

**Families' Experiences with Medical Research for Pediatric Rare Diseases:
A Qualitative Ethnographic Study of Parents and Children Participating in Clinical Trials
for Duchenne Muscular Dystrophy (DMD)**

by

Christopher J. Condin

M.A., The University of British Columbia, 2005

B.A., The University of Victoria, 2002

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

The Faculty of Graduate and Postdoctoral Studies
(Anthropology)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

October 2014

© Christopher J. Condin, 2014

Abstract

The biopharmaceutical industry has recently expanded its focus on developing new cures for rare diseases. As a growing number of personalised genomic treatments are tested in clinical trials, there is uncertainty about how to account for patient perspectives, and how to measure functional changes reported by patients and caregivers. The illness experiences of patients and families are also being reshaped as they adopt roles as collaborative stakeholders and participants in clinical studies.

This dissertation examines these changes using data from qualitative ethnographic research conducted with families of children with Duchenne muscular dystrophy, a progressive and fatal genetic disease diagnosed in boys. Canadian and American families were followed using semi-structured interviews and observational methods as they participated in clinical trials testing a genomic treatment for DMD, called ataluren (formerly known as PTC124). Ethnographic work was also carried out with physicians, patient-advocates, and other professionals engaged in clinical neuromuscular research.

The dissertation contributes to scholarly understanding of families' everyday experiences in the clinical trial, the significance and meaning of investigational treatments from the patient perspective, and the social context in which pharmaceutical development for rare diseases occurs. I show how genetic research is reconfiguring patient communities and altering moral sensibilities about treatment and care, by revealing “lucky mutations” and new axes of biosocial commonality and difference. I explore the paths families take to the clinical trial, and the “stories of waiting” they tell about their experience in it. Finally, I examine how families

navigate the uncertainty and liminality of their experience as trial subjects. I discuss how the trial unsettles taken-for-granted social roles, constraining clinical relationships and leaving parents to construct the significance of an experimental treatment in the context of limited information. In so doing, parents assemble and tell “narratives of efficacy” while administering study-drug to their children, drawing on their observations and those made by others. Though parents’ narratives are often dismissed as mere anecdote, I suggest they also offer insight for developing more personalised approaches to clinical research and outcome measurement for rare diseases, by restoring focus on the nuance, idiosyncrasy, and context of families’ experiences with investigational treatments.

Preface

This dissertation is original, unpublished, independent work by the author, Christopher J. Condin. This research was approved by the University of British Columbia Behavioural Research Ethics Board (Certificate #H08-01205), and by the Institutional Review Boards of all hospital sites from which participants were recruited.

Table of Contents

Abstract	ii
Preface.....	iv
Table of Contents	v
List of Abbreviations	viii
Acknowledgements.....	x
Chapter 1: Introduction	1
1.1 Thematic Overview of the Dissertation and Ethnographic Questions Addressed	3
1.2 A Brief Overview of Duchenne Muscular Dystrophy and Ataluren (PTC124)	7
1.3 The Clinical Trial	15
1.4 Argument, Contribution, and Significance of the Dissertation.....	22
Chapter 2: Actors, Methods, and Research Design	29
2.1 Parent Patient-Subjects	29
2.2 Patient Advocates.....	32
2.3 Clinicians and Site-Investigators	34
2.4 Research Co-ordinators.....	37
2.5 Trial Sponsors	39
2.6 Others Involved in Research.....	42
2.7 Data and Field-Sites	43
2.8 Ethnography	46
2.9 Semi-Structured Interviews	48

2.10	Direct Observation and Accompaniment.....	49
2.11	Multi-Sited Design.....	51
2.12	Recruitment.....	52
2.13	Ethics and Access	56
2.14	Strategies for Data Analysis.....	60
Chapter 3: Study Setting and Context.....		63
3.1	The Duchenne Illness Experience: The Case of Carol Williamson.....	64
3.2	Stories of Waiting	71
3.3	Waiting for the Drug: The Case of Garrett Petersen.....	73
3.4	Lost Milestones and the Reversed Teleology of Childhood.....	83
3.5	The Duchenne Community and “Duchenne as Culture”	90
3.6	Personalized Medicine and Segmented Patient Communities.....	101
3.7	New Contours and “Lucky Mutations”.....	108
Chapter 4: Parents’ Paths to the Clinical Trial.....		117
4.1	“The Connected Parent”	117
4.2	“The Semi-Connected Parent”	121
4.3	“The Actively Unconnected Parent”	125
4.4	Discussion	130
4.5	Conclusion	138
Chapter 5: The Clinical Trial Experience I: The Clinical Trial as Extended Liminality.....		141
5.1	The Beginning.....	143
5.2	Time	147
5.3	Living on the Edge.....	153

