect of direct benefit to patients (Miller & Joffe, 2008).

One of the rare cases of direct medical benefit in phase I clinical trials occurred in the LCA study cited by many study participants as analogous to CHM gene transfer. LCA gene transfer trials have limitations similar to those of the oncology trials discussed above. Surrogate end-point measures in gene transfer for retinal dystrophies such as LCA and CHM also have significant shortcomings. At this point, long-term measures of safety and efficacy are still absent. For example, ongoing safety concerns include the oncogenic risk of insertional mutagenesis, which has occurred as a latent adverse event in previous gene transfer trials (Johnston & Baylis, 2004). Efficacy concerns include the continued expression of the gene of interest, such that the gene transfer application will only be necessary once (Schneider & Celis, 2010). Additionally, measures of “clinical meaningfulness”, empirically displaying that improvement in visual function increases patient quality of life have yet to be established.

Since the LCA clinical trials are the closest analogs to CHM gene transfer, and have served as a major impetus for its commencement, it is not surprising that stakeholders in the CHM community look to the LCA results and expect direct visual benefits from phase I clinical trials. The contiguity to this exceptional case heightens the potential for therapeutic misconception in the CHM community. While all stakeholder groups discussed visual benefits, the visual benefit perspectives of clinicians raise prominent concerns. These perspectives hint of a subtle conflation of the goals of research with those of clinical care. Commentators suggest that common study design practices in safety trials may

obscure the distinction between research and treatment. For example, the reform of accelerated dose-escalation regimes was introduced to enhance the therapeutic potential of phase I studies (Kimmelman, 2009). Dose-escalation regimes were employed in both LCA as well as CHM phase I clinical trials. Additionally, ocular gene transfer trials necessitate the utilization of visual outcome tests (e.g. microperimetry, optical coherent tomographic imaging, electroretinogram, fundus imaging etc…) to ensure safety and to aid in the development of appropriate efficacy end-point measures for later clinical trial phases. Contrary to their aim, the use of imaging techniques in phase I clinical trials could capture improvements in vision, as was seen in the LCA trials. Uncertainty remains about how clinicians and researchers are influenced by study designs with the capacity to introduce, enhance, or measure efficacy in early-phase clinical trials and, how these might mediate their perspectives about direct benefit.

When communicating about gene transfer, particularly with patients within the context of clinical trial enrolment, it is important to emphasize that the goal of phase I CHM gene transfer trials is to establish measures of safety rather than those of efficacy. The purpose of phase I trials, however, does not preclude the prospect of direct benefit to patients (Miller & Joffe, 2008). Patients could therefore ask questions about the likelihood of direct visual benefit. In this case, it is appropriate to explain that LCA clinical trials and CHM preclinical data establish *theoretical* grounds that CHM gene transfer could result in direct visual benefit, but highlight the equipoise that exists given the lack of CHM-specific empirical data. Informing patients about the relevant risks and uncertainties, qualifying the incremental nature of evidence in cases where medical benefits were observed in early-phase clinical trials, and emphasizing that collateral and aspirational benefits are more likely than direct medical benefits are key in promoting informed consent.

Situating Time Frame Estimates Within the Clinical Trial Infrastructure

Critics highlight that "gene transfer has often been characterized as permanently 5 years away from clinical application" (Kimmelman, 2008). It is clear that predicting the future of novel CHM gene transfer trials with certainty is impossible, however, the urgency of patients and disappointment and confusion of patient advocates stemming from uncertain and delayed time frames necessitate the implementation of more precise communication strategies about time frames for gene transfer. Generating overly-optimistic expectations about time frames may lead not only to patient and advocacy group disappointment and disillusionment, but may undermine trust in researchers (Caulfield, 2004) and ultimately threaten the continued support of funding for gene transfer trials (Petersen, 2009). While research about communicating time frames associated with prognosis or the delivery of bad news is abundant, a deficit exists in

literature about communicating time frames for the clinical application of novel biotechnologies.

For patients who hope for a time-sensitive therapeutic intervention, it is not only important to be reassured by information about the progress made in gene transfer research, but to also understand the stage at which this research is positioned within the context of the clinical trial infrastructure. Clinicians indicated that educating patients about the phases of clinical trials might facilitate their understanding of time frames. By educating patients about the goals and hierarchy of clinical trial phases and situating the current state of CHM gene transfer within this framework, clinicians may be able to provide patients with some context for the uncertainty. Another strategy might be to illustrate the progress of an analogous ocular gene transfer research effort. It could be beneficial to highlight that LCA clinical trials, which began in 2007, are now beginning to enroll patients in phase III studies (NCT00999609) (National Institutes of Health & Children's Hospital of Philadelphia, 2012), presenting an ongoing time frame of five years.

Historical evidence suggests that it takes 10-14 years and an investment of $1.2 billion (USD) in research and development to move from novel target to drug approval (Glassman & Sun, 2004). Novel gene transfer ventures, however, have unique considerations stemming from their vastly uncharacterized nature of risk and uncertainty. Public attention to these risks has historically been heightened as a consequence of serious adverse events, and resulted in a stringent regulatory environment (Spink & Geddes, 2004) that employs a necessary system of redundancy to manage risk (Kimmelman, 2008). For example, in the US, drug trials require an application to the Food and Drug Administration (FDA) as well as to an institutional review board (IRB). In addition to the approvals required by any other drug trial, gene transfer trials necessitate a complex regulatory oversight of local and federal authorities. Gene transfer requires the federal approval of the Recombinant DNA Advisory Committee (RAC) and the Office of Biotechnology Activities (OBA) at the National Institutes of Health (NIH), as well as the Center for Biologics Evaluation and Research (CBER) at the FDA. Local approvals of an IRB and an institutional biosafety committee (IBC) evaluation are also required. Both the FDA and the NIH review the protocol of the trial (Wolf et al., 2009). After trial initiation results must be reported to data-safety monitoring boards and adverse events must be reported to the NIH and to the FDA, and at the discretion of institutional policies, to the IRB and IBC (Manilla et al., 2005). The regulatory requirements of gene transfer would therefore cause a longer development time than that of drugs. Positioning the uncertainty surrounding CHM gene transfer timelines within the context of historical clinical trial time frames and the infrastructure of clinical trials ensures that clinicians honour patient urgency for gene transfer application without dismissing patient concerns with vague responses.

Limitations

This study is limited by recruitment methods. I began this study by recruiting patients from the clinical practice of one of the investigators of this study, who is an ophthalmologist. In order to recruit a suitable sample size to reach saturation in interviews, I had to outsource and recruit patients from patient advocacy group websites. Consequently, the majority of patients enrolled in this study had contacted me after having viewed our recruitment notices on advocacy group websites. Patients who access information from patient advocacy websites may be more knowledgeable about CHM gene transfer than the average CHM patient. Extensive knowledge about developments in gene transfer could mediate risk perspectives as well as hopes. Despite these limitations, this number of participants illustrates patient emotional stakes, concerns and hopes about CHM gene transfer clinical trials.

Another limitation exists due to the small number of patient advocates interviewed. Moreover, patient advocates displayed the most heterogeneous perspectives of all stakeholder groups. These factors may limit the transferability of patient advocate data to other studies. As CHM is a rare disease, few patient advocacy organizations exist. To the best of my knowledge, I captured the views of a representative from every existing CHM patient advocacy organization in this study.

3.5 Conclusion

Polarized between portrayals of great promise and uncertainty, and oscillating between positive and negative public scrutiny (King et al., 2005), gene transfer is situated in a culture of sensationalism. This sensationalism renders patients vulnerable to high hopes and to subsequent disappointment (Petersen, 2009), which might compromise the integrity of informed consent in phase I clinical trial enrollment (Kimmelman, 2010). To ensure that patients are well informed about the risks and benefits of CHM gene transfer, clinicians must highlight the risks of gene transfer and explain the spectrum of potential visual benefits in the context of clinical care. The incremental nature of evidence suggesting benefit in other phase I clinical trials must also be described. In the context of clinical trial enrollment, clinicians must emphasize that the goal of a phase I trial is to establish safety, rather than efficacy. When communicating with both patients and patient advocates, clinicians must position the current research efforts in the clinical trial infrastructure by illustrating time frames for the clinical application of gene transfer based on the time frames associated with previous clinical trials. With these strategies communicators may counter the sensationalism historically associated with gene transfer and honour patient hope while grounding communications in current clinical realities.

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CHAPTER FOUR: OCULAR GENE TRANSFER IN THE SPOTLIGHT: MEDIA COMMUNICATIONS AND PATIENT PERSPECTIVES

4.1 Introduction

The field of gene transfer, colloquially known as 'gene therapy', has followed a trajectory of high hopes and high profile failures. Historical abuses, including non-disclosure of adverse events in clinical trials to regulatory agencies and highly publicized conflicts-of-interest, have sullied the reputation of gene transfer (Wilson, 2009; Wilson, 2010; Wolf, Gupta, & Kohlhepp, 2009), eroded public trust in the biotechnology, and presented significant setbacks for its clinical development (Smith & Byers, 2002; Yarborough & Sharp, 2009). Adverse events have included deaths and several incidents of leukemia (Wolf et al., 2009).

On the heels of these high profile failures, the first tangible successes began to materialize in the area of ocular gene transfer. The first successful ocular gene transfer clinical trials began in 2007 for a rare, blinding retinopathy called Leber congenital amaurosis (LCA); the phase I[12] trials established both indexes of safety and improved visual function (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). The successes of the LCA trials have been sustained since, demonstrating continued safety and efficacy (Simonelli et al., 2010). Gene transfer for LCA is currently entering into phase III clinical trials (NCT00999609) (National Institutes of Health & Children's Hospital of Philadelphia, 2012). The LCA studies have served as an impetus for the development of several gene transfer clinical trials for related ocular diseases (Smith, Bainbridge, & Ali, 2009), including Stargardt disease (NCT01367444) (National Institutes of Health & Oxford Biomedica, 2011), retinitis pigmentosa (NCT01482195) (National Institutes of Health & Fowzan Alkuraya, 2011), and choroideremia (NCT01461213) (National Institutes of Health & University of Oxford, 2011).

Recent advances in ocular gene transfer have triggered a great deal of media attention (Kaplan, 2008), raising patient hopes (Héon, 2009) for the mediation of

[12] According to Health Canada: "Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical. Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses" (Health Canada, 2008). See Appendix XVVIII for clinical trial phase definitions.

previously untreatable genetic diseases. Commentators describe the universal patient hope for a treatment, regardless of the gene under investigation of clinical trials (Héon, 2009; Kaplan, 2008). The media are a major source of information on biomedical research for the public and patients. Media coverage, therefore, if exaggerated or misrepresentative of gene transfer, may influence societal and patient expectations for this field of biotechnology (Bubela & Caulfield, 2004; Holtzman et al., 2005). In particular, exposure to overly hyped[13] media coverage about gene transfer research may influence patient hopes and affect the integrity of informed consent in the context of clinical trial enrolment.

The media is often blamed for much of the sensationalism associated with science. This is likely because the media is the most accessible (Caulfield & Condit, 2012), and therefore the main source of information for publics about science (Geller, Bernhardt, & Holtzman, 2002). Sensationalism in media communications has been termed "genohype", and describes the exaggerated portrayal of the risks and benefits of genetic research and biotechnologies (Holtzman, 1999). For example, most diseases with a genetic component are multigenic and multi-factorial, involving gene-environment and gene-gene interactions. Genohype occurs when a single gene of small effect-size associated with such a complex disease phenotype is deemed to be highly deterministic of the phenotype. In other words, its contribution to the phenotype is exaggerated. Genohype also occurs when early-stage genetic discoveries or technologies are represented as promising imminent cures (Bubela & Caulfield, 2004). Additionally, the media often 'frame' complex research or genetic advances through a partisan lens to attract readership. Frames are interpretive presentations of an issue that highlight its importance and how it should be addressed (Gamson & Modigliani, 1989). Through framing techniques, the media are able to simplify complex research endeavors and bias contentious issues by placing greater emphasis on certain considerations while omitting others (Nisbet & Mooney, 2007). Most often, the frame celebrates progress in research, emphasizing benefits over risks (Bubela et al., 2009).

Many critics describe the instability of biotechnologies subject to genohype. From a health policy perspective, genohype may divert attention from pragmatic long-term policy concerns to short-term unrealistic and sensationalistic endeavors (Caulfield, 2000). For instance, genohype may undermine the necessity of basic science research and direct research funding to premature translational efforts aimed at clinical applications. Beyond skewing priorities of research agendas (Evans, Meslin, Marteau, & Caulfield, 2011; Sung & Hopkins, 2006), scholars suggest that hype inflates public expectations and engenders a loss of trust[14] when

[13] The Oxford Dictionary
defines hype as ''extravagant or intensive publicity or promotion" (Hype, 2012)
[14] Defined as "the expectation that a trustee is both able and motivated to behave in a way that is valued by the trustor" (Critchley, 2008).

promises are unmet, compromising public support (Cunningham-Burley, 2006; Illes et al., 2010; Petersen, 2009). Genohype may also result in public desensitization, disengagement, and ultimately threaten the nature of 'informed public citizenry' in debate and policy concerning research priorities (Ransohoff & Ransohoff, 2001). From a clinical perspective, sensationalism surrounding genetic research may lead patients, patient families and clinicians to form high expectations, only to be followed by disappointment when reality falls short of hope. This disappointment may cause disillusionment among clinicians and despair among patient communities (Petersen, 2009). Additionally, hype associated with clinical trials may present challenges to informed consent, such as heightening patient hope for therapeutic benefits (Daugherty, Banik, Janish, & Ratain, 2000). This may lead to patient misunderstanding of the safety focus of early-phase clinical trials (Daugherty et al., 1995; Joffe, Cook, Cleary, Clark, & Weeks, 2001).

In light of the sensationalism historically associated with gene transfer and the backdrop of genohype in media communications, emerging ocular gene transfer clinical trials necessitate an examination of the communications landscape surrounding this biotechnology. Here, I combine a content analysis of newspaper communications about ocular gene transfer with a qualitative analysis of patient perspectives on media coverage about ocular gene transfer. The patients were affected by choroideremia (CHM), a blinding retinopathy currently under the investigation of a phase I gene transfer clinical trial (NCT01461213) (National Institutes of Health & University of Oxford, 2011). I explore errors of omission in media content, representations of risks, benefits, as well as misrepresentations of the therapeutic potential for gene transfer. I further assess the response of CHM patients to media reporting, and the potential implications for participant recruitment in a gene transfer clinical trial for CHM, which will commence at the University of Alberta, Canada, in 2013. Accounting for media communications and the resultant ethical challenges will ensure the responsible translation of this biotechnology as it moves forward to clinical development.

4.2 Methods

Newspaper Communications

I examined newspaper communication about ocular gene transfer between January 1, 1990 and June 30, 2012 in the top 50 American, Canadian, and British newspapers by circulation (Audit Bureau of Circulation, 2011). These countries ranked within the top ten for gene transfer trials; the United States ranked highest (National Institutes of Health, 2011; The Journal of Gene Medicine, 2011). Ocular gene transfer trials for CHM have commenced or will shortly commence in these three countries. I developed a search strategy that captured articles about ocular

gene transfer (see search terms in Table 2-1 in chapter 2) in newspaper articles from both Factiva (for US and UK newspaper search) and Canadian Newsstand databases (for Canada newspaper search) to ensure completeness of newspaper article inclusion (Table 2-1 in chapter 2).

I conducted a deductive content analysis on the selected articles using an *a priori* coding frame (see Appendix XV) that investigated the balance of communications about ocular gene transfer, including descriptions of research methods, portrayal of risks and benefits, and visual outcomes. The coding frame was developed in response to the concerns voiced by patients, clinicians and patient advocates about a CHM gene transfer clinical trial in 20 semi-structured interviews (see Chapter 3). Additionally, the coding frame was informed by other content analyses of media about genetic technologies (Bates, 2005; Bubela & Caulfield, 2004; Condit, 2007; Holtzman et al., 2005).

A trained research assistant coded the articles. The research assistant had no post-secondary education, to ensure that the coding captured a lay perspective. To ensure reliability, I coded 30 articles (19% of the articles), and then used a Cohen's Kappa test to indicate agreement among coders. The Cohen's Kappa test yielded a kappa range between 0.71-1.0, displaying acceptable inter-coder agreement (Neuendorf, 2002). Using STATA 11 (StataCorp 2009) I performed Fischer's chi squared tests to detect statistically significant differences in coverage between countries. I performed a Kruskal–Wallis analysis of variance to assess differences in the median number of benefit and risk representations between countries.

Patient Perspectives

I interviewed 20 American and Canadian CHM patients (P) about their perspectives on media coverage of gene transfer in general, and in response to a video clip about the LCA clinical trial. These patients were mainly recruited through notices on CHM patient advocacy group websites as well as through physician-mailed recruitment letters at an Edmonton eye clinic. CHM gene transfer phase I clinical trials are projected to begin in both the United States (University of Pennsylvania) and in Canada (University of Alberta) in 2013. The video (see Box 1 for description) was the most viewed YouTube clip depicting LCA gene transfer, which covered the perspectives of study investigators, patient advocates, and patient families (BIOchannel, 2010). I explored patient responses to the video clip using semi-structured interviews; questions included how the clip made interviewees feel about participating in a gene transfer clinical trial (Appendix XI).

I analyzed interview transcripts using NVivo 9.1 qualitative analytic software (QSR international, 2010). I coded a subset of interview transcripts "line by line",

and analyzed these codes for similarities and differences between transcripts using the "constant comparison method" (Charmaz, 2006). I then continued to develop a codebook, which I further refined through an iterative process of continual comparison between transcripts. Finally, I organized the codes into themes and more nuanced sub-themes.

To ensure that the narrative I present is representative of patient perspectives, I reviewed each selected quote in its original context. Finally, I sent each participant a set of interpreted results (Appendix XVII), and invited them to contact me with further comments or concerns. Participant comments were integrated into the analysis to generate an informed final analysis.

Box 1: YouTube clip description "New Hope for Gene Therapy: A Young Boy's Fight Against Blindness"

The video first introduces Corey Haas, a child affected by the rare genetic disease, LCA. Stephen Rose, PhD, Chief Research Officer of the Foundation Fighting Blindness then describes the pathophysiology of LCA with the aid of graphics of the affected retina. This clinical explanation is followed by the description of Nancy and Ethan Haas, Corey's parents, of their emotional journey following their son's LCA diagnosis. Jean Bennett, Professor at F.M. Kirby Center for Molecular Ophthalmology, scientist at Children's Hospital of Philadelphia, and an investigator on the phase I/II LCA gene transfer clinical trial then explains the experimental procedure. The explanation, along with a video simulating the procedure, depicts gene delivery using a viral vector to Corey's retina, the restoration of functional protein production, and the restoration of visual function in the treated eye. Nancy Haas then tearfully recalls how four days following surgery, for the first time, the sun hurt Corey's eyes. This is significant because LCA affects light perception. Dr. Bennett then comments on the success of this gene transfer clinical trial, and expresses her opinion that this success will only be one of many in the future. Dr. Rose also comments on the success of the trial, and explains that the restoration of vision as seen in Corey's case was a "real milestone". Finally, Dr. Bennett describes her overwhelming excitement in response to the success of the trial, giving credit to the patients as "the real pioneers". The video concludes with footage of Corey participating in activities requiring sight, such as throwing and catching a baseball with his father, riding a bicycle, and playing a video game on a Wii. The final screen states, "In 2009, Corey Haas completed his first full season of little league baseball".

4.3 Results

Newspaper Communications

The initial search produced 2070 newspaper articles (84 Canadian, 647 UK, and 1339 US). After reading each article, I excluded all but articles about gene transfer for retinopathies, resulting in 158 articles (26 Canadian, 55 US, and 77 UK) for analysis.
I combined articles from the three countries when there was no statistically significant difference in coverage.

Voices

The most prominent voice represented in newspaper articles was that of public sector researchers, represented in 85% of Canadian, 57% of UK, and 38% of US articles. The voice of affected individuals was the second most prominent, represented in 28% of all articles. The voice of patient advocacy organizations was also frequently represented and appeared in 20% of all articles. Friends and family of affected individuals were represented in 20% of all articles. The opinions of columnists were represented in 19% of all articles. Regulatory voices were seldom represented, only 3% mentioned parliament or congress, 1% mentioned ethics committees, and no articles represented a judicial or legal voice. Industry voices were also scarce with only a single article interviewing a private sector scientist, and another representing the views of a biotechnology company spokesperson. The voices of investors were not represented in newspaper articles.

Dominant Frame

Forty seven newspaper articles were framed as human-interest stories. Sixty eight percent of these depicted the challenges of affected individuals living with genetic retinopathies. Forty percent of human-interest stories portrayed affected patients as heroic, empowered or hopeful, while only one conveyed the challenges of affected individuals through a lens of fatalism, depicting sorrow and hopelessness. The challenges of family members of affected individuals were described in 17% of the human-interest stories, and narratives of heroism, empowerment and hope were present in 19%. Only 4% of human-interest stories illustrated narratives about the clinicians and scientists involved in gene transfer research, portraying them as heroes.

Descriptions of Research

Thirty nine percent of all articles clearly indicated that gene transfer remains experimental, while 8% did not mention that gene transfer is research. However, 51% of all articles contained language that subtly conflated research and treatment. For example:

> To hear such quick progress in a gene therapy *treatment* is fantastic. We hope this success will lead to more funding of gene therapy *research* into conditions that currently have no cure or treatment. (Italics added) (Sample, 2007).

> A groundbreaking *therapy* to treat blindness by injecting healthy genes into the eye improved patients' sight a thousand fold a year after the initial treatment. *Researchers* said that the *therapy* appeared to cause "stable" improvement and triggered adaptations in the brain. The *treatment* was tested on three patients with a rare, incurable form of blindness called Leber's congenital amaurosis. (Italics added) (Devlin, 2009).

Explanations of Genetic Conditions and Gene Transfer

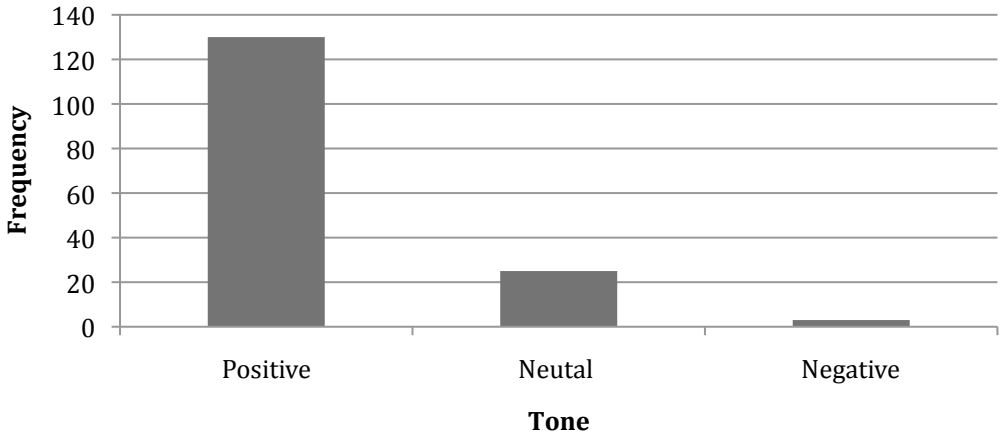
Sixty one percent of all articles indicated that a genetic mutation causes the retinopathy. While 58% of Canadian, 53% of UK, and 22% of US articles mentioned that a working copy of the mutated gene is transferred to ameliorate the disease phenotype, 15% of Canadian, 3% of UK, and 18% of US articles used misleading terminology to describe the gene transfer (eg., “gene replacement”). Only 23% of articles indicated that a modified viral vector is used to transport the gene of interest into the eye. Twelve percent of articles explained that a viral vector is used to transport the gene of interest to its target but did not mention the modification of the viral vector to ensure that it will not cause infection in the body. The majority of articles (54%) mentioned that the gene of interest must be transferred to the retina, and 51% of all articles explained that the transfer process required a surgical intervention involving an injection of the viral vector to its target cite. Most articles (65%) did not discuss sample sizes in research. Only 4% of Canadian, 3% of UK, and 5% of US articles indicated phases of gene transfer clinical trials. Funding sources were mentioned in 39% of all articles. Controversies and conflicts of interest were only described in 3% of articles. For example, one article explained that while the prospect of a blindness treatment through gene transfer may be exciting for some, it might present challenges for congenitally blind children who had adjusted to visual impairment:

> While the prospect of a cure is exciting, it can also be scary for people living with limited or no sight, said Maureen Hartnett of Oakville, Ont., who has a son and daughter…with LCA.
> "If they said, 'there's a cure and you're going to be able to see', they wouldn't just jump and say, 'Yes!' Because the whole world would change on them," said Ms. Hartnett. "They've both been able to carry on with their lives without sight. Then all of a sudden if you could see it wouldn't make sense…They wouldn't be able to read" (Mick, 2008).

Representations of Risks, Benefits, and Time Frames

The tone of newspaper coverage was overwhelmingly positive (see Figure 4-1) as 85% of all articles had an overall positive tone. Only 2% of articles had a negative tone, and 16% were neutral.

Figure 4.1: Tone of ocular gene transfer newspaper coverage in Canada, United Kingdom and United States



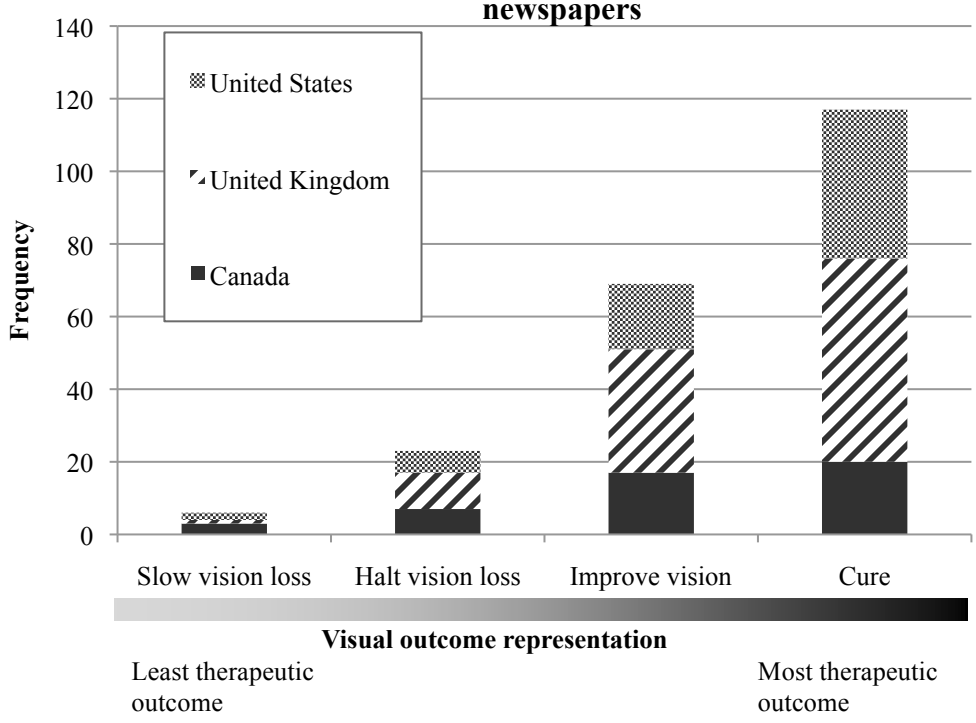
Overall, there was a disproportionately high representation of benefits in the newspaper articles, as the median number of benefits was 3, and the median number of risks described was 0. While gene transfer risks were not discussed in the majority of articles (57%), the risks that were represented are detailed in Table 4-1.

Table 4-1: Representations of ocular gene transfer risks and caveats in Canadian, British and American newspaper articles

Gene transfer risks, challenges, or caveats	No. and (%) of articles
Not mentioned	90 (57)
General health risk	36 (23)
Efficacy concerns	26 (16)
New research or first-in-human experimentation	12 (8)
Long timeframes to clinical implementation of gene transfer	11 (7)
Historical adverse events in gene transfer clinical trials	8 (5)
Eye health risk	8 (5)
Unknown risk or uncertain risk	7 (4)
Complexity of gene transfer	6 (4)
Economic risk	7 (4)
Ethical challenges	4 (3)
Social challenges	1 (0.6)
Quality of life concerns arising from clinical trial participation	1 (0.6)
Legal risk	0

The most prominent benefit of ocular gene transfer described in the newspaper articles was direct visual benefit, with 100% of Canadian, 91% of UK and 87% of US articles mentioning it as a benefit. Visual benefit representations ranged along a continuum of nuanced outcomes, ranging from the most conservative benefit of slowing vision loss, to the least conservative outcome of a complete cure. Frequency of representation in newspaper articles increased as the visual outcome became less conservative, such that slowing down vision loss was the least represented, and a cure was the most frequently mentioned outcome (Figure 4-2). Some articles (12% of Canadian, 31% of UK and 45% of US) indicated treatment as a benefit of ocular gene transfer, but did not specify what this treatment might offer. None of the articles indicated that deriving visual benefit from ocular gene transfer is unlikely.

Figure 4.2: Ocular gene transfer visual outcome representations in Canadian, British, and American newspapers



While the majority of articles predicted visual benefit as an outcome of ocular gene transfer, 87% of all articles did not provide time estimates for the commencement of gene transfer clinical trials or for the clinical implementation of this biotechnology.

Patient Perspectives

Perspectives about General Media Coverage

Patients articulated a wavering or somewhat qualified trust in media coverage.

> [I trust media coverage] to the extent I need to. It's not like I'm going to base life decisions on it, but it's interesting to read and…I trust that it's correct. —P16

This limited sense of trust was fueled by beliefs about omissions of detail or inaccuracies in media coverage.

> One of the things that frustrate me about reading stuff in the media is that media…introduces the topic and gives you a few hits on the topic, it doesn't

> tell you the background, the information they impart is frequently contradictory with the thing you read last year on the same paper about the same thing. –P4

Despite their skepticism about media coverage, patients explained that media pieces often make them feel positive.

> Usually the focus of those kinds of articles that I've seen had been intended to be positive and usually they help me feel positive too. —P16

Patients explained that a prevalent form of positive media coverage exists through human-interest stories.

> The focus is on [the] human-interest side, so it's really focusing on the positives of what that particular person has been able to accomplish despite the disease. It is not an article so much of the disease itself, so the articles are typically uplifting. —P16

One of the reasons that patients felt positive about media coverage of their disease was because it raises awareness, generating attention and funding opportunities. This was important for patients in light of the rarity of CHM and consequent relative anonymity of the disease.

> [CHM media coverage made me feel] somewhat relieved because…finally…we're not sitting in a bad corner of a hallway…having to play second hand to everybody else's illnesses or diseases. —P2

> It was good just to get some coverage…the more people know then the better chance of getting money. –P5

Patient Perspectives about the LCA Clinical Trial Video Clip

The video triggered emotional responses for many patients as they identified with Corey's practical challenges resulting from his diminished vision, and the emotional struggles related to disease management.

> The frustrations like the parents are talking [about]: to see their kid can't find things in front of him…I've lived that…I know what that is like. So there's a deep emotional component to listening to that account. –P13

Many patients not only identified with Corey's struggles, but with those of his parents, drawing parallels between the parents' accounts, and the experiences of their own family members.

> I could empathize with [Corey's] mother and her tears when she recalled the diagnosis, and [it] reminded me of my tears when I got told I shouldn't drive anymore, reminds me of my mother's tears when she thinks about her role in passing the gene onto us. So, the emotion is very telling in there. —P16

The most prominent response to the video, expressed by every interviewed patient, was that of hope. Patients recognized the similarity between gene transfer for LCA and CHM, fueling their hopes for a treatment.

> My impression is that it's [LCA gene transfer] hopeful...because…Leber's disease…is similar to…choroideremia. –P7

Patients expressed their excitement, encouragement, and renewed sense of hope for a treatment despite their prognoses of continued visual decline.

> It gives hope where there was none…because before last 10 years the prognosis was there's no treatment. So it's certainly hopeful and encouraging to see the doctors coming this far and with trials just around the corner, and knowing that Leber trials went well and proved safe. –P3

While patients depicted accounts of hopefulness, some also articulated worries. The main concerns expressed centered on the efficacy of gene transfer.

> You can't necessarily say what works for [LCA] would also work for choroideremia, although it's possible. And also in this case the child is still young and still had functional [photoreceptor] cells. In older adults where they don't have the functional cells that they may have already degenerated it may not be applicable. –P14

Other patients articulated a fear of disappointment in light of their renewed hopes. To ameliorate their anxiety surrounding disappointment, patients adopted an attitude of cautious optimism - they avoided excessive hope by grounding their hopes in the current reality of their prognosis.

> [Media coverage made me feel] hopeful, but at this stage of life, I'm hopeful and I try not to get myself too excited because I've been let down before. I want to be hopeful, but I don't want to be hopeful because I don't want to get too excited and be disappointed again.—P17

> I…try and be grounded about [gene transfer] because it just doesn't seem real, like I know it is, but it doesn't seem real. —P5

Despite sentiments of caution, patients explained that the video left them with an overall impression of hopefulness and encouragement that appeared more salient than any associated worries.