5.4	A Blackout Period.....	162
5.5	Conclusion	170
Chapter 6: The Clinical Trial Experience II: Narratives of Efficacy.....		173
6.1	The Case of Carol Williamson.....	175
6.2	The Case of Maria Pauling	181
6.3	The Case of Aaron Murphy	187
6.4	Discussion: Paying Closer Attention to Parents' Narratives of Efficacy	198
6.5	Conclusion	211
Chapter 7: The Results and Impact of the Ataluren Trials		213
7.1	Outcomes	213
7.2	Delivery of the News	217
7.3	Fallout	220
7.4	Conclusion	228
Chapter 8: Conclusion to the Dissertation		230
References.....		240

List of Abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
AE	Adverse Event
BMD	Becker muscular dystrophy
BWS	Best-Worst Scaling
CF	Cystic fibrosis
CK	Creatine kinase
CIHR	Canadian Institutes of Health Research
CORD	Canadian Organization for Rare Disorders
CRO	Contract Research Organization
DBMD	Duchenne/Becker muscular dystrophy
DMC	Data Monitoring Committee
DMD	Duchenne muscular dystrophy
EKG	Electrocardiogram
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
IRB	Institutional Research Board

MDA	Muscular Dystrophy Association
MPS I	Mucopolysaccharidosis I
NIH	National Institutes of Health (United States)
PEM	Personalized Evaluation Model
POSI	Personal Outcomes of Specific Interest
PPMD	Parent Project Muscular Dystrophy
PROM	Patient Reported Outcome Measure
RCT	Randomized Controlled Trial
REB	Research Ethics Board
SAE	Serious Adverse Event
SAM	Step Activity Monitor
SMA	Spinal muscular atrophy
SSHRC	Social Sciences and Humanities Research Council (Canada)

Acknowledgements

I gratefully acknowledge the parents, children, and men within the Duchenne community who contributed their time and energy to this study. I have learned much from your strength in facing a difficult, often overwhelming condition with grace and perspective. Your efforts to change the horizons and possibilities for yourselves, your children, and others who follow are admirable and inspiring.

I offer my thanks to the physicians and researchers who participated in this study as both interviewees and interlocutors, by connecting me with their colleagues and patients. In particular, I thank the neurologists and pediatricians who generously offered their time by acting as site-investigators on the study. I also acknowledge the research co-ordinators at each of the study sites who assisted me with ethical approvals, recruitment, travel arrangements, and hospital fieldwork. Though I withhold the names of these individuals to protect the confidentiality of their patients, I appreciate all of their efforts in making this research possible.

I thank my supervisor Dr. Bill McKellin for his patient, inspired, and thoughtful mentorship. I also thank my advisory committee members Dr. Keith Benson, Dr. Kathryn Selby, and Dr. Jean Paul Collet for their guidance, contributions, and feedback throughout the PhD. I owe a debt of gratitude to all of my mentors and colleagues at UBC and BC Children's Hospital for the support and encouragement I have received.

Lastly, my deepest appreciation goes to my family: to my wife Carolynn, my sons Evan and Benjamin, our parents Marilyn, John, Margret, and Dennis, and to my brother Andrew and his wife Brenna, for their always dependable encouragement as I undertook this work.

This research was supported by an independent research grant from Parent Project Muscular Dystrophy (PPMD), which I gratefully acknowledge. I also acknowledge academic and financial support from the Canadian Institutes of Health Research Institute of Genetics (CIHR-IG), the Social Sciences and Humanities Research Council of Canada (SSHRC), and the University of British Columbia.