> The encouragement is probably the stronger [than the worries]. I already had the concerns about safety [prior to watching the video] but I think [the video] definitely accentuates the encouragement now. –P16

> I don't think so much about the risks, and I think more about the benefits. So it does make me feel a little more excited to try [gene transfer]. –P10

With a hopeful impression undermining risk perspectives, the main concern for patients after viewing the LCA video became that of access to a gene transfer clinical trial.

> After seeing pieces like that [LCA video]…it gave me a realization…of…the power of gene therapy. And pieces like that…remind you that this is real science and people are doing real things with it…and if the opportunity arises, think about getting involved [in a gene transfer clinical trial]. —P19

When asked how the video makes them feel about participating in a gene transfer clinical trial, patients responded with certainty and enthusiasm:

> I'll do it tomorrow. —P2

> I want to find out where to sign up. —P11

Nevertheless, after viewing the LCA video, one patient expressed concerns about how sensationalistic media coverage might influence patient hopes, highlighting the importance of providing balanced information during the informed consent process of clinical trial enrollment to counter hyped media communications.

> If people have a realistic expectation of what the true odds are [for visual benefit in the context of ocular gene transfer] and they don't read about the miracle cure in the newspaper and expect it to do everything…I think it's okay. But…the medical profession would explain to you the risks involved and the chances of success and…and the prognosis…If people enter into these testing regimes with realistic expectations that's all you can ask. —P4

4.4 Discussion

This content analysis of Canadian, UK and US newspaper articles provides insights into media reports that shape and reflect public opinion about ocular gene transfer. Unlike most media content analyses, this study integrates the perspectives of a key audience for information about ocular gene transfer: CHM patients. Here, I discuss (1) concerns raised by my analysis of newspaper coverage and (2) ethical considerations in light of CHM patients' interactions with media communications.

Media Communications

Scholars maintain that media hype is not blatantly present in inaccurate reporting (Bubela et al., 2009; Bubela & Caulfield, 2004; Bubela & Caulfield 2005; Holtzman et al., 2005). Instead, overly enthusiastic or exaggerated claims in the media are evident through more subtle shifts in framing and errors of omission. Despite this subtlety, however, sensationalism associated with media reporting often remains salient in the public sphere. It serves to discredit media claims (Ransohoff & Ransohoff, 2001) and build unrealistic social expectations about the promise of a given technology (Hedgecoe, 2004). As such, scientists, policy makers, government officials, and ethicists view hype as a major shortcoming of media reporting (Bubela et al., 2009). Scholars have suggested various methods to address sensationalism in the media, including encouraging researchers to provide reporters with information about conflicts-of-interest (Caulfield, 2004), context about the importance of medical advances (Geller et al., 2002), and descriptions of scientific roadblocks, including the possibility of findings to be invalidated by further studies (Condit, 2007). Additionally, several educational strategies have been proposed with the aim of reducing hype, such as improving the training of journalists about science reporting (Holtzman et al., 2005), training researchers to "stick to the facts" when communicating with reporters, and teaching graduate students as future spokespeople about the social and political dynamics of science communication and how to best convey messages to the media and the public (Bubela et al., 2009). Unfortunately, this study confirms that following more than a decade of attention on science media hype and initiatives to improve journalism on novel health technologies (Bubela et al., 2009; Bubela & Caulfield, 2004; Caulfield, 2004; Condit, 2007; Henderson & Kitzinger, 1999; Holtzman et al., 2005), little improvement is discernible in the context of ocular gene transfer.

Voices: The Views Represented in Newspaper Articles

In this study, the most prominently represented voice was that of public sector researchers. Scholars suggest that "genetic stories are framed as ones of hope, with scientists depicted as warriors or heroes" (Bubela & Caulfield, 2005 p. 122).

Since such public sector researchers engender a high degree of trust among publics (Critchley, 2008), their statements lend credibility to media reports. However, researchers, including investigators of clinical trials, are often "complicit collaborators" (Ransohoff & Ransohoff, 2001) with the media in promoting the promise of their research to attract funds and public support for their research (Kimmelman, 2010; Wilkes & Kravitz, 1992). Indeed, scientists who perceive that media attention will promote their work are most often represented in the media (Tsfati, Cohen, & Gunther, 2011). As such, trusted researchers are compelled by careerist pressures (Caulfield & Condit, 2012) to serve as partisan stakeholders in media communications. Such actions are most concerning in the context of clinical trials, which involve experimental interventions in participants. To address the pressures on clinical researchers to exaggerate the potential impacts for their research in the media, Kimmelman (2009) recommends that institutional review boards might require investigators of clinical trials to submit a portfolio of their press releases as a component of ethics review (Kimmelman, 2009).

Other prominently represented voices were those of patients and families. The accounts of these stakeholders were usually captured through human-interest stories. Such accounts frame gene transfer through a "voice of compassion and hope" (Kitzinger & Williams, 2005), and are a "powerful way of both universalizing and personalizing human experience" (Petersen, 2001). Human-interest stories appeal to publics through emotive framing and remain salient in the public sphere, generating the most public conversation and reflection (Henderson & Kitzinger, 1999). In agreement with previous studies, the human-interest stories in this media analysis were framed through a lens of hope, empowerment and heroism. Additionally, human-interest stories were the most prominently recalled by CHM patients, and elicited positive feelings among them. Human-interest stories are memorable for audiences, however, they may mask the scientific information presented in media reports (Henderson & Kitzinger, 1999).

Research Design and Conflicts-of-Interest

In agreement with Racine et al. (2010), I found explanations of the research and clinical studies limited. Most striking was the lack of clarity provided with respect to gene transfer, as descriptions oscillated between terminology associated with research and treatment. Other information necessary for readers to contextualize the significance of gene transfer efforts, such as sample size and study design, was largely absent.

The lack of reporting of conflicts-of-interest or funding information, a finding common in other studies (Bubela & Caulfield, 2004; Holtzman et al., 2005; Racine, Waldman, Rosenberg, & Illes, 2010), also diminishes transparency and the ability of publics to critically evaluate the stakes of interested and affected

parties in the research effort. Scholars suggest that reporters should always ask for, and scientists should always declare funding or other conflicts-of-interest (Caulfield, 2004; Holtzman et al., 2005). In the case of gene transfer reporting, declaration of conflicts-of-interest—particularly those of a financial nature—is key in light of the highly publicized ornithine transcarbamylase deficiency gene transfer clinical trial at the University of Pennsylvania. The principle investigator of this clinical trial was accused of holding shares in Genovo, a biotechnology company sponsoring his research, estimated at $28.5- $33.3 million (Wilson, 2010). This clinical trial has been described as "the most famous conflict-of-interest case in medicine" (Wilson, 2010), and was associated with a loss of public trust in gene transfer research (Yarborough & Sharp, 2009). In light of the historically sullied reputation of gene transfer, transparency with respect to conflict-of-interest disclosures is necessary to maintain public trust—an essential component for the sustainable translation of this biotechnology (Chalmers & Nicol, 2004).

Representations of Risks, Benefits, and Time Frames

This study as well as others point to a reporting trend of emphasizing the benefits while omitting discussion of many risks (Bubela & Caulfield, 2004; Holtzman et al., 2005; Racine et al., 2010). Scholars suggest that it is difficult for the media to represent risks because both journalists and publics find risk-related probabilistic information inaccessible (Condit, 2001). However, it is not only probabilistic, but also ethical and social risks that go underreported (Bubela et al., 2009), displaying a lack of balance in media representations of the costs and benefits of genetic research. Adverse events have historically occurred in the field of gene transfer and have presented setbacks to its clinical development (Wolf et al., 2009). These point to an oncogenic risk as a result of insertional mutagenesis, as well as death caused by immune response to the viral vector carrying the gene of interest (Johnston & Baylis, 2004; Wilson, 2009). Other risks associated specifically with ocular gene transfer include surgical complications, loss of an eye due to inflammation, loss of vision, as well as brain toxicity due to viral vector integration into the optic nerve (MacDonald, 2012). Highlighting the risks of gene transfer in media communications is necessary to contextualize to audiences that gene transfer is in an early research stage and historically associated with risk and uncertainty.

Given the close contiguity of the LCA gene transfer trials to other retinopathies under investigation for gene transfer, it is understandable that patients may feel hopeful for a similar outcome of direct visual gain as a result of phase I studies. However, such hope may be indicative of a subtle conflation between the goals of research and of clinical care. This conflation, termed therapeutic misconception, (Appelbaum, Roth, & Lidz, 1982; Appelbaum, Roth, Lidz, Benson, & Winslade, 1987) may be ethically problematic as it could undermine informed consent in the

context of clinical trial enrolment. An understanding of the goals of a clinical trial is necessary for autonomous decision making for participation and hence informed consent (Horng & Grady, 2003).

However, in a survey of prospective participants for a phase I oncology clinical trial, Pentz et al. (2002) showed that exposure to media reports did not result in therapeutic misconception among patients. Indeed, while 47% of patients who first heard about the trial from the media correctly identified the purpose of the trial prior to informed consent, only 15% of patients who did not first learn about the trial from media reports identified the purpose of the trial correctly prior to informed consent. Nevertheless, therapeutic benefit was the most prominent motivator for patients to participate in the clinical trial, evincing that therapeutic optimism can coexist with a correct understanding of the purpose of a phase I clinical trial and a low probability for therapeutic benefit (Pentz et al., 2002). It is therefore, important for clinical investigators to avoid shifts between research and treatment terminology when discussing early-phase clinical trials with the media. This will promote clarity in reporting and ethical representations that are responsive to the therapeutic optimism of clinical trial participants.

The representations of visual benefit in the media present an additional concern with respect to curative discourse. The results show that discussions of a cure through gene transfer were the most common visual benefit representation. Such curative language is common in media pieces about prospective biotechnologies, engendering a voice of hope (Kitzinger & Williams, 2005). With respect to gene transfer, however, the hope for a cure may be misplaced. Gene transfer studies show that while vision loss can be halted and even improved by restoring function of dormant but otherwise viable photoreceptors, a cure is not theoretically afforded by gene transfer (Jacobson et al., 2005). This is because gene transfer is non-regenerative, and therefore cannot revive degenerated photoreceptors; gene transfer requires the presence of viable photoreceptors to stabilize vision (Jacobson et al., 2005).

Media representations of a cure, while catchy, are inaccurate and misrepresent the theoretical promise of gene transfer research. Curative portrayals may be particularly concerning with respect to their potential influence on patient perspectives. Patients reading about cures with respect to gene transfer research may be vulnerable to therapeutic misestimation, a condition defined by the overestimation of benefits or underestimation of risks associated with clinical trials (Horng & Grady, 2003). While therapeutic misestimation may sometimes be ethically tolerable because an understanding of the exact probability of benefit is not necessary to make autonomous decisions about participating in a clinical trial (Horng & Grady, 2003), curative perspectives present a misestimation of the magnitude of benefit rather than its probability. While it is impossible to convey exact probabilities for benefits in novel clinical trials, there is an ethical obligation to avoid raising patient hopes for benefits known to be theoretically infeasible. In

light of the prevalence of curative discourse in the media, it is important that study investigators highlight to patients that a complete cure is not a theoretical possibility for gene transfer. Such communications will ensure patients are not misinformed about the magnitude of possible visual benefits when entering clinical trials.

While media representations focused on visual benefit portrayals, emphasizing curative discourse, the majority of articles failed to contextualize the time frames for the delivery of benefits described. The time frames for commencement of clinical trials or of clinical application were often not mentioned. Furthermore, articles rarely described the phase of clinical trials underway. In this manner, media coverage conveyed the impression that the projected therapeutic benefits were imminent, despite their early stages of development (Bubela et al., 2009). Such portrayals may be ethically problematic for patient populations, as they may inflate patient expectations for a therapy within a limited therapeutic window[15] and set patients up for disappointment (Petersen, 2009).

In summary, newspaper communications about ocular gene transfer were replete with errors of omission and used optimistic frames commonly used to generate social expectations about novel biotechnologies (Hedgecoe, 2004). Benefits were over-represented and risks were not discussed, even in light of the checkered history of gene transfer clinical trials. Most importantly, the focus on curative language within a therapeutic spectrum raises challenges for the ethical communication about ocular gene transfer in the context of recruiting clinical trials.

Patient Perspectives

Several studies examine public perspectives about media representations and media hype (Bates, 2005; Eyck, 2005; Smerecnik, Mesters, Candel, De Vries, & De Vries, 2010), defining the "public" as the general population, but under-representing the views of specific publics (Master & Resnik, 2011). One group under-represented by such studies is patient groups that have a more immediate stake as potential beneficiaries in the development of biotechnologies. My analysis of patient perspectives in light of media communications highlighted both patient vulnerability and critical thinking capacity.

[15] In this context, refers to the range of time in which GT could alter the outcome for a patient with a progressive disease.

Patients Engage in Information Seeking through Media Venues

My analysis confirms that the media is an important source of information for patients about disease-specific research. Similarly, a survey of prospective participants in a phase I oncology clinical trial revealed that 47% of participants first heard about the trial from media reports (Pentz et al., 2002). Another survey of cancer patients indicated that television, radio and the press were their most important sources of information about a high profile experimental cancer therapy (Passalacqua et al., 2004).

Furthermore, study participants found media coverage personally relevant and often related to media content emotionally. Peddie et al. (2009) compared the perspectives about embryonic stem cells of couples who underwent assisted reproduction, the general public, and two patient groups (diabetes mellitus and Parkinson's disease). In addition to highlighting the media as an important information source, Parkinson's patients in that study were the most motivated to engage in information seeking from media sources. These patients found personal relevance in the biotechnology because they perceived their quality of life to be affected by their disease and wanted to alter the course of their prognosis (Peddie et al., 2009).

Patients as Vulnerable but Critical Thinkers

Patient populations not only seek information about potential therapies in the media but also are often vulnerable to the information portrayed because they relate to it emotionally. In a study by Passalaqua et al. (2004), patients reported increased confusion and a decreased sense of hope of being cured following media coverage of an oncologic clinical trial that demonstrated inefficacy in phase II studies (Passalacqua et al., 2004). While Peddie et al. (2009) demonstrated the objectivity of the general public to media sensationalism, they highlighted patient vulnerability to overly optimistic media representations. Their study demonstrated the disappointment of both Parkinson's disease and diabetes mellitus patients after exposure to curative statements in the media, which have not materialized clinically (Peddie et al., 2009).

Despite this vulnerability, patients articulated skepticism surrounding the use of curative representations, claiming that short-lived or transient treatments have been represented as cures in the media (Peddie et al., 2009). In my study, patients also conveyed a vulnerability to curative discourse; they were afraid to hope for mediation of their own prognosis in light of the possibility of disappointment. Much like the patients in Peddie et al.'s (2009) study, CHM patients were also

critical of media coverage, articulating skepticism with respect to the accuracy of media reports and qualifying hopes for a therapeutic intervention in light of the risk of disappointment. Additionally, patients worried about the media's role in influencing patient expectations. These findings suggest that while overly optimistic claims in the media may affect vulnerable patient populations through emotional or hopeful appeals, they do not render patients uncritical.

Decision-Making in Light of Hype and Hope

Gordon and Daugherty (2001) suggest that patients often make the decision to participate in phase I clinical trials prior to discussion with the investigators conducting the trials (Gordon & Daugherty, 2001). In this study, following exposure to a highly positive and much-viewed media clip, many CHM patients indicated that they would be interested in participating in a gene transfer clinical trial. This finding raises the concern that overly optimistic media reports may influence patient decisions to participate in clinical trials and may potentially undermine informed consent. While media exposure may not be the *primary* impetus for a patient's desire to enroll in a clinical trial, media coverage will likely reinforce the pre-existing beliefs of the patient and underlying hope for a therapeutic intervention. In a study of cancer patient perspectives about media coverage related to a high profile cancer therapy, exposure to both positive and negative media coverage did not affect the decision making process of patients (Passalacqua et al., 2004), suggesting that while patients are vulnerable to media representations, they are not passively influenced by media coverage.

Earlier scholarship opined that media coverage might shape public attitudes (Nelkin & Lindee, 1995) and that omissions or misrepresentations in media coverage engender a deficit in public understanding that may influence public beliefs (Durant, Evans, & Thomas, 1989; Evans & Durant, 1995). More recently, however, scholars have shifted their perspectives away from the notion that a deficit in information accounts for public understanding of science, but rather, that underlying trust, beliefs, values and worldviews shape public opinions about science (Connor & Siegrist, 2010; Nisbet & Goidel, 2007; Priest, 2001; Siegrist, 2000). Publics are often "cognitive misers" and look for information in the media that aligns with their beliefs or confirms their values, and reject information that may conflict with their worldviews (Bubela et al., 2009). As such, underlying patient hope for a therapeutic intervention may be reinforced rather than incited by hopeful media messages. With this hope in mind, patients may be more inclined to participate in clinical trials.

In summary, patients actively engage in information seeking through media venues with the desire to learn about cutting-edge therapeutics. They also relate to the content of media coverage emotionally, and display vulnerability to hyped

coverage. Despite this vulnerability, patients are not "passive receptacles" (Kimmelman, 2010, p. 168) who automatically accept media messages as an unassailable truth. Rather, patients critically evaluate the content of media communications, and engage in autonomous decision-making regarding their clinical care and potential clinical trial participation. However, overly optimistic media coverage likely reinforces patient hopes for therapeutic benefit from clinical trial participation.

Limitations

This study did not assess media hype through "errors of commission" (Bubela et al., 2009) as it does not compare the content of media coverage with that of scientific journal publications. Despite this shortcoming, this study explored nuanced hype in the more common form of omission, and described analogous concerns of media hype present in early accounts of media sensationalism about genetics research (Bubela & Caulfield, 2004; Holtzman et al., 2005).

An additional limitation of this study relates to the patient perspectives represented. As CHM is a rare disease, recruitment of study participants was facilitated by notices on patient advocacy organization web sites. Patients who visit these web sites may engage in more information seeking than patients who do not access the resources of patient advocacy groups. Often, patient advocacy web sites also post media coverage related to the disease. This could mean that patients recruited through these web sites were exposed to more media coverage than patients recruited through other venues (eg, an eye clinic). Increased exposure to information about CHM, whether media-related or not, may mean that these patients were more knowledgeable about the disease or about research, and may as a result think more critically about media representations. Still, the accounts of these patients shed light on patient vulnerabilities and critical thinking. This study does not display a causative relationship between media representations and decision-making, and further research is necessary to tease apart the influence of patient hope and decision-making for clinical trial enrolment.

4.5 Conclusion

This study shows little improvement in science media communications about gene transfer in the past decade, predominantly through errors of omission, despite initiatives to improve journalism on novel health technologies (Bubela et al., 2009; Bubela & Caulfield, 2004; Caulfield, 2004; Condit, 2007; Henderson & Kitzinger, 1999; Holtzman et al., 2005). Media reports continue to be overly optimistic and framed as human interest stories, whether from the perspective of the heroic researcher or hopeful patient and family. Most concerning, however, is

the continued lack of coverage of issues closely tied to public trust, such as funding and conflicts of interest. Given the history of gene transfer, such issues should be at the forefront.

However, the media, as an industry, has its own needs and interests in an increasingly competitive environment. This study suggests that while patients actively engage in information seeking from media sources and respond to such coverage emotionally, they critically evaluate the content of media communications. Nevertheless, overly optimistic narratives of cure, well beyond the realistic spectrum of outcomes for gene transfer, may reinforce patient hopes for therapeutic benefit from early-phase clinical trial participation.

In light of these finding, the onus must be on clinicians and clinical trial investigators to address media coverage in the context of clinical care and clinical trial enrolment. While patients critically appraise media coverage and actively mediate their own hopes for therapeutic interventions, this study as well as others (Peddie et al., 2009; Pentz et al., 2002) demonstrates the vulnerability of patient populations to the hope engendered and reflected by sensationalistic media coverage. The autonomy as well as vulnerability of patients must be taken into consideration both in clinical researchers' interactions with the media and with their patients. In seeking informed consent from potential clinical trial participants, study investigators must consider the existing media communications landscape and the information from media sources that patients find personally relevant. Open discussion in the context of clinical care or of clinical trial enrolment about media representations and patient perspectives may serve to counter misinformation or omissions in media coverage, contextualize information in light of patient-specific prognoses, and explore underlying patient beliefs in clinical trial outcomes.

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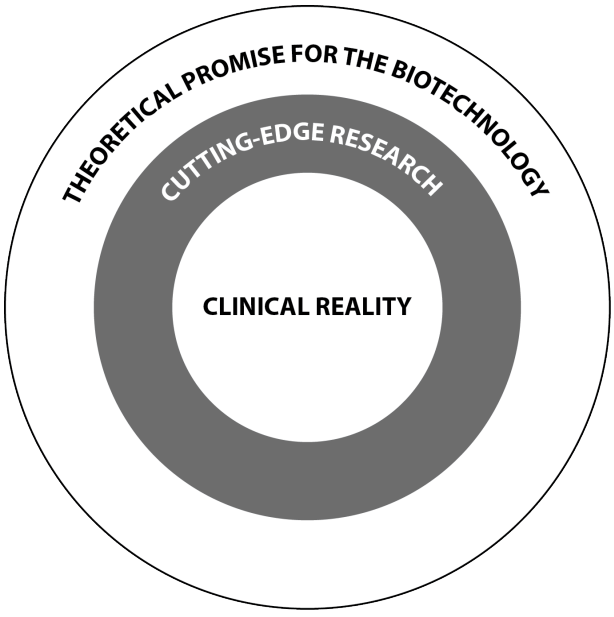
CHAPTER FIVE: CONCLUSION

A complex environment of communications surrounds novel ocular gene transfer clinical trials. The interests of various stakeholders, such as the media, clinical investigators, clinicians, patient advocates, and patients align to construct this environment. The communications reflect perspectives on this cutting-edge biotechnology and are externally shaped more by surrounding visions of future promise than the core current realities (See Figure 5-1). Clinical investigators as well as patient advocates promote the promise of research efforts to attain funds and public support. At the same time, "media interest in cutting-edge research is intense, and patients—along with their families and advocates—often track development closely" (Kimmelman, 2010, p. 154). This combination of stakeholder agendas, termed the "cycle of hype" (Caulfield, 2005) engenders an environment of highly optimistic communications that are visible to the public and more specifically, to hopeful patients.

Figure 5-1: Distinguishing between theoretical promise and current realities in cutting edge research

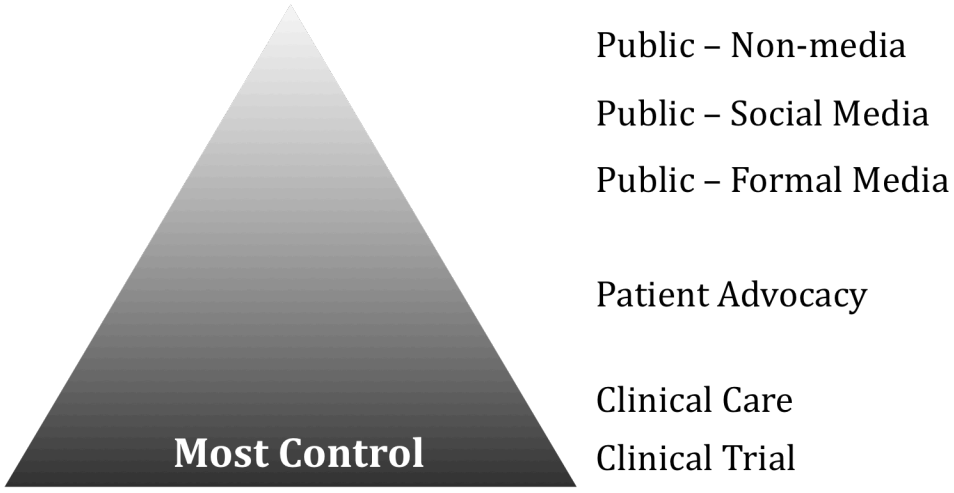


While the optimistic environment associated with genetic research and biotechnologies is often critiqued as "hype" (Holtzman, 1999), a certain degree of promotion or "expectation management" (Kimmelman, 2010) is a necessary and natural component of constructing technological futures (Hedgecoe, 2004).

Considering the high expectations initially associated with gene transfer, the high profile disappointments experienced by the field (Branca, 2005), and the vulnerability of hopeful patients, establishing balance in communications about ocular gene transfer is essential to its translation. This task, however, is challenging in light of the variable degree of regulation, stakeholders, and stakeholder control over information communicated in diverse venues (See Figure 5-2).

My research demonstrates that despite over a decade of scholarship and academic recommendations focused on reducing hype in media reports about science (Bubela et al., 2009; Bubela & Caulfield, 2004; Caulfield, 2004; Condit, 2007; Henderson & Kitzinger, 1999; Holtzman et al., 2005), overly optimistic claims as well as framing and omission biases continue to compromise the content of media coverage about ocular gene transfer. As such, the content of the most accessible source of scientific information for the public and patients (Caulfield & Condit, 2012) remains the least credible. Accordingly, the onus of establishing balance in communications with patients about gene transfer lies with clinicians in the context of clinical care, and clinical investigators in the context of clinical trial enrollment. In these venues, gene transfer communications and patient perspectives may be discussed to distinguish between current realities and theoretical promise surrounding them (Figure 5-1). It is especially important for clinicians and clinical investigators to be aware of the media communications environment and to address its content and patient perspectives about its messaging. Clinicians may employ a 'two-pronged approach' of sharing in patient hope for future outcomes supported by theoretical grounds (i.e. preclinical evidence) while grounding specific patient expectations in current clinical realities.

Figure 5-2: Level of control over gene transfer information by clinicians and clinical investigators in various communication venues



In light of my analyses of stakeholder perspectives and media communications about ocular gene transfer, I propose recommendations for communications strategies about phase I gene transfer clinical trials for choroideremia (CHM). Here, I outline key communication recommendations for clinicians, clinical investigators, and patient advocacy organizations. I also highlight study limitations and propose areas for future research.

5.1 Recommendations

Focusing on Benefit Communications

My research demonstrates that patients were focused on the potential benefits of gene transfer. While many recognized that risks are associated with this experimental biotechnology, patient risk perspectives were often attenuated in light of their attention on the theoretical benefits. As "cognitive misers" people often look for information that aligns with their beliefs or worldviews (Bubela et al., 2009). As such, messages about the potential benefits of gene transfer may appeal to patients on an emotional level, as they confirm underlying hopes. On the other hand, while many patients may be aware of some risks associated with gene transfer, they likely do not relate emotionally to risk information. Thus an emotional appeal would be necessary to emphasize risk information to patients, but this endeavour would be highly unethical. Instead of emphasizing risk

information, it is important to manage messaging about the potential benefits of gene transfer.

Research NOT Treatment

Therapeutic discourse surrounding gene transfer is prominent, and exemplified by the colloquial reference to gene transfer as 'gene therapy' (Deakin, Alexander, & Kerridge, 2009). In contrast with this therapeutic vernacular, the goal of phase I CHM gene transfer clinical trials is to establish indexes of safety (Health Canada, 2008). Despite this goal, clinicians, patient advocates, and patients interviewed for this study hoped that early-phase gene transfer would provide direct visual benefits. Additionally, media coverage of gene transfer not only described visual benefits in the majority of articles, but also shifted between research and treatment terminology when describing gene transfer studies. This use of language engenders confusion about the goals of gene transfer and the state of its development.

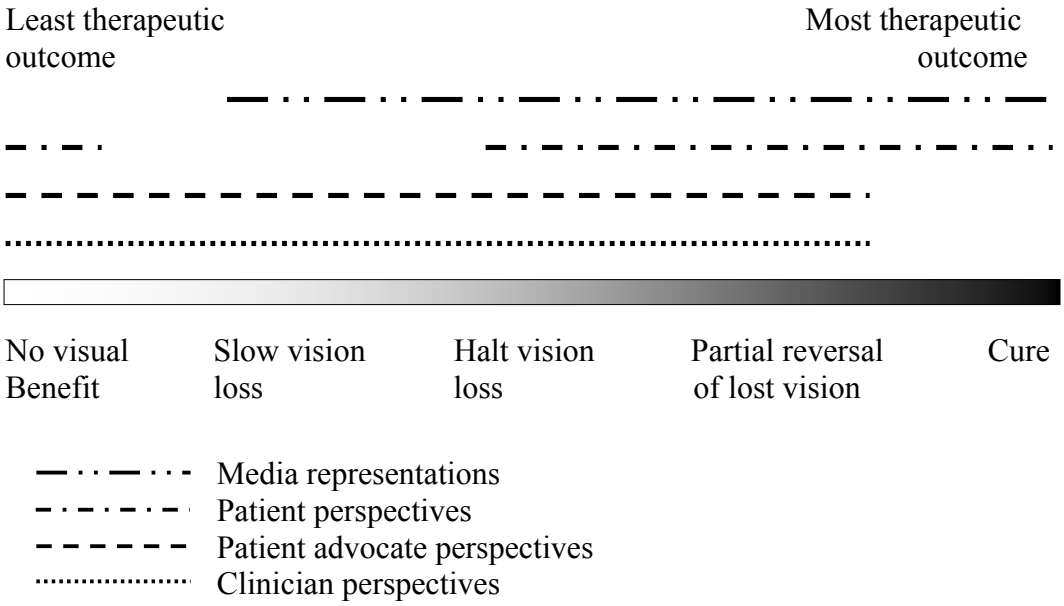
The hope for direct visual benefit in the context of phase I clinical trials was reinforced by the closely-related Leber congenital amaurosis (LCA) gene transfer clinical trials, that produced both indexes of safety and efficacy in phase I studies (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008). Hopes for visual benefit in the context of a phase I CHM gene transfer trial are ethically problematic because they conflate the goals of research and treatment, and are indicative of the therapeutic misconception (Appelbaum, Roth, & Lidz, 1982; Appelbaum, Roth, Lidz, Benson, & Winslade, 1987). An understanding of the goals of research is necessary for autonomous decision-making, and for informed consent; thus, the therapeutic misconception may undermine the integrity of informed consent (Horng & Grady, 2003). While Pentz et al (2002) demonstrate that therapeutic optimism can co-exist with a correct understanding of the goal of establishing measures of safety in phase I clinical trials and the low probability of incurring therapeutic benefit (Pentz et al., 2002), my research highlights that the prevalence of therapeutic discourse in the context of phase I CHM gene transfer may be problematic.

In the context of clinical trial enrollment, it is essential that investigators highlight to prospective research participants that the goal of phase I CHM gene transfer is to establish indexes of safety, and that future studies will test for efficacy if the phase I trials raise no or manageable safety concerns. Additionally, investigators should highlight that previous gene transfer studies point to a probability of less than 1% for deriving direct benefit from phase I trials (Kimmelman 2009). In light of media communications promoting therapeutic misconception and therapeutic optimism, it is important that clinicians, clinical investigators, and patient advocates emphasize to patients, patient families as well as in media communications that at this point CHM gene transfer is a research endeavour, not a treatment.

Curative discourse is prominent in public circles, including in the media and the communications of patient advocacy organizations. Ocular gene transfer presents a future theoretical possibility for visual improvement, but does not present an opportunity for a cure. Gene transfer may, at best, restore the function of dormant yet viable photoreceptors, but since it does not have regenerative potential, a complete cure will not be afforded through gene transfer (Jacobson et al., 2005).

Figure 5-3 displays the visual outcome representations in ocular gene transfer newspaper articles and the visual outcome perspectives of interviewed stakeholders. My research demonstrates that a cure is the most prominently described visual benefit in newspaper articles about ocular gene transfer. Despite the frequent representation of a cure, patient perspectives were most prominently centered on the possibility that CHM gene transfer may halt the progression of vision loss. Still, the hope for a cure was present among a minority of patients interviewed. Curative expectations are indicative of a therapeutic misestimation, where benefits may be overestimated (Horng & Grady, 2003). While the therapeutic misestimation may be ethically tolerable in cases where the probability of benefit may be difficult to convey or perceive (Horng & Grady, 2003), curative expectations present a misestimation of the magnitude of benefit. In this situation, communications about a theoretically infeasible cure are ethically problematic as they present an unattainable magnitude of benefit. It is therefore important for clinicians and clinical investigators to explain to their patients about the spectrum of possible visual benefits that could be theoretically derived as a result of gene transfer (as illustrated in Figure 5-3). Clinicians should also emphasize that gene transfer is non-regenerative, and therefore will not revive cells that have already degenerated. After successful phase 3 trials, gene transfer may, therefore, serve as a treatment, not a cure, for genetic retinopathies. Patient advocates should also avoid the use of curative discourse in patient communications and fund-raising efforts.

Figure 5-3: Visual outcome perspectives of choroideremia gene transfer stakeholders and ocular gene transfer media representations



Representing Time Frames

The field of gene transfer has been historically associated with premature time frame projections (Kimmelman, 2008). My research shows that the media as well as clinicians and patient advocates provide vague time frame estimates for the clinical application of ocular gene transfer. Moreover, because clinicians and patient advocates actively seek funding for research and often frame time estimates as a series of steps towards a treatment (Evans, Kotchetkova, & Langer, 2009), and because media portrayals of promising research efforts often do not provide time frame estimates for clinical implementation, the public, patients and their families are left with the impression that early-stage research efforts represent imminent therapies (Bubela et al., 2009).