Chapter 1: Introduction

It's an emotional thing, really, to watch a father carry his grown 16 year-old son on his back—you're not supposed to have to carry your son at this age, but Paul lifts Jesse, all 200 lbs of him, several times a day. We have arrived at the physiotherapy department and the first step is to get Jesse on the exam bed, but of course, he cannot move himself. In one smooth, practiced motion, Paul squats down in front of Jesse's wheelchair, first stabilizing himself with his hands on the hospital floor, and then sending his elbows in the air, reaching back over his shoulders toward his son. Hands around elbows, he grasps Jesse's arms one at a time; they're floppy, dystrophic, fleshy—the muscle in his arms has wasted, replaced with fatty and scar tissue, and Jesse can barely lift them at all on his own. First Jesse's left, and then his right arm are guided gently around dad's shoulders and Paul tugs down, hard but with a fatherly tenderness, son's arms now dangling around father's neck as Paul grips him at each bicep. Rolling his weight onto the balls of his feet, Paul pulls Jesse's torso forward and in an instant, son's weight is collapsed—splayed, really—around father's back. Legs dangling around hips as Paul heaves them both into a standing position. A “piggy-back” for a child much too old. At the age of 52, lean and maybe 5'11”, I wonder what it's like for Paul to carry his own, heavier son on his back. Denise, the physiotherapist, is standing off to the side, ready to help if necessary. She is used to seeing this mode of father-son locomotion, but I am not.

I struggle to contain my own emotion as Jesse, and his dad beneath him, swing around in front of me, settling gently and together on the hospital bed. Each arm is unwrapped gingerly from around his father's neck, and in one swift motion Paul is up, standing and rotating himself—running, spinning—around the foot of the bed to get behind Jesse, to catch him on the other side of the bed as he begins to teeter and fall backward. It's a kind of dance, really, but it's hard not to see sadness and tragedy in the lumbering grace of their movements together.

*-Fieldnote entry July 15, 2009
Valleyview Children's Hospital
Physiotherapy Exam Room*

The field entry quoted above is taken from my observations of Jesse's physical therapy evaluation as he participates in a clinical trial at Valleyview Children's Hospital in the

Midwestern United States.¹ Jesse is taking an experimental new drug for his disease called Duchenne muscular dystrophy (DMD), or simply “Duchenne.” A progressive and fatal neuromuscular condition, the disorder is presently incurable, and at age 16, Jesse is getting “old” for a Duchenne patient. In the absence of a scientific breakthrough, he is faced with the statistical reality that the average date of death in this disorder is 27 years. Paul and Jesse have travelled halfway across the country to enroll in this trial of a new drug, known as PTC124 (or ataluren),² which they hope will slow the destruction of Jesse’s muscles. It is also possible that the drug will restore some of his lost muscle function, and with it a measure of independence. Ataluren is the first potentially curative therapy for DMD to be tested in large-scale human trials. Invested in these trials are the hopes of a community of afflicted families: that their child’s premature death due to a progressive neuromuscular illness may be averted.

I opened this chapter with a description of Paul transferring Jesse to the hospital bed because this short moment encapsulates many of the themes I will take up in the pages that follow. As a new wave of molecular therapies—borne of the genomic revolution of the past two decades—begins to reach the clinic, parents of children with many serious genetic illnesses are doing much of the “heavy lifting” to carry their children, both metaphorically and, in Paul’s case, physically, through clinical research trials. Every six weeks for the past nine months, Paul has piggy-backed his son onto a plane to fly across the United States for study visits like this one. The two to three day trip involves many transfers like the one above, from car to airport terminal, from terminal to airplane seat, from airplane to disability-equipped van, from van to wheelchair, and from wheelchair to hospital bed, where Jesse will undergo a series of frequently painful

¹ Names of study participants and hospital sites used throughout this dissertation are pseudonyms.

² Henceforth I will use these names interchangeably.

medical procedures to test whether he is responding to the study drug. Jesse depends on Paul, his mother Karen, and his brother and sister for nearly everything—moving, eating, and toileting, to name a few. As for Paul, he is driven by a strong sense of parental duty to do the best he can for his son—a sense of fatherly obligation whose limits seem ever more difficult to pin down. Paul is not alone in going to extraordinary lengths to find “the best” medical care for his son, and his efforts have involved researching investigational treatments, supplements and services, as well as engaging in fundraising and advocacy for Duchenne scientific research. These activities now constitute a significant portion of the moral and illness experience of many North American families with DMD and other rare genetic disorders.