My research reveals that patients were confused by vague time frame estimates and that they experienced challenges making practical life choices for the future because they remained uncertain about whether gene transfer would be available within their therapeutic window for visual gain. Patient advocates were similarly frustrated by unmet time frames provided by clinical investigators. Premature time frame estimates may raise the expectations of stakeholders, and when unmet, may lead to disappointment and to loss of trust (Cunningham-Burley, 2006; Evans, Meslin, Marteau, & Caulfield, 2011). Such loss of trust, particularly of patient advocates who often fund or engage in fundraising for CHM gene transfer clinical trials, threatens the sustainability of gene transfer efforts.

While it is impossible to predict time frames for the clinical implementation of novel CHM gene transfer efforts with accuracy, stakeholder concerns raise the necessity of increasing attention on effective communications about time frames. I propose that time frames for CHM gene transfer be situated within the infrastructure of clinical trial stages. Clinicians should aim to explain about the phases associated with clinical trials and situate CHM efforts in relation to the phases of clinical research to market approval and clinical implementation following adoption by health systems. It is important for clinicians to note that historical evidence points to a time frame of 10-14 years from phase I initiation to market approval of drugs (Glassman & Sun, 2004). However, in the case of gene transfer the novelty and risks of gene transfer lead to a more stringent regulatory environment (Kimmelman, 2008) and will result in even longer time frames. The closest analogous clinical trials to CHM gene transfer are the LCA clinical trials. The time frame for CHM could be compared to that precedented by LCA trials, which began phase I/II clinical trials in 2007 (Bainbridge et al., 2008; Hauswirth et al., 2008; Maguire et al., 2008) and are currently entering phase III clinical trials (NCT00999609) (National Institute of Health & Children's Hospital of Philadelphia, 2012).

Respecting Patient Critical Thinking Skills

My research demonstrates that CHM patients are vulnerable to communications about ocular gene transfer. This vulnerability was evident through patient descriptions of the emotional stakes associated with the development of a therapeutic intervention, such as a fear of hoping for visual improvement in light of the possibility of disappointment, as well as through the emotional identification of patients with human-interest stories about ocular gene transfer in the media. It is important for communicators to recognize the vulnerability of patients in the context of highly uncertain translational gene transfer research efforts and to tailor communications in a manner sensitive to these vulnerabilities (e.g. avoiding representations that promote the therapeutic misconception or therapeutic misestimation).

Despite patient vulnerabilities, my research reveals the critical thinking capacity of patients as many mediated their emotional stakes in the development of a CHM treatment by hoping for visual gain, but situating their expectations in the reality of their current prognosis. Additionally, despite prevalent curative representations in media communications the majority of patients hoped for the theoretically feasible outcome of a halt in vision loss. Effective communicators must therefore recognize patient vulnerabilities while honouring patients as critically thinking experts (Petersen, 2006). With this in mind, communicators must manage their own messaging rather than attempt to manage patient perspectives.

5.2 Study Limitations

A limitation of this study concerns the patient perspectives represented. Many of the patients in this study were recruited through notices on patient advocacy web sites. As such, my research may represent the perspectives of patients that access more support or information resources than if I had limited recruitment to notices at eye clinics. Patient advocacy web sites often inform patients about research efforts and direct patients to media coverage about research; therefore, patients recruited through advocacy groups may be better informed about CHM gene transfer research. As such, they may have had more exposure to media communications than patients who do not access patient advocacy resources.

An additional limitation relates to the content analysis of gene transfer media communications. In this study I did not compare the claims of media reports with the original scientific articles. As such, this study does not detect media hype through "errors of commission" (Bubela et al., 2009). Despite this limitation, my media analysis captures the more pervasive "errors of omission" (Bubela et al., 2009).

5.3 Future Research

The theme of hope emerged in gene transfer communications prominently, through stakeholder interviews as well as in media accounts of human-interest stories. Future research could address the role of hope with respect to the development of novel gene transfer efforts. My research as well as that of Pentz et al (2002) demonstrated that patients are motivated to participate in phase I clinical trials after exposure to positive media coverage about analogous research efforts (Pentz et al., 2002). Future research could aim to distinguish between the influence of (1) preexisting hope for therapeutic benefit and (2) the hope engendered by media communications on patient decision-making in the context of clinical trial enrolment. My research also describes clinician hope for therapeutic benefit as an outcome of a phase I CHM gene transfer clinical trial. Future research is necessary to understand whether the therapeutic optimism of clinicians may be influenced by the study design of this clinical trial, where indexes of safety are captured through visual outcome tools that may detect improvement in vision.

In this thesis I examine the content of newspaper communications, which set the stage for communications at other media venues. The Internet, however, has become a prominent source of health information for patients (McMullen 2006). While I describe difficulties in developing communications strategies about gene transfer for advocacy organizations and researchers in the public realm and the persisting concerns about media reports of novel health technologies, one important and potentially more malleable source of information in the public

sphere is patient advocacy organization web sites. These web sites are often accessed by the public and by patients and their families. In my study I describe the unique position of patient advocates, as they must engage in promotional communications to raise funds for research, but at the same time also provide patient support, and thus temper communications of promise to avoid raising excessive patient hopes. The latter role of ensuring patient support may render patient advocacy organizations receptive to ensuring conscientious communications about gene transfer. Research raises concerns about the content of patient advocacy web sites, particularly with respect to therapeutic claims (Di Pietro, Whiteley, & Illes, 2012; Di Pietro, Whiteley, Mizgalewicz, & Illes, 2012). Future research could investigate the content of patient advocacy web sites to make recommendations about how to help patient advocacy communications educate patients about gene transfer in an effort to mediate the impact of errors of omission and the therapeutic discourse in the media.

The growth of Web 2.0 platforms such as blogs, wikis, and other forms of social media has transformed the unidirectional flow of information that traditionally characterized Web 1.0 venues, into an interactive communication platform (Black, 2007; Cooke & Buckley, 2008). Web 2.0 venues, thus, present unregulated sources of information about gene transfer. These interactive venues are often afforded through patient advocacy web sites or Facebook groups. Future research could utilize an ethnographic approach to examine the inter-personal communications of CHM patients in Web 2.0 venues. This research would yield a better understanding of the informational needs of patients about gene transfer research.

Finally, to continue the assessment of patient information needs, emerging ocular gene transfer clinical trials present an opportunity to follow the experiences of patients as they enter phase I clinical trials. An understanding of patient experiences as they participate in a gene transfer clinical trial could enhance communications about these trials and improve the informed consent process for future trials.

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APPENDICES

Appendix I: University of Alberta Health Research Ethics Board Study Approval Letter

Health Research Ethics Board

308 Campus Tower
University of Alberta, Edmonton, AB T6G 1K8
p. 780.492.9724 (Biomedical Panel)
p. 780.492.0302 (Health Panel)
p. 780.492.0459
p. 780.492.0839
f. 780.492.9429

Approval Form

Date:	May 4, 2011
Principal Investigator:	Tania Bubela
Study ID:	Pro00019863
Study Title:	Genetic Risk Communication to Vulnerable Population: A Case Study of Gene Therapies for Retinal Dystrophies
Approval Expiry Date:	May 2, 2012

Thank you for submitting the above study to the Health Research Ethics Board - Health Panel . Your application, including revisions received April 19, 2011, has been reviewed and approved on behalf of the committee.

A renewal report must be submitted next year prior to the expiry of this approval if your study still requires ethics approval. If you do not renew on or before the renewal expiry date, you will have to re-submit an ethics application.

Approval by the Health Research Ethics Board does not encompass authorization to access the patients, staff or resources of Alberta Health Services or other local health care institutions for the purposes of the research. Enquiries regarding Alberta Health Services administrative approval, and operational approval for areas impacted by the research, should be directed to the Alberta Health Services Regional Research Administration office, #1800 College Plaza, phone (780) 407-6041.

Sincerely,

Dr. Jana Rieger
Chair, Health Research Ethics Board - Health Panel

Note: This correspondence includes an electronic signature (validation and approval via an online system).

UNIVERSITY OF ALBERTA Alberta Health Services Covenant Health

Appendix II: Alberta Health Services Operational Approval Letter

Alberta Health Services

APPLICATION FOR
OPERATIONAL APPROVAL
to Conduct Research at Alberta Health Services

NACTRC
The Northern Alberta Clinical Trials and Research Centre

ROYAL ALEXANDRA HOSPITAL
OPHTHALMOLOGY

RESEARCH TITLE:

Genetic Risk Communication to Vulnerable Population: A Case Study of Gene Therapies for Retinal Dystrophies

Expected Start Date:	2011-06-01
Expected End Date:	2013-12-31
Expected Number of Research Subjects:	44
Research Category:	Observational
Research Type:	Qualitative

PI INFORMATION:

Name:	Tania Bubela
Zone:	Edmonton
Faculty:	School of Public Health
Phone:	780-935-5223
Email:	tania.bubela@ualberta.ca

PRIMARY CONTACT: Student

Name:	Shelly Benjaminy
Zone:	Edmonton
Phone:	780-710-9325
Email:	sbenjami@ualberta.ca

AREA IMPACT:

1) Will AHS staff from this area be expected to participate and/or carry out any duties related to this study?

Yes We will be recruiting the participation of ophthalmologists and genetic counselors with expertise in patient care in the area of ocular genetics, particularly in hereditary retinal dystrophies. Participants will be recruited on a voluntary basis, and will be asked to contribute 45 minutes to an hour of their time to be interviewed. The interview guide is designed to elicit responses about how best to communicate information about genetic risk in light of gene therapy trials to patients affected by genetic retinal dystrophies.

2) Will AHS staff from this area require any training or education?

No

3) Are you expecting this AHS area to provide you with supplies and/or equipment?

No

4) Funding Type: Investigator-Initiated / Internal and/or Contingency Funding

NOTE: If the area being impacted determines that there are costs associated with your research, they will contact you prior to issuing Operational Approval.

QUESTIONS SPECIFIC TO THE AREA:

PROTOCOL SYNOPSIS:

Gene therapies present novel possibilities in health care, and exist in a culture of hype. The goal of this study is to investigate the nature of genetic risk communications and perceptions in light of gene therapies. 22 patients affected by ocular genetic disorders under the investigation of gene therapy clinical trials, and 22 clinicians responsible for the care of patients with these disorders will be interviewed. The interviews will be semi- structured and based on a grounded-theoretical framework. This project may contribute to the field of genetic risk communication by increasing knowledge about the state of risk perceptions and clinical care expectations of patients with ocular genetic disorders in light of gene therapy trials. This information may be used to construct guidelines of best practice for communications about a potential cure for chronic genetic diseases and to improve clinical care outcomes for genetics patients.

SUBMITTED BY / ASSESSORS / APPROVERS:

Requested By: Tania Bubela Date Requested: 2011-05-24

Assessed By: Susan Young Date Assessed: 2011-05-25

Appendix III: Clinician/ Patient Advocate Recruitment Letter

DATE

Dear <Name>;

As Investigators on the project titled *Genetic Risk Communication with Vulnerable Populations: A Case Study of Gene Therapies for Retinopathies*, we are writing to request your participation in one interview of approximately forty-five minutes to one hour in length. Our team is carrying out an analysis of communications in light of gene therapy trials with patient populations and their families who are affected by genetic retinopathies.

We are conducting interviews with clinicians, researchers, patient advocacy organizations, as well as patients and families affected by choroideremia or Leber congenital amaurosis. As an expert in the (*insert appropriate field*), we would appreciate the contribution of your views and opinions to our study. The benefits of your participation include the opportunity to provide feedback on the issues surrounding communications with affected populations about gene therapy trials, which could facilitate their translation and regulation.

Your identity will remain confidential, as results will be de-identified or described in the aggregate.

If you would be interested in participating or would like additional information, please contact:

Shelly Benjaminy	OR	Dr. Tania Bubela
Department of Public Health Sciences		Department of Public Health Sciences
University of Alberta		University of Alberta
(780) 492-6408		(780) 492-9335
sbenjami@ualberta.ca		tbubela@ualberta.ca

We thank you for your consideration and we look forward to your participation in this research effort.

Sincerely,

Tania Bubela
Associate Professor, Department of Public Health Sciences
University of Alberta

Ian MacDonald
Professor and Chair, Department of Ophthalmology, University of Alberta

Appendix IV: Patient Recruitment Letter

Alberta Health Services

DATE

Dear PATIENT,

I am contacting you to inform you of a research project that you are eligible to participate in. This research aims to study the views of choroideremia patients about gene therapy clinical trials for genetic eye diseases. The goal of this research is to identify how to best communicate genetic information about eye conditions and the risks and benefits of gene therapy. This research is conducted through the Departments of Public Health Sciences and Ophthalmology at the University of Alberta. For more information about the study, please refer to the appended information sheet.

Your participation in this research project is voluntary. You may decide if you would like to participate with no consequence to your clinical care. Additionally, participation in this research project will not promote preferred access to therapeutic interventions.

Your personal information will not be released to the investigators of this research project without your consent. If you are interested in asking more questions about this research or would like to participate, please contact:

Shelly Benjaminy
Department of Public Health Sciences
University of Alberta
(780) 492-3013
sbenjami@ualberta.ca

OR

Dr. Tania Bubela
Department of Public Health Sciences
University of Alberta
(780) 492-9335
tbubela@ualberta.ca

Sincerely,

Ian M. MacDonald, MD CM

Appendix V: Website Recruitment Notice for Patients

Do you have choroideremia?
Genetic Risk Communication: Case Study of Gene Therapies for Retinal Dystrophies

The Study: We are conducting a study about communicating genetic risks for hereditary eye conditions in with the Departments of Public Health Science and Ophthalmology at the University of Alberta, Canada .

Participants: We are recruiting patients who are affected by choroideremia (affected males). All participants must be over the age of 18. You will be interviewed for about 45 minutes to an hour about where you get information about your eye condition, how you balance living with your eye condition, and about how you feel about gene therapies.

Confidentiality: Your responses will be de-identified or described in the aggregate and therefore remain confidential.

Consent: Your participation in this research project is voluntary. You may decide if you would like to participate with no consequence to your clinical care. Additionally, participation in this research project will not promote preferred access to therapeutic interventions.

Please Contact: Shelly Benjaminy
sbenjami@ualberta.ca
(1-780) 492-3013

Appendix VI: Patient Recruitment Poster

Do you or your family members have Leber congenital amaurosis or choroideremia?
Genetic Risk Communication: Case Study of Gene Therapies for Retinal Dystrophies

The Study: We are conducting a study about communicating genetic risks for hereditary eye conditions in with the Departments of Public Health Science and Ophthalmology .

Participants: We are recruiting patients who are affected by either choroideremia or Leber congenital amaurosis as well as the unaffected family members of these patients. All participants must be over the age of 18. You will be interviewed for about 45 minutes to an hour about where you get information about your eye condition, how you balance living with your eye condition, and about how you feel about gene therapies.

Location:

Royal Alexandra Hospital Research
10240 Kingsway NW Edmonton

Katz Group Centre for Pharmacy and Health
87 Avenue 114 Street NW Edmonton

Please Contact: Shelly Benjaminy
sbenjami@ualberta.ca
(780)710-9325

Shelly Benjaminy
sbenjami@ualberta.ca
(780) 492-6408

Appendix VII: Information Sheet for Patients

INFORMATION SHEET for the University of Alberta Research Project:

Communicating the Risks and Benefits of Ocular Gene Therapy

Purpose: This research project is done to understand how to best communicate genetic information about eye conditions and the risks and benefits of gene therapy. Gene therapy is now in early stages of clinical trials for some eye conditions.

Background: At this time there are many advances in genetic technologies and research, but most patients with genetic diseases still don't receive treatment. Up to now, clinical genetics has focused on prevention, diagnosis and management. Now, there is some potential for gene therapy to treat genetic eye conditions. We are interested in helping clinicians and the media communicate the risks and benefits of gene therapy to patients, their families, and the general public.

What will you be asked to do?

A project researcher will interview you. This interview will take approximately three-quarters to one hour of your time. We will give you the option to review our notes on your comments, and you may request to receive the final report by providing your contact information on the last page.

What type of personal information will be collected?

Should you agree to participate in this study you will be asked to express your point of view and tell us about your experiences with choroideremia. We will ask your permission to audio record our conversation. You may request the audio recording device to be shut off at any time.

Are there risks or benefits for participating?

You may find some of the questions upsetting. If you feel uncomfortable answering any question you don't have to answer it. We are not aware of any long-term risks posed by participating in an interview. There are no costs for you to participate in this study, other than the investment of your time. The benefits include the opportunity to provide feedback on your experiences with choroideremia and to help us

understand how to improve clinical care for patients with genetic diseases.

Participation:

Participation in this research is voluntary. If you choose not to participate or if you choose to withdraw from the study, you will continue to have access to the same quality of clinical care. Participation in this research will not promote access to therapeutic interventions that are not standard-of-care.

Withdrawal from the study:

Even after you have agreed to participate in the interview you can decide at any point that you do not wish to continue. You may decide that you do not want what you said to be used up until the time the results of this study are put together for publication. The researchers then cannot use this information and it will be destroyed.

Confidentiality:

The information you provide will be de-identified by being assigned a number rather then your name. The de-identified data will be made available to the study researchers working on this project. The audio recordings will be used for research reference only. The data collected, including tapes, transcripts of tapes, and any notes, will be stored in a secure manner by the principal investigators and kept for 5 years after which the data will be destroyed.

Use of the Information:

From the results of this research, the researchers will make recommendations to clinicians and the media on the communication of genetic information about eye conditions and the risks and benefits of gene therapy. The results may also be used in academic presentations and be published in academic journals.

Contacts: This study is run by Shelly Benjaminy (Department of Public Health Sciences) and co-supervised by Drs Tania Bubela (Department of Public Health Sciences) and Ian MacDonald (Department of Ophthalmology).

If you have any further questions or want to clarification regarding this research and/or your participation, please contact:

Shelly Benjaminy
Public Health Sciences
University of Alberta
(780) 492-0392
sbenjami@ualberta.ca

OR

Dr. Tania Bubela
Public Health Sciences
University of Alberta
(780) 492-9335
tania.bubela@ualberta.ca

Additional Contacts:

The plan for this study has been reviewed for its adherence to ethical guidelines and approved by the University of Alberta Research Ethics Office. For questions regarding participant rights and ethical conduct of research, contact the University of Alberta Research Ethics Office at 492-2615.

Appendix VIII: Information Sheet for Patient Advocates

INFORMATION SHEET for the University of Alberta Research Project:

Communicating the Risks and Benefits of Ocular Gene Therapy

Purpose: This research project is done to understand how to best communicate genetic information about eye conditions and the risks and benefits of gene therapy. Gene therapy is now in early stages of clinical trials for some eye conditions.

Background: At this time there are many advances in genetic technologies and research, but most patients with genetic diseases still don't receive treatment. Up to now, clinical genetics has focused on prevention, diagnosis and management. Now, there is some potential for gene therapy to treat genetic eye conditions. We are interested in helping clinicians and the media communicate the risks and benefits of gene therapy to patients, their families, and the general public.

What will you be asked to do?

A project researcher will interview you. This interview will take approximately three-quarters to one hour of your time. We will give you the option to review our notes on your comments, and you may request to receive the final report by providing your contact information on the last page.

What type of personal information will be collected?

Should you agree to participate in this study you will be asked to express your point of view and tell us about your organization's experiences with genetic retinopathies. We will ask your permission to audio record our conversation. You may request the audio recording device to be shut off at any time.

Are there risks or benefits for participating?

You may find some of the questions upsetting. If you feel uncomfortable answering any question you don't have to answer it. We are not aware of any long-term risks posed by participating in an interview. There are no costs for you to participate in this study, other than the investment of your time. The benefits include the opportunity to provide feedback

on your experiences with genetic retinopathies and to help us understand how to improve clinical care for patients with genetic diseases.

Participation:

Participation in this research is voluntary. If you choose not to participate or if you choose to withdraw from the study, you, your family or members of your organization will continue to have access to the same quality of clinical care. Participation in this research will not promote access to therapeutic interventions that are not standard-of-care.

Withdrawal from the study:

Even after you have agreed to participate in the interview you can decide at any point that you do not wish to continue. You may decide that you do not want what you said to be used up until the time the results of this study are put together for publication. The researchers then cannot use this information and it will be destroyed.

Confidentiality:

The information you provide will be de-identified by being assigned a number rather then your name. The de-identified data will be made available to the study researchers working on this project. The audio recordings will be used for research reference only. The data collected, including tapes, transcripts of tapes, and any notes, will be stored in a secure manner by the principal investigators and kept for 5 years after which the data will be destroyed.

Use of the Information:

From the results of this research, the researchers will make recommendations to clinicians and the media on the communication of genetic information about eye conditions and the risks and benefits of gene therapy. The results may also be used in academic presentations and be published in academic journals.

Contacts: This study is run by Shelly Benjaminy (Department of Public Health Sciences) and co-supervised by Drs Tania Bubela (Department of Public Health Sciences) and Ian MacDonald (Department of Ophthalmology).

If you have any further questions or want to clarification regarding this research and/or your participation, please contact:

Shelly Benjaminy Public Health Sciences University of Alberta (780) 492-6408 sbenjami@ualberta.ca	OR	Dr. Tania Bubela Public Health Sciences University of Alberta (780) 492-9335 tbubela@ualberta.ca

Additional Contacts:

The plan for this study has been reviewed for its adherence to ethical guidelines and approved by the University of Alberta Research Ethics Office. For questions regarding participant rights and ethical conduct of research, contact the University of Alberta Research Ethics Office at 492-2615.

Appendix IX: Information Sheet for Clinicians

INFORMATION SHEET for the University of Alberta Research Project:

Communicating the Risks and Benefits of Ocular Gene Therapy

Purpose: This research project is done to understand how to best communicate genetic information about eye conditions and the risks and benefits of gene therapy. Gene therapy is now in early stages of clinical trials for some eye conditions.

Background: At this time there are many advances in genetic technologies and research, but most patients with genetic diseases still don't receive treatment. Up to now, clinical genetics has focused on prevention, diagnosis and management. Now, there is some potential for gene therapy to treat genetic eye conditions. We are interested in helping clinicians and the media communicate the risks and benefits of gene therapy to patients, their families, and the general public.

What will you be asked to do?

A project researcher will interview you. This interview will take approximately three-quarters to one hour of your time. We will give you the option to review our notes on your comments, and you may request to receive the final report by providing your contact information on the last page.

What type of personal information will be collected?

Should you agree to participate in this study you will be asked to express your point of view and tell us about your clinical and research experiences with genetic retinopathies undergoing gene therapy trials. We will ask your permission to audio record our conversation. You may request the audio recording device to be shut off at any time.

Are there risks or benefits for participating?

You may find some of the questions upsetting. If you feel uncomfortable answering any question you don't have to answer it. As the number of expert clinicians and researchers involved in the area of ocular genetics is small, there may be a risk that someone may recognize your opinions, even though we will de-identify you when presenting data. We are not

aware of any long-term risks posed by participating in an interview. There are no costs for you to participate in this study, other than the investment of your time. The benefits include the opportunity to provide feedback on your experiences with genetic retinopathies and to help us understand how to improve clinical care for patients with genetic diseases.

Participation:

Participation in this research is voluntary and you may choose whether you would like to participate or withdraw without consequence.

Withdrawal from the study:

Even after you have agreed to participate in the interview you can decide at any point that you do not wish to continue. You may decide that you do not want what you said to be used up until the time the results of this study are put together for publication. The researchers then cannot use this information and it will be destroyed.

Confidentiality:

The information you provide will be de-identified by being assigned a number rather then your name. The de-identified data will be made available to the study researchers working on this project. The audio recording device will be used for research reference only. The data collected, including audio recordings, transcripts of recordings, and any notes, will be stored in a secure manner by the principal investigators and kept for 5 years after which the data will be destroyed.

Use of the Information:

From the results of this research, the researchers will make recommendations to clinicians and the media on the communication of genetic information about eye conditions and the risks and benefits of gene therapy. The results may also be used in academic presentations and be published in academic journals.

Contacts: This study is run by Shelly Benjaminy (Department of Public Health Sciences) and co-supervised by Drs Tania Bubela (Department of Public Health Sciences) and Ian MacDonald (Department of Ophthalmology).

If you have any further questions or want to clarification regarding this research and/or your participation, please contact:

Shelly Benjaminy Public Health Sciences University of Alberta (780) 492-0392 sbenjami@ualberta.ca	OR	Dr. Tania Bubela Public Health Sciences University of Alberta (780) 492-9335 taniabubela@ualberta.ca

Additional Contacts:

The plan for this study has been reviewed for its adherence to ethical guidelines and approved by the University of Alberta Research Ethics Office. For questions regarding participant rights and ethical conduct of research, contact the University of Alberta Research Ethics Office at 492-2615.

Appendix X: Consent Form

CONSENT FORM

To Participate in the University of Alberta Research Project:

Genetic Risk Communication: Case Study Gene Therapy for Genetic Retinal Dystrophies

Investigator:
Shelly Benjaminy
Department of Public Health Sciences
University of Alberta
(780) 492-0392
sbenjami@ualberta.ca

Do you understand that you have been asked to be in a research study? Yes No

Have you read and received a copy of the attached Information Sheet? Yes No

Do you understand the benefits and risks involved in taking part in this Yes No research study?

Have you had an opportunity to ask questions and discuss this study? Yes No

Do you understand that you can quit taking part in this study at any time without giving a reason? Yes No

Has the issue of confidentiality been explained to you? Yes No

Do you consent to being audio recorded? Yes No

Do you understand who will have access to the records from this interview? Yes No

Do you understand that the information you provide will be used to make recommendations for communicating genetic risk in health settings? Yes No

Can we use this information in the future for presentations and publications? Yes No

This study was explained to me by: _____

I agree to take part in this study.

_____

Signature of Research Participant Date Printed Name

I would like to receive a copy of research results (check one): ☐ No
☐ Yes

If you would like to receive a copy of the research results please provide us with your address:

_____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

_____

Signature of Investigator Date

Appendix XI: Interview Guide for Patients

Preamble

First of all, I would like to thank you very much for taking the time to talk to me about your experiences. They will assist us in helping clinicians and the media communicate about genetic information for eye conditions and the risks and benefits of gene therapy.

I would like to remind you that you are not obligated by to participate in this research. You may tell me as little or as much information as you feel comfortable with. In addition, you may choose to end this interview at any point. Choosing not to participate or withdraw from this interview will not affect your clinical care in any form.

I am going to ask you questions about your experiences with [*insert name of genetic retinal dystrophy* [16]] and about gene therapy. Your experiences will later be analyzed to help us understand how to improve genetic risk communication strategies surrounding gene therapy.

General info

1. Tell me a little bit about yourself [ie. Family, profession, hobbies etc…]
2. Tell me about your history with [*insert name of genetic retinal dystrophy*]

Understanding of and living with the disease

3. Can you explain your understanding of [*insert name of genetic retinal dystrophy*]? [PROMPT ON CAUSES AND DISEASE COURSE]
4. How did your doctor explain [*insert name of genetic retinal dystrophy*] to you when you were first diagnosed?
5. What current care are you receiving for [*insert name of genetic retinal dystrophy*]?
6. Can you tell me about your emotional responses from learning the news to living with [*insert name of genetic retinal dystrophy*]?
7. What hopes do you have for the future?

Awareness of gene therapy trial/ CHM research

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[1]This is a semi-structured interview guide. The nature of this guide may require some follow up probing questions as to further explore participants' responses. The inherent flexibility of this semi-structured interview guide may result in some variance in question wording or probing while keeping with the spirit of the interview guide topics.

[2] Genetic retinal dystrophies include choroideremia, Leber congenital amaurosis,

8. What have you heard about efforts to treat [*insert name of genetic retinal dystrophy*]?
9. Have you heard of gene therapy trials to treat ocular genetic conditions?

Risk/benefit perception

10. If you were given the chance to participate in a gene therapy trial, what might be some advantages?
11. If you were given the chance to participate in a gene therapy trial, what would be some of your worries?
12. If you were given the opportunity to participate in a gene therapy trial, how do you feel this therapy might affect your life both practically and emotionally?

PART 2

Now, with your permission, I am going to switch gears and ask you about various sources of information on [*insert name of genetic retinal dystrophy*] that you have been exposed to. This will help us understand where you get information about [*insert name of genetic retinal dystrophy*], what you think about the quality of that information, and its impact on you.

Source of information- provide questionnaire

Media

1. Have you seen or heard any media coverage of [*insert name of genetic retinal* dystrophy]

If yes →

a. Can you remember the source and approximately when it was?
b. Could you describe what the coverage was about?
c. What were your impressions of the content of the coverage? [PROMPT ON ACCURACY AND TRUST]
d. How did the coverage make you feel?

3. Have you seen any media coverage of gene therapy?

If yes →

a. Can you remember the source and approximately when it was?
b. Could you describe what the coverage was about?
c. What were your impressions of the content of the coverage? [PROMPT ON ACCURACY AND TRUST]
d. How did the coverage of gene therapy make you feel?
e. Would this coverage play any role in your decision to participate in the gene therapy trial if it were available?

Now I am going to show you the most viewed news clip on YouTube on a gene therapy trial for Leber congenital amaurosis involving the perspectives of a participant's family and ask you some questions about it.
http://www.youtube.com/watch?v=H0RvTOF1fEc

4. Have you seen this clip before?
5. What is your overall impression of the clip and how does it make you feel?
6. Is there anything that stood out for you?
7. How does this clip make you feel about potentially participating in a gene therapy trial if it were available to you?

Appendix XII: Interview Guide for Patient Advocates

Preamble

First of all, I would like to thank you very much for taking the time to talk to me about your experiences. They will assist us in helping clinicians and the media communicate about genetic information for eye conditions and the risks and benefits of gene therapy.

I would like to remind you that you are not obligated to participate in this research. You may tell me as little or as much information as you feel comfortable with. In addition, you may choose to end this interview at any point.

I am going to ask you questions about your organization's experiences with [*insert name of genetic retinal dystrophy* [17]] and gene therapy. These experiences will later be analyzed to help us understand how to improve genetic risk communication strategies surrounding gene therapy.

General

1. Tell me about the organization/ your role in it
1. How do you serve your membership?

Supporting Membership

2. Does [*insert organization name*] provide support to its members about managing their lives with their disease? If so, in what ways?

Stance on Gene Therapy

3. Does [*insert organization name*] have a stance on gene therapy?
    a. In case of supportive stance:
        - How does [*insert organization name*] support gene therapy?
        - What are [*insert organization name*]'s hopes for gene therapy efforts?
    b. In case of unsupportive stance: Why is [*insert organization name*] unsupportive of gene therapy?

---

[1] This is a semi-structured interview guide. The nature of this guide may require some follow up probing questions as to further explore participants' responses. The inherent flexibility of this semi-structured interview guide may result in some variance in question wording or probing while keeping with the spirit of the interview guide topics.

[17] Genetic retinal dystrophies include choroideremia, Leber congenital amaurosis,

Communication with Members

4. What kind of information do you provide your members about [*insert name of genetic retinal dystrophy*]?
5. What methods do you employ to inform your members about [*insert name of genetic retinal dystrophy*]?
6. Does your membership ask you about potential interventions for [*insert name of genetic retinal dystrophy*]?
7. Do you provide your membership with information regarding gene therapy?
8. If yes, what information do you provide? (Could you provide me with a copy of this material?)

PART 2

Now, with your permission, I am going to switch gears and ask you about various sources of information on [*insert name of genetic retinal dystrophy*] that you have been exposed to. This will help us understand where you get information about [*insert name of genetic retinal dystrophy*], what you think about the quality of that information, and its impact on your organization and membership.

Source of information- provide questionnaire

Media

1. Have you seen or heard any media coverage of [*insert name of genetic retinal dystrophy*]

If yes →

a. Can you remember the source and approximately when it was?
b. Could you describe what the coverage was about?
c. What were your impressions of the content of the coverage? [PROMPT ON ACCURACY AND TRUST]
d. How did the coverage make you feel?

3. Have you seen any media coverage of gene therapy?

If yes →

a. Can you remember the source and approximately when it was?
b. Could you describe what the coverage was about?
c. What were your impressions of the content of the coverage? [PROMPT ON ACCURACY AND TRUST]
d. How did the coverage of gene therapy make you feel?

Now I am going to show you the most viewed news clip on YouTube on a gene therapy trial for Leber congenital amaurosis involving the perspectives of a participant's family and ask you some questions about it.
http://www.youtube.com/watch?v=H0RvTOF1fEc

4. Have you seen this clip before?
5. What is your overall impression of the clip and how does it make you feel?

6. Is there anything that stood out for you?
7. How does this clip make you feel about gene therapy?

Appendix XIII: Interview Guide for Clinicians

Preamble

First of all, I would like to thank you very much for taking the time to talk to me about your experiences. They will assist us in helping clinicians and the media communicate about genetic information for eye conditions and the risks and benefits of gene therapy.

I would like to remind you that you are not obligated to participate in this research. You may tell me as little or as much information as you feel comfortable with. In addition, you may choose to end this interview at any point.

I am going to ask you questions about your experiences with [*insert name of genetic retinal dystrophy* [18]] and gene therapy. Your experiences will later be analyzed to help us understand how to improve genetic risk communication strategies surrounding gene therapy.

General info

1. Tell me a little bit about your research/ practice
2. How did you get involved in this field?

Communication with Patients

3. How do you explain [*insert name of genetic retinal dystrophy*] to your patients when they are diagnosed?
4. What are the questions that your patients ask you regarding [*insert name of genetic retinal dystrophy*]?