1.1 Thematic Overview of the Dissertation and Ethnographic Questions Addressed

This dissertation is based on multi-sited ethnographic work with a group of Canadian and American families who enrolled their children in a series of clinical trials testing the drug ataluren (formerly known as PTC124). The trials were designed to determine, first, whether the drug is safe, and secondly, whether it is effective. Arguably, such parents are “moral pioneers” (Rapp 1999) in offering their children’s bodies to a burgeoning scientific and biopharmaceutical project that aims to understand, develop, and market treatments for the 5-8,000 diseases officially classified as “rare.” Though individually these diseases affect less than 1 in 2,000 patients, collectively they are estimated to affect one out of every 15—or 400 million—people worldwide (de Vruh and de Haan 2013). In the United States, the rare disease burden is estimated at 25 million patients (*ibid.*), and in Canada, roughly 3 million patients have a rare disease (Canadian Organization for Rare Disorders [CORD] 2013). Approximately 80% of rare disorders are considered “genetic,” and 50% of them are diagnosed in children.

DMD is one such disorder, and it is currently in the vanguard of a massive shift in both capital investment and political attention toward rare diseases. This is occurring as efforts to translate the biotechnical discoveries of genomics into usable treatments gather steam. For the biopharmaceutical industry, the rare disease market is attractive because, in an era of increased competition and drug-saturation for common conditions, orphan diseases represent a largely “untapped” segment of patient-consumers with a great deal of “unmet medical need.” Companies like GSK, Roche, Sanofi, and Pfizer are presently investing billions in research and development (R&D) for orphan indications.³

This investment is in turn producing a translational wave of experimental personalized medicines that aim to modify genes or modulate gene expression, many of which are now reaching human trials (Hedgecoe 2004; Hamburg and Collins 2010). Importantly, in DMD, many of these treatments are mutation-specific, meaning that they are matched to a patient’s individual genotype and thus available only to those patients with the “correct” mutation, and not others. DMD is a hereditary muscle-wasting disorder diagnosed in young boys, that is universally both fatal and incurable, with a median age at death of 27 years (Passamano et al. 2012).⁴ Though it is diagnosed in fewer than 500 new cases per year in the US, the disease has attracted billions in private-sector capital investment in just the past 5 years alone, and there are presently some 22 companies working in the Duchenne space, and approximately a dozen

³ Henceforth I use the terms “orphan” and “rare” interchangeably, though their origins differ. The term “orphan disease” was largely popularized with the passage of the *Orphan Drug Act (1983)* in the United States. There are jurisdictional and national differences in how these terms are defined in policy and law (Aronson 2006).

⁴ This figure is taken from a study of Italian patients. Life expectancy for DMD has improved dramatically over the last several decades. Notably however, such statistics generally sample populations with access to developed, comprehensive health care, corticosteroids, ventilation and other interventions which are not universally available or affordable. The median age-at-death reported for a group of British patients in 1960 was reported to be 14.4 years (Eagle et al. 2002).

investigational treatments in clinical testing.

Parents (and depending on their age, children) have diverse, multilayered and sometimes contradictory reasons for participating in such trials—for, as it is often colloquially described, providing their children as “guinea pigs” for experimental medicine. This study addresses parents’ stories of and motives for enrolling their children in the first large-scale, multi-sited therapeutic trials testing a new treatment for Duchenne. The central focus of the dissertation is on what “treatment”—or even its mere prospect, given that many therapies for genetic diseases are still highly experimental and not yet clinically available—*means* to this group of families coping with a degenerative, physically debilitating, and ultimately fatal childhood disease. I will argue that as parents enroll their children in the creation of scientific knowledge, they are also constructing new moral sensibilities around parenthood and illness, and rewriting their narratives of illness, muscles, and genes. Where most previous work on the subject of research participation has focused on clinical interactions and informed consent, I explore instead how the meaning and impact of an experimental treatment is constructed, negotiated, and contested not only in the presence of clinicians and hospitals, but more importantly in the interstitial practices of everyday life.

The research was designed as a *qualitative* project to examine families’ experiences as they engaged in a highly *quantitative*, structured clinical trial to assess whether a new drug was effective. My initial aim was to address three overarching research questions:

- 1.) What are the meanings of experimental treatments for families in whom a child has been diagnosed with an incurable and rare genetic disease, and how are they narrated?

- 2.) How do families come to participate in clinical trials for rare diseases, and what is the nature of their experience with new personalised medicines?; and
- 3.) How is the efficacy of experimental medicines assessed in rare disease clinical trials, and how do such assessments correspond or differ from those made by parents?

In the process of designing and carrying out the research, I quickly discovered that these questions raise others in turn. Accordingly, the dissertation also takes up questions about the background illness experience of DMD in North America, from which families cobble their narratives of investigational treatment and decide whether to participate in clinical research. I also explore the effect of genetic biotechnologies on moral sensibilities, role obligations, and social relationships within the patient community. My ethnographic research with Jesse, Paul, and families in similar circumstances illuminates how new molecular compounds are not just biochemically complex, but have complicated social biographies as well (Appadurai 1986; Latour and Woolgar 1979; Rabinow 1996a). In the same way that these compounds intervene in chemical processes within the cell, they also intervene in patients' lives, engendering dilemma, uncertainty, hope, disappointment, friendship, and discord for families as they navigate the terrain of genetics, biopharma, and neurology. As a new menu of treatments for rare diseases begins to materialize, these social, cultural, and political dimensions of therapeutic research are at the centre of contemporary discussion about the role of biopharmaceuticals in both health care and in everyday life (Dumit 2012). Debates about how to develop, evaluate, regulate, and ensure equitable access to new treatments (Bartfai and Lees 2013; Sherman et al. 2013; Biehl and Petryna 2011), are, at their core, conversations about social and cultural values. Ultimately, this dissertation aims to contribute to a deeper understanding of this social life of new personalised

medicines for rare diseases, by undertaking granular, qualitative exploration of how new treatments are viewed, used, and understood by parents of children with a rare disease.

1.2 A Brief Overview of Duchenne Muscular Dystrophy and Ataluren (PTC124)

Duchenne muscular dystrophy is a neuromuscular disease typically diagnosed in children around age five. Primarily affecting boys, the disorder is caused by a mutation on the X-chromosome in the gene that codes for the protein dystrophin, which is necessary for proper muscle function.⁵ Children with abnormalities in this gene experience progressive loss of muscle function because muscle cells without dystrophin are easily broken down and the muscles are replaced with fibrous tissue and fat, leading to a loss of strength and ability. Typically, children with DMD walk on their tiptoes and begin to fall frequently as they enter the first years of elementary school. They “come off their feet,” losing the ability to walk around age 10, after which they need a wheelchair for mobility.⁶ Later, they progressively lose more independence, including the ability to lift their arms to eat, hug, write, play, use the bathroom, move, and eventually, to breathe on their own.

In their late teens, these young men require full-time care, which is typically provided by their parent(s) and/or siblings. Many undergo surgery for scoliosis, having steel rods placed in

⁵ Since females inherit two copies of the x-chromosome, and since their unaffected copy of the dystrophin gene is usually functional, they do not typically manifest symptoms to the same degree. However, they are at risk of passing their mutation on to their offspring, and an estimated 3-8% of female carriers develop some degree of muscle weakness and/or cardiomyopathy, often later in life. In extremely rare cases females may manifest a severe DMD-like disease (Seemann et al. 2011). These are theorized to result from a mutation in one copy of the dystrophin gene, combined with inactivation of the other normal x-chromosome, causing a Duchenne-like phenotype (estimated incidence 1:50,000,000, or around 10-15 documented cases in the US). Soltanzadeh et al. (2010) report the first documented case of a Duchenne female with different mutations in each copy of the dystrophin gene. See also Furlong (2010a).

⁶ The phrase “come off their feet” is used colloquially in the community to refer to a child’s permanent loss of ambulation and entry into a wheelchair full-time. I discuss common patterns of language and social interaction in the Duchenne community in Chapter 3.

their spines to support their upper bodies and help maintain respiratory function. In the latter stages of the disease, they require full-time respiratory support with ventilation. Family life is dramatically different, involving modified activity, medication, physical therapy, medical devices such as orthotics, and hopeful resiliency. About a third of those affected have associated cognitive, behavioural, learning, linguistic, and memory disorders, thought to be caused by a lack of dystrophin in the brain (Anderson et al. 2002; Cyrulnik et al. 2008). A high burden of care is thus borne by parents, disproportionately by mothers, who often take on caregiving roles within the household (Kenneson and Bobo 2010). All parents of children with DMD experience profound and enduring psychological trauma, and a great deal of unmet need exists for familial counselling, respite, and social support (Rapp and Ginsburg 2001). Children with Duchenne also experience a considerable burden of social, psychological, and emotional difficulty in coping with their disorder and disability, particularly in the middle and late stages. As I discuss below, they often “struggle to be normal” but are excluded from the usual activities and friendships of childhood (Gibson, Zitzelsberger, and McKeever 2009; Gibson et al. 2007). DMD is universally fatal: as the disease progresses, patients typically die of respiratory or cardiac failure in their 20s. Though recent advances in care are allowing some patients to live into their 30s (in Northern countries), deaths in the teens and early/mid-twenties are still common (Eagle et al. 2002; Passamano et al. 2012).⁷