Patient Expectations

5. What kinds of expectations do your patients express to you about their clinical care?

Living with a genetic retinopathy

6. How do you help patients manage with their diagnosis?

---

[1] This is a semi-structured interview guide. The nature of this guide may require some follow up probing questions as to further explore participants' responses. The inherent flexibility of this semi-structured interview guide may result in some variance in question wording or probing while keeping with the spirit of the interview guide topics.

[2] Genetic retinal dystrophies include choroideremia, Leber congenital amaurosis,

7. How do you help patients balance their lives with their disease?

Gene Therapy

8. What is your opinion of the current state gene therapy efforts for [*insert name of genetic retinal dystrophy*]?
9. What are your expectations for gene therapies in treating ocular genetic diseases in the future?

Patients and Gene Therapy

10. Do patients ask you questions about gene therapy for ocular genetic diseases?
11. What do you tell them?

PART 2

Now, with your permission, I am going to switch gears and ask you about various sources of information on [*insert name of genetic retinal dystrophy*] that your patients have been exposed to. This will help us understand where your patients get information about [*insert name of genetic retinal dystrophy*], what you think about the quality of that information, and its impact on you and your patients.

Knowledge Translation

1. Who is best positioned to communicate about research on gene therapy?
2. In your opinion, how should research on gene therapy be communicated to manage the expectations of patients and the public?

Media Coverage of gene therapy

3. Has your practice or research ever been covered in the media and if so what did you think of the coverage? [PROMPT ON TECHNICAL ACCURACY AND OVERALL MESSAGE]
4. Have you seen any coverage of gene therapy in the media and, if so,
   a. How accurately did the media portray gene therapy?
   b. In what light did the media portray gene therapy?

Sources of information- provide questionnaire

5. How do you perceive that this external information affects your patients' expectations, hopes or coping strategies, if at all? [PROMPT ON DIFFERENCES IN SOURCES]

Appendix XIV: Confidentiality Agreement for Hired Study Personnel

Project title - Genetic risk communication with vulnerable populations: A case study of gene therapies for retinal dystrophies

I, _____,
the _____
(specific job description, e.g., interpreter/translator)
have been hired to _____

I agree to -

1. keep all the research information shared with me confidential by not discussing or sharing the research information in any form or format (e.g., disks, tapes, transcripts) with anyone other than the members of Dr. Tania Bubela's research team.

2. keep all research information in any form or format (e.g., disks, tapes, transcripts) secure while it is in my possession.

3. return all research information in any form or format (e.g., disks, tapes, transcripts) to Dr. Bubela when I have completed the research tasks.

4. after consulting with Dr. Bubela, erase or destroy all research information in any form or format regarding this research project that is not returnable to Dr. Bubela (e.g., information stored on computer hard drive).

_____

(Print Name) (Signature) (Date)

Researcher(s)

_____

(Print Name) (Signature) (Date)

Appendix XV: Ocular Gene Transfer Coding Frame

1. Basic Information

a. Country

US
UK
Canada

b. The Name of the Newspaper

(e.g, Globe and Mail, National Post, Washington Post, The Independent, etc.)

c. Enter the date of the article

(Day-Month-Year e.g., 17-Jul-2001)

2. Attention Structure

With these variables we are measuring the editorial importance of an article; the means used to attract the reader's attention.

a. Newspaper Section

Type name of newspaper section (e.g, Lifestyle, Business, National News)

b. Newspaper Section Number

(e.g., A, H, F)

c. Page Number

d. Word count for the article

Number of words

e. News Format

Here we are attempting to distinguish between facts and opinion

1. Article with latest News
2. Investigation, reportage, background
3. Interview (mainly)
4. Column, commentary by regular columnist
5. Editorial (paper's editor)
6. Commentary from other people (e.g., politicians, religious leaders, special interest groups)
7. Letters to the editor
8. Review of books, films etc.
9. Other

3. Disease

Name the disease the article is about

4. Voices

Who/what is the main spokesperson/group/institution quoted or described?

1. Not applicable, unknown
2. Affected individuals
3. Family members of affected
4. Friends of affected
5. Public Sector Researchers
6. Parliament/Congress
7. Ethics committees
8. National patent offices
9. Judicial, legal voice
10. The Public, public opinion (e.g., surveys)
11. The media, published opinion
12. Celebrity (sports, film TV)
13. Scientists in private laboratories
14. Biotechnology Company/Spokesperson
15. CEO or upper management
16. Venture Capital
17. Private Investors
18. Stock Exchange
19. Political parties
20. Religious organizations
21. Patient Groups/Lobbies
22. Professional organizations (medical, legal etc.)
23. Developing countries
24. European Union
25. European Parliament
26. United Nations Organizations
27. Other International Organizations
28. Other

5. Personal Interest Story

a. Is this article framed as a personal interest story?

1. Yes
2. No

b. If personal interest, what frame?

1. patient victim/sympathy/fearful
2. patient frustration/helplessness/fatalism
3. patient hero/empowerment
4. patient hope
5. family victim/sympathy/fearful
6. family frustration/helplessness/fatalism
7. family hero/empowerment
8. family hope
9. clinician/scientist frustration/helplessness/fatalism
10. clinician/scientist hero
11. clinician/scientist hope
12. Other

6. Tone

What is the tone of GT representation in the article?

1. Positive
2. Neutral
3. Negative

7. Controversy

a. Is the article framed as a controversy?

1. Yes
2. No

b. If controversy, how was it presented?

1. Controversy is presented in imbalanced manner in a positive light
2. Controversy is presented in a balanced manner
3. Controversy is presented in imbalanced manner in a negative light

8. Funding Sources

Are funding sources discussed?

1. Yes
2. No

9. Conflict of Interest

Are conflicts of interest discussed?

1. Yes
2. No

10. GT Methods

a. Does the article clearly state that gene therapy is research?

1. Not mentioned
2. Conflation between research and treatment (e.g, mentioned, but interchangeably called "treatment")
3. Clearly mentioned

b. Does the article mention the gene mutation causing the disease?

1. Yes
2. No

c. Does that article mention that GT transfers a working copy of the mutated gene to ameliorate the disease?

1. Yes
2. Yes, but incorrect/misleading terminology (e.g, gene replacement)
3. No

d. Does the article mention the modified viral vector used to transport the gene into the eye?

1. Yes
2. Yes, but viral modification not mentioned
3. No

e. Does the article explain that the working gene needs to be transferred to the back of the eye?

1. Yes
2. No

f. Does the article explain that GT involves eye surgery (e.g, needle to back of eye)

1. Yes
2. No

g. Are sample sizes of gene therapy trial stated?

1. Not applicable
2. Yes
3. No

h. Did the article indicate phase of clinical trial?

1. Not applicable
2. Yes
3. No

11. Risk/Benefit

a. Number of benefits

b. Number of risks

c. GT Visual Outcome Representations

Are visual outcomes as a result of gene therapy discussed?

1. Not applicable
2. Not mentioned
3. No visual benefit
4. Slow down vision loss
5. Halt vision loss
6. Partial reversal of lost vision/ improvement in vision
7. Cure
8. Treatment in general

d. GT Risks

Are the risks of gene therapy discussed?

1. Not applicable
2. Not mentioned
3. Historical adverse events
4. Eye health risk
5. General health risk
6. Economic risk
7. Legal risk
8. Ethical challenges
9. Social challenges
10. New research (but must be stated in cautionary tone)
11. Unknown risk
12. Efficacy concerns
13. Long timeframes
14. Quality of life concerns
15. Complexity

12. Time Frame Projection

a. Does the article make time frame projections for the application of GT?

1. Yes
2. No

b. If applicable, state year for commencement of human clinical trial

c. If applicable, state year for human clinical implementation

13. Public Health Claims

Does the article make public health claims about GT?

1. Yes
2. No

Appendix XVI: Report of Patient Interview Results- Clinical Interview Perspectives

CONFIDENTIAL

Communicating the Risks and Benefits of Gene Transfer

Report of Preliminary Results from Patient Interviews

Summary:
We are conducting a study about choroideremia (CHM) gene transfer (GT) communications. This research will facilitate the translation of GT from bench to bedside. You participated in an interview as a part of this study. In this document we discuss preliminary results based on patient interviews. We welcome your feedback about our findings. The preliminary research findings that we discuss in this report will be subject to change based on your feedback and on further analysis. You will receive a report of the final results. Please do not share these preliminary results.

Shelly Benjaminy
Tania Bubela
Ian MacDonald

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Our Study

Purpose:

- Hype and high hopes historically surrounded the field of gene transfer, also known as gene therapy (GT). These hopes were followed by high-profile failures.
- High-profile failures compromised public trust and threatened the support of funding and regulatory bodies.
- At this time, ocular GT clinical trials are emerging and necessitating responsible communication strategies to avoid hype. This will promote the sustainable translation of GT from bench to bedside.
- We are conducting a multi-stakeholder analysis of GT communications (see figure 1 for research overview) to develop these strategies.

Figure 1: Ocular Gene Transfer Communications Research Overview

Preliminary Results

We audio recorded and transcribed all interviews. After careful analysis of the transcripts, four key ideas stood out:

Hope:

- CHM GT clinical trials are renewing the hopes of patients for a treatment.
- Some patients experience a dissonance that is difficult to manage: hoping that CHM GT will become a treatment, but fearing disappointment.
- Some patients differentiate between hope and expectation to avoid disappointment.

CHM GT Risk:

- The main risk patients identify is vision loss.
  - Two main perspectives around risk of vision loss:
    - Some patients would be willing to risk vision loss because their vision is significantly deteriorated, so there is not much vision left to lose.
    - Other patients still have precious vision and would be hesitant to risk losing it.
- Some patients worry about adverse effects on the body.
- Some patients worry about GT surgical risks.
- Some patients worry because GT is new: this is the first time that GT is being tested on humans.
- Some patients are concerned because some CHM GT risks remain unknown.
- Many patients trust the clinicians and researchers working on CHM GT, and feel reassured about CHM GT despite the risks.

CHM GT Benefits:

- Many patients would like to participate in a CHM GT clinical trial with the hope that it will increase their quality of life.
- While most patients hope that CHM GT will stop vision loss, others hope that it will result in some visual improvement or a partial restoration of lost vision. Very few patients hope for a cure through GT.
- Patients hope that in the future, stem cell therapies will reverse vision loss or cure CHM.
- Some patients explain that if CHM GT would stabilize their vision, they would not have to worry about future vision loss.
- Many patients hope to personally benefit from CHM GT. Others hope that this intervention will be available in time for their grandchildren.
- Many patients want to participate in CHM GT because they would like to contribute to research, particularly because CHM is a rare disease.
- Patients would like to participate in a GT trial to help others with CHM, family members, or future generations.

Immediacy:

- Many patients have an immediate and definitive interest to participate in CHM GT.
- Many patients explain that they would be willing to make sacrifices (ex. financial, time, etc…) to participate in a CHM GT clinical trial.
- Many patients ask about possible ways to gain access to CHM GT.
- Patients are aware of their limited therapeutic window, and would like to know how long it will take until CHM GT is available in the clinic.

Call for contribution:

We thank you for sharing your perspectives with us during your interview. We value the expertise of our research participants and would appreciate and welcome your input about our preliminary results. To ask questions, make suggestions, or address any concerns please contact:

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Appendix XVII: Report of Patient Interview Results- Media Perspectives

CONFIDENTIAL

Communicating the Risks and Benefits of Gene Transfer

Report of Preliminary Results from Patient Interviews about Media

Summary:
You participated in a study about choroideremia (CHM) gene transfer (GT) communications by providing an interview. This study will facilitate the translation of GT from bench to bedside. In this document, we discuss preliminary results based on clinician interviews. We welcome your feedback about our findings, which will be subject to change based on your comments and on further analysis. You will receive a report of the final results. Please do not distribute these preliminary results.

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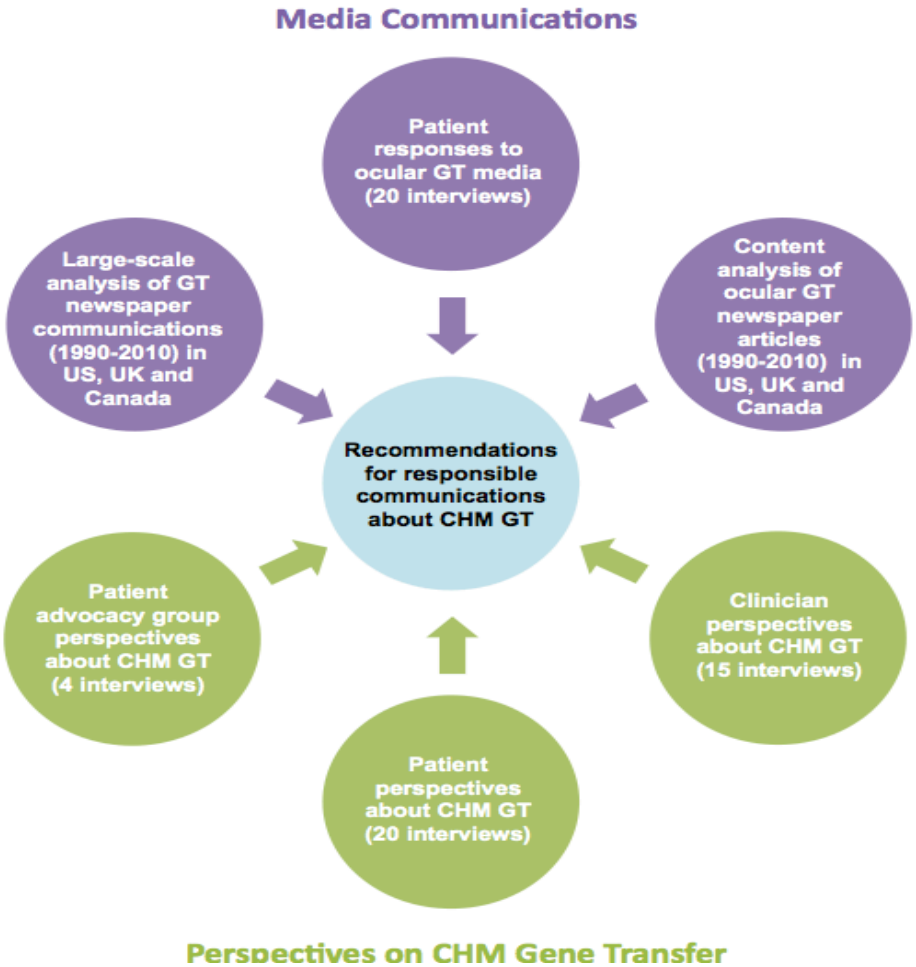
Our Study

Purpose:

- Historically, the field of GT gave rise to high expectations, which were followed by high-profile failures.
- High-profile failures compromised public trust and threatened the support of funding and regulatory bodies.
- At this time, success is being realized in early- stage ocular GT clinical trials. These necessitate responsible communication strategies about the risks and benefits of participating in ocular GT clinical trials.
- We are conducting a multi-stakeholder analysis of communications (see Figure 1 for research overview) to develop ethically grounded communication strategies.

Figure 1: Ocular Gene Transfer Communications Research Overview



Preliminary Results

In this portion of the interview, you were asked about your overall impression of media coverage about ocular GT. Following this discussion, you watched the most viewed YouTube video depicting Leber congenital amaurosis (LCA) GT, which covered the perspectives of study investigators, patient advocates, and patient families. Description of video in Box 1 to follow. Link to video: http://www.youtube.com/watch?v=H0RvTOF1fEc.

We audio recorded and transcribed all interviews. After careful analysis of the transcripts, the following key ideas stood out:

General Impressions about Ocular GT Media Coverage:

- Participants indicated that they trust media reporting about ocular GT to a certain extent.
- Many participants, however, believed that the media omits some details and simplifies stories about research.
- Other participants indicated that there is some inaccuracy in media coverage of ocular GT.
- Despite this skepticism, many participants indicated that media coverage about ocular GT is often positive. This is because many of the pieces are human-interest stories that are framed in a positive light.
- Other participants indicated that media attention on CHM is beneficial because it raises awareness and funding.
- Participants perspectives on media coverage closely resembled what we found in our analysis of newspaper coverage – the media does indeed frame most stories as personal interest stories and covers ocular GT in a very positive light with little mention of the risks. The media also focuses on potential therapeutic benefits even though the clinical trials are early stage and experimental.