⁷ Parents suffer devastating loss when their son dies of Duchenne, no matter his age. Public accounts written by family members and parents who have gone through this experience are often published in the Grief and Loss forum of the Parent Project Muscular Dystrophy Community (PPMD) website (2013). See also the Facebook group “Mitchell’s Journey,” poignantly written by parents whose son died of heart failure at the age of 10 and Weisman’s *Intensive Care: A Family Love Story*, written by mother Mary-Lou Weisman (2000) and chronicling her journey caring for her son Peter until his death in 1980 at the age of 15 years-old.

The gene for dystrophin was one of the first to be identified as part of the Human Genome Project, nearly three decades ago (Koenig et al. 1987). Bound up with the promise of a new genomic era, the discovery led to hope that a gene-based therapy was close-at-hand (Martin 1999; Martin 2001). However, now nearly three decades after the gene for dystrophin was identified, there are still no approved effective pharmacological treatments for DMD, with the exception of the corticosteroids, either prednisone or deflazacort.⁸ These drugs, combined with better respiratory, orthopaedic, nutritional, and cardiac care, have altered the natural history of the disease and led to improved outcomes, including a near-doubling of the median age at death since the 1960s.⁹ But although these interventions slow the disease progression and allow better quality of life, they are still only partial, symptomatic, and incapable of averting the disease's final outcome. Steroids also have the potential to cause many side effects, including weight gain, behavioural problems, short stature, delayed puberty and osteoporosis, and cataracts.

However, DMD is currently at a watershed moment in medical research, owing to technical advances in genetics, basic muscle biology, animal-modeling and imaging techniques. Laboratory scientists can now routinely “cure” Duchenne in cell cultures, mice, and dogs using a variety of therapeutic strategies that target the disease's underlying genetic pathway.¹⁰ Recently, several personalised genomic treatments have shown promising results in human trials (Flanigan, Voit, et al. 2013; Mendell et al. 2013; Finkel et al. 2013; Ruegg 2013).

⁸ The latter is approved in Canada and Europe, but not in the United States, where parents must import it for personal use.

⁹ This improvement due to improved care standards is in itself remarkable and has occurred in the absence of gene-based treatments—a fact that is often overlooked. See also note 4.

¹⁰ On the social and cultural dimensions of the use of animal models in scientific research, see Fujimura (1996).

This study focuses on the first of these experimental treatments to reach critical mass and be tested in large-scale, multi-sited pivotal clinical trials.¹¹ The drug ataluren is a small molecule that targets the process by which DNA is translated first into RNA, and subsequently into dystrophin protein. Exploiting a mechanism called “forced read-through,” the compound is hypothesized to act upon the ribosome to make the cell’s transcription machinery overlook one type of genetic mutation causing the disease (called a nonsense mutation or premature stop codon), and to continue performing its work until a correct, full length, and functional dystrophin protein is produced.

Parents who participated in this study were enrolled in one of two trials testing the drug simultaneously underway between 2008 and 2010. The first was a Phase 2a extension trial, in which children received the drug open-label in powdered form, to be mixed as a drink and taken three times per day.¹² They attended hospital every 6 to 12 weeks to undergo clinical assessments over a two-day study visit. As a Phase 2 study, this trial’s primary purpose was to evaluate long-term safety (its primary outcome measure) and, secondarily, to determine whether PTC124 led to any changes in dystrophin expression, muscle function, ambulation, heart function, cognitive ability, or quality of life (among other secondary measures). In the second, larger Phase 2b pivotal trial, children were administered the drug in a blinded fashion for 48 weeks, meaning that they, along with their caregivers, physicians, and researchers, were not aware whether the patient was receiving placebo or active drug.¹³ Children in this study took the

¹¹ In this stage, usually referred to as Phase 3, a drug is tested in a large population—typically in a randomized, placebo-controlled trial. If the results of pivotal trials are positive, they can then be used as the basis for applying for regulatory approval to market the drug.

¹² For a description of the different trial phases, see ClinicalTrials.gov (2008). For an ethnography of research subjects’ experiences as “guinea pigs” in Phase 1 trials, see Abadie (2010).

¹³ There were two active treatment arms, with patients in the “low-dose” arm receiving 40 mg/kg/day and patients in the “high-dose” arm receiving 80 mg/kg/day.

drug in the same way, and were required to attend the hospital every six weeks for a two-day study visit, interspersed with laboratory testing performed by labs in their home communities. The primary objective of this second study was to demonstrate efficacy of the drug, and thus its primary outcome measure was the 6-Minute Walk Test (6MWT), in which the distance a child can walk in 6 minutes is measured.

The 6MWT was chosen because it was (and remains) one of the only standardized, validated outcome measures applicable to patients with Duchenne (McDonald et al. 2013). In other, well-trodden diseases, these endpoints are often well-established and refined through repeated use over time. There are, for example, more than nine clinically validated endpoints used in trials for diabetes mellitus (Wieczorek et al. 2008), including surrogate measures. However, because few drugs have been tested for most rare diseases, there are usually no surrogate endpoints that have been validated and accepted for use by regulatory agencies, and even direct, functional endpoints are sparse or non-existent. Moreover, in Duchenne and many other rare diseases, there is a paucity of natural history data (usually derived from large epidemiological cohort studies) to help better differentiate those who may be responding to a drug from those who are not. Companies working in rare disease are thus constrained by the limited menu of outcome measures accepted by regulatory agencies as convincing evidence of a drug's efficacy. In the present case, a near-complete lack of validated outcome measures and biomarkers for the disease meant that PTC Therapeutics had to choose and validate the 6MWT for the disease before a trial could be undertaken, an effort in which it invested significant resources. The company ultimately chose the measure because it had been used successfully in both rare and common diseases to obtain drug approval, earning a credibility with regulators often referred to as "regulatory precedent." It also seemed feasible to standardize and perform

across sites and was directly linked to one of the main functional impacts of Duchenne on overall health—that is, loss of ambulation and strength.

The trial hypothesized that, if effective, a difference between the placebo group and the active treatment arm(s) of at least 30 metres in 6-Minute Walk Distance (6MWD) would be observed at the end of the study. In addition, various other secondary measures were used to collect additional data on safety and efficacy, including timed function tests, blood tests, cardiac function tests (EKG), quality-of-life questionnaires, activity journals, and the wearing of a home step-activity-monitor (SAM, similar to a pedometer). Children in both studies were required to undergo two surgical muscle biopsies at the beginning and end of the trial in order to determine whether the study drug caused an increase (as hoped) in dystrophin expression. Both trials were therefore cumbersome and intensive, requiring extensive commitments from participants who often travelled long distances to the hospital study-sites (necessitating a 3-4 day trip), in many cases crossing oceans and borders. The payoff for participants was access to a potential breakthrough treatment, either as part of the blinded study or afterward in a planned Phase 2b extension trial, during which all patients would receive the active treatment open-label in return for their participation in the placebo-controlled study.

The ataluren trials were historic, since it was the first time that therapy specifically targeting the genetic abnormality in Duchenne reached the pivotal stage of drug development, meaning that if the trial was successful, the company could apply for approval on the basis of its results. However, ataluren is applicable only to the estimated 13% of DMD patients whose disease is caused by a premature stop codon or “nonsense” mutation, a point that has significant

implications as I discuss below.¹⁴ In a disease with a high burden of care where treatment is severely lacking, the drug is the object of considerable hope, enthusiasm, and attention, both on the part of patients and the wider drug development community.¹⁵ The small biotechnology company developing it—PTC Therapeutics Inc.—was formed by a group of researchers at Robert Wood Johnson Medical School in Rutgers University (NJ), lauded in *Forbes Magazine* in 2007 (Herper 2007), and signed a \$437 million licensing agreement with Genzyme (a much larger pharmaceutical company focused on rare diseases) to push the drug into pivotal trials. As but one example of the attention focused on the drug, the company was sued in 2008 by Minnesota parents Cheri and John Gunvalson, seeking compassionate access to the medication for their 16 year-old son Jacob in a widely watched case that was ultimately unsuccessful (Abelson 2008).