Call for contribution:

We thank you for sharing your perspectives with us during your interview. We value the expertise of our research participants and would appreciate and welcome your input about our preliminary results. To ask questions, make suggestions, or address any concerns please contact:

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Box 1: YouTube clip description "New Hope for Gene Therapy: A Young Boy's Fight Against Blindness"

The video first introduces Corey Haas, a child affected by the rare genetic disease, LCA. Stephen Rose, PhD, Chief Research Officer of the Foundation Fighting Blindness then describes the pathophysiology of LCA with the aid of graphics of the affected retina. This clinical explanation is followed by the description of Nancy and Ethan Haas, Corey's parents, of their emotional journey following their son's LCA diagnosis. Jean Bennett, Professor at F.M. Kirby Center for Molecular Ophthalmology, scientist at Children's Hospital of Philadelphia, and an investigator on the phase I/II LCA gene transfer clinical trial then explains the experimental procedure. The explanation, along with a video simulating the procedure, depicts gene delivery using a viral vector to Corey's retina, the restoration of functional protein production, and the restoration of visual function in the treated eye. Nancy Haas then tearfully recalls how four days following surgery, for the first time, the sun hurt Corey's eyes. This is significant because LCA affects light perception. Dr. Bennett then comments on the success of this gene transfer clinical trial, and expresses her opinion that this success will only be one of many in the future. Dr. Rose also comments on the success of the trial, and explains that the restoration of vision as seen in Corey's case was a "real milestone". Finally, Dr. Bennett describes her overwhelming excitement in response to the success of the trial, giving credit to the patients as "the real pioneers". The video concludes with footage of Corey participating in activities requiring sight, such as throwing and catching a baseball with his father, riding a bicycle, and playing a video game on a Wii. The final screen states, "In 2009, Corey Haas completed his first full season of little league baseball".

Perspectives about Leber Congenital Amaurosis Video

- Participants related to the video emotionally, drawing parallels between their own experiences with vision loss and those of Corey.
- Participants felt hopeful about CHM GT after viewing the LCA clip.
- Some participants articulated worries about GT. In particular, participants worried that there is no guarantee that GT will work for CHM as well as it did for LCA.
- Some participants explained that they were afraid to be too hopeful about GT; they feared future disappointment if the trials do not result in visual benefit.
- Many patients explained that watching the LCA video made them feel very positive about GT, and that they would want to participate in a CHM GT clinical trial if it were available to them.
- This optimism means that clinicians must be very careful in explaining all the risks of participating in an experimental gene therapy trial so that consent to participate is well though through and fully informed.

Appendix XVIII: Report of Patient Advocate Interviews

CONFIDENTIAL

Report of Preliminary Results from Patient Advocate Interviews

Summary:
You participated in a study about choroideremia (CHM) gene transfer (GT) communications by providing an interview. This study will facilitate the translation of GT from bench to bedside. In this document, we discuss preliminary results based on clinician interviews. We welcome your feedback about our findings, which will be subject to change based on your comments and on further analysis. You will receive a report of the final results. Please do not distribute these preliminary results.

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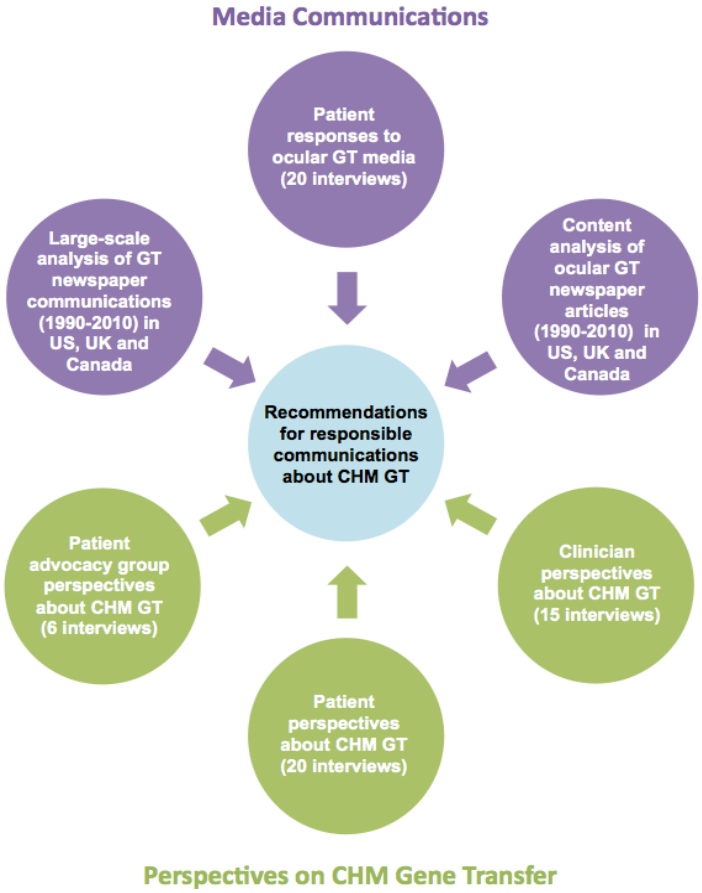
Our Study

Purpose:

- Historically, the field of GT gave rise to high expectations, which were followed by high-profile failures.
- High-profile failures compromised public trust and threatened the support of funding and regulatory bodies.
- At this time, success is being realized in early- stage ocular GT clinical trials. These necessitate responsible communication strategies about the risks and benefits of participating in ocular GT clinical trials.
- We are conducting a multi-stakeholder analysis of communications (see Figure 1 for research overview) to develop ethically grounded communication strategies.

Figure 1: Ocular Gene Transfer Communications Research Overview



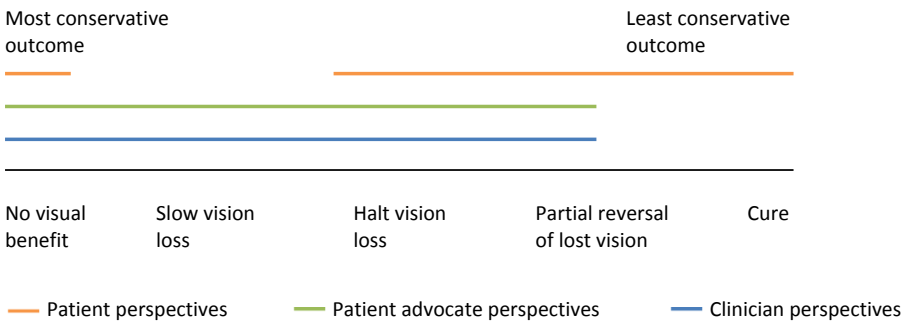
Preliminary Results

We conducted 6 interviews with representatives of patient advocacy organizations with expertise in genetic retinal dystrophies. Patient advocacy representatives displayed the most diverse perspectives of all the stakeholder groups interviewed. Patient advocates also indicated the most diverse stakes in GT: while some patient advocates were unaffected professional patient advocates, others were researchers, CHM patients, or had family members affected by CHM. We audio recorded and transcribed all interviews. After careful analysis of the transcripts several key ideas stood out:

Gene Transfer Benefits and Risks

- Patient advocates recognized that CHM GT is a research effort, and as such, it might not result in visual benefits.
- Patient advocates hoped that CHM GT would provide visual benefit. Visual benefit expectations ranged between slowing down the rate of vision loss to a partial reversal of lost vision (Figure 2).
- Patient advocates emphasized that regeneration of dead photoreceptors would not be possible through GT, therefore it is important to clarify to patients that in the future GT might offer a treatment but not a cure for CHM.
- Some patient advocates worried that patient questions are focused on gaining access to GT clinical trials, rather than about the risks involved in participation.

Figure 2: Multi-stakeholder visual outcome perspectives for choroideremia gene transfer clinical trials



Balance in Communications

- Patient advocates emphasized that their main goal is to raise funds for research.
- At the same time, patient advocates were also concerned with providing patient support.
- Some patient advocates explained that there is a fine balance between the promotional communications needed to generate funds for research and the more nuanced messaging necessary to avoid excessively raising patient hopes.

Time Frames for Clinical Application

- Patient advocates explained that patients have an urgency to access GT within their individual and limited therapeutic window.
- Some patient advocates explained that they are confused and frustrated as time frame estimates provided by clinical trial investigators are often delayed.
- Patient advocates identified that patients often ask how long it will take for GT to become clinically available.
- Patient advocates had a hard time answering this question:
    - Some patient advocates indicated that they couldn't predict a time frame.
    - Some patient advocates commented on the progress in clinical trials and explained that it is important to highlight this progress when speaking with patients about time frames.
    - Some patient advocates believed that GT would be available in time to provide visual benefit to young CHM patients, but not likely to be available in time for adults with advanced disease. Others hoped that GT would be available for them or for their affected family members.
    - Some patient advocates quantified expected time frames. These estimates ranged between 3-10 years.

Call for contribution:

We thank you for sharing your perspectives with us during your interview. We value the expertise of our research participants and would appreciate and welcome your input about our preliminary results. To ask questions, make suggestions, or address any concerns please contact:

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Appendix XIX: Report of Clinician Interviews

CONFIDENTIAL

Communicating the Risks and Benefits of Gene Transfer

Report of Preliminary Results from Clinician Interviews

Summary:
You participated in a study about choroideremia (CHM) gene transfer (GT) communications by providing an interview. This study will facilitate the translation of GT from bench to bedside. In this document, we discuss preliminary results based on clinician interviews. We welcome your feedback about our findings, which will be subject to change based on your comments and on further analysis. You will receive a report of the final results. Please do not distribute these preliminary results.

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Purpose:

- Historically, the field of GT gave rise to high expectations, which were followed by high-profile failures.
- High-profile failures compromised public trust and threatened the support of funding and regulatory bodies.
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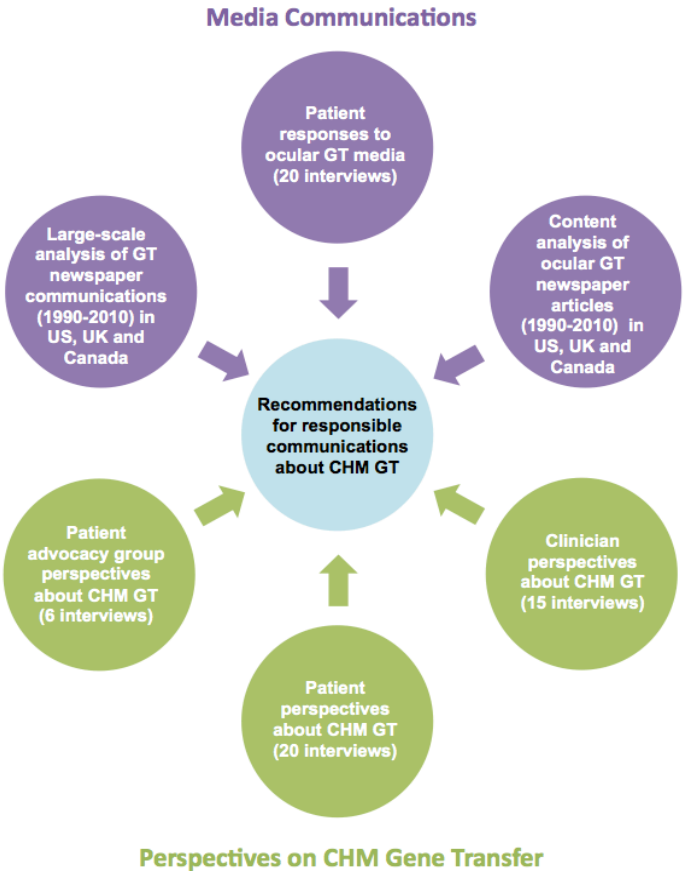


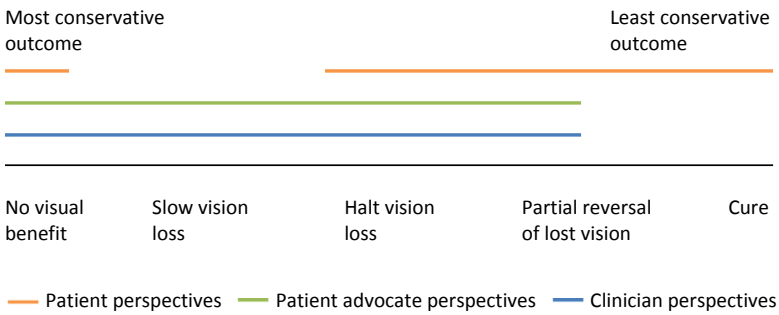
Preliminary Results

We conducted 15 interviews with experts in ocular genetic disease, including genetic counselors and ophthalmologists. We audio recorded and transcribed all interviews. After careful analysis of the transcripts several key ideas stood out:

Gene Transfer Benefits and Risks

- Clinicians hoped that CHM GT would provide visual benefit. Visual benefit expectations ranged between slowing down the rate of vision loss to a partial reversal of lost vision (Figure 2).
- Clinicians emphasized that regeneration of dead photoreceptors would not be possible through GT, therefore it is important to clarify to patients that in the future GT might offer a treatment but not a cure for CHM.
- Some clinicians did not believe that their patients have a nuanced understanding of what a treatment for CHM might mean practically, particularly in light of how the word "treatment" is used in the context of other diseases.
- Clinicians worried that patients do not prominently ask questions about the risks of GT and that the main patient concern is gaining access to therapeutic interventions through participating in a GT clinical trial.

Figure 2: Multi-stakeholder visual outcome perspectives for choroideremia gene transfer clinical trials



Time Frames for Clinical Application

- Clinicians identified that patients and patient advocates often ask how long it will take for GT to become clinically available.
- Clinicians had a hard time answering this question:
    - Some clinicians indicated that they couldn't predict a time frame.
    - Some clinicians commented on the progress in the field of ocular GT and explained that it is important to highlight this progress when speaking with patients about time frames.
    - Some clinicians quantified expected time frames. These estimates ranged between 3-10 years.

Clinicians Recommendations

1. Collaborative communications

- Clinicians highlighted that communication is a collective effort that requires engagement with a variety of stakeholders to facilitate responsible knowledge exchange.
    - Stakeholders include: clinical trial investigators, clinicians (ophthalmologists, geneticists, genetic counselors), patients, patient advocacy organizations, and the media.

2. Patient education

- Clinicians noted a discrepancy between expert communications and patient understanding.
- To address this discrepancy, it is important to communicate about the natural history of the disease and research efforts in lay language.
- To address a major gap in understanding of time frames, clinicians noted that an educational strategy, which clearly explains the different phases of clinical trials, might provide the necessary context. It is important to note the length of time interventions spend on average in each phase and to highlight that GT is novel and risky, meaning timelines for clinical studies will likely be extended.

3. "Two-pronged approach"

- Communications about CHM GT must balance patient hopes with the uncertainties inherent in the investigational nature of early-stage clinical trials.
- In light of these circumstances, clinicians identified a "two-pronged approach" to promote balanced communications about GT. This approach encourages clinicians to share in patient hope for a future treatment, while emphasizing the risks and experimental nature of CHM GT clinical trials.
- The two-pronged approach could also ensure that while patients remain hopeful for therapeutic interventions, they concentrate on managing life with CHM and preparing for a prognosis of continued visual impairment in the case that a treatment will not be available in time for visual benefit.

4. Taking account of the media environment

- Our analysis of the ocular GT media environment and patient responses to a video about the LCA GT clinical trial indicate that clinicians need to be aware of the heightened expectations for ocular GT, particularly the prevalent curative portrayals in the media

Call for contribution:

We thank you for sharing your perspectives with us during your interview. We value the expertise of our research participants and would appreciate and welcome your input about our preliminary results. To ask questions, make suggestions, or address any concerns please contact:

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Appendix XX: Health Canada Clinical Trial Phase Definitions

Phase I
Initial safety studies on a new drug, including the first administration of the drug into humans, usually conducted in healthy volunteers. These trials may be conducted in patients when administration of the drug to healthy volunteers is not ethical.
Phase I trials are designed mainly to determine the pharmacological actions of the drug and the side effects associated with increasing doses. Pharmacokinetic as well as drug-drug interaction studies are usually considered as Phase I trials regardless of when they are conducted during drug development as these are generally conducted in healthy volunteers. Phase I trials also include trials in which new drugs are used as research tools to explore biological phenomena or disease processes.

Phase II
Clinical trials to evaluate the efficacy of the drug in patients with medical conditions to be treated, diagnosed or prevented and to determine the side effects and risks associated with drug. If a new indication for a marketed drug is to be investigated, then those clinical trials may generally be considered Phase II trials.

Phase III
Controlled or uncontrolled trials conducted after preliminary evidence suggesting efficacy of the drug has been demonstrated. These are intended to gather the additional information about efficacy and safety that is needed for further risk/benefit assessment of the drug. In this phase, clinical trials are also conducted in special patient populations (e.g., renal failure patients), or under special conditions dictated by the nature of the drug and disease.

Phase IV
All studies performed after the drug has been approved by the regulator for the market, and related to the approved indication. These studies are often important for optimizing the drug's use. They may be of any type but must have valid scientific objectives. Commonly conducted studies include safety studies and studies designed to support use under the approved indication such as mortality and morbidity studies, or epidemiological studies.

Source:

Health Canada. (2008). Guidance for clinical trial sponsors: Clinical trial applications. Retrieved from http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/ctdcta_ctddec-eng.php on September 10, 2012.