Ataluren's mechanism of action is particularly interesting because its novelty and biochemical complexity create a rich space for interpretation and meaning-making—perhaps more so than “routine” pharmaceuticals for common conditions like depression, heart disease, or high cholesterol. The drug transcends conventional nosologies of disease since it is theoretically applicable to any patient with a genetic disorder that is caused by a nonsense mutation. The drug is currently also being tested in a Phase 3 trial for cystic fibrosis (CF), and has been proposed as a potential treatment for hemophilia A and B and mucopolysaccharidosis I (MPS I), among other diseases (Peltz et al. 2013). Its applicability across different diseases has enhanced its business case among investors and enabled the company to move it forward despite the small percentage

¹⁴ This estimate is provided by the company manufacturing the drug, and is widely cited in the medical literature. The company estimates that there are 2,000 patients in the United States, and 2,500 in the European Union whose disease is caused by a nonsense mutation.

¹⁵ The situation evokes parallels with Delvecchio-Good's (1990) discussion of discourses of hope in oncology.

of patients in each disease category for whom it may be useful. There has also been much speculation about how it works on the part of both patients and bench scientists alike. In a hallway conversation with me at a patient advocacy conference, a young mother whose son had just been diagnosed with DMD described the drug—which comes in powdered form to be mixed and consumed in a drink—as “just like magic.” “It can make the cell just *forget* that there’s something’s wrong with it [i.e. with the dystrophin gene] and just *skip over* it,” she explained. “It will just *carry on* and make the full protein, like nothing is wrong.” This mother had not yet received a genetic diagnosis confirming her son’s specific mutation, but like others with new or recent diagnoses, she expressed hope that her child would be “one of the lucky ones” who has a nonsense mutation.¹⁶

As personalised treatments like ataluren emerge from the pharmaceutical pipeline and are translated into medicines used in the clinic, they are also leading to reconfigurations in the taxonomy of genetic diseases. In the present case, for example, the recognition that the separate diseases of Duchenne and Becker muscular dystrophy (when caused by nonsense mutations) may in fact be treatable using the same molecular compound, has occasioned the appearance and promotion (mainly by PTC Therapeutics) of a new disease category—namely, nmDBMD, or

¹⁶ Conjecture as to how the drug works is not solely the purview of non-technical laypersons, as ataluren has also been the subject of considerable debate among scientists. Two recent papers have questioned whether the drug’s observed activity in reporter assays might instead be caused by an off-target effect—a molecular anomaly or “fluke” which causes it to bind with and stabilize the luciferase reporter assay widely used in pharmaceutical and genetic research. If true, the authors question whether ataluren’s activity may in fact result from a false-positive reading of molecular activity, by generating a signal that isn’t really there (McElroy et al. 2013; Auld et al. 2009; Auld et al. 2010; Yandell 2013). For its part, the company has responded that it has demonstrated the compound’s molecular activity in other assays, animal models, and *in vivo* (Peltz et al. 2013). However, there remains some controversy as to whether the dissenting authors’ hypothesis may hold merit, and how it can be reconciled with observations of activity in other systems and laboratory experiments. The debate underscores just how little is currently known about the drug and about the phenomenon of forced readthrough (a characteristic of other drugs and small molecules) more generally. Notably, this debate has occurred only recently, and was not “on the radar” when data were collected for the present study.

“nonsense-mediated Duchenne-Becker Muscular Dystrophy.” This process, in which pharmaceutical companies launch marketing and promotional discourse promoting new disease categories in the hope of defining new consumer markets, has also been described in other settings (e.g. Petryna, Lakoff, and Kleinman 2006; Dumit 2012; Van der Geest, Whyte, and Hardon 1996; Applbaum 2006; Lock and Nguyen 2010; Nguyen 2010). The proliferation of new disease categories is perhaps the defining feature of the industry-driven biopharmaceutical paradigm in Western medicine.

However, the conventional political and economic scaffolds of biopharma take unique forms in the setting of rare disease—at least in middle-class North America—as we see below.¹⁷ Parents (as proxies of their child-patients and thus “patients” themselves) are not merely passive consumers of pharmaceutical rationalities but are often key agents, facilitators, and sometimes collaborators in creating them, as they seek to advance the translation of new drugs in an area that is not saturated by, but rather desperately lacking in them (Rabeharisoa 2003; Rabeharisoa 2006; Novas 2009).

1.3 The Clinical Trial

This dissertation examines families’ experiences as they engage, most for the first time, with the logic and rationality of the randomized controlled clinical trial (often abbreviated RCT). Though the trial can take many forms, its optimal structure is the double-blind, randomized study, in which a new intervention¹⁸ is tested by administering it to one group of patients while

¹⁷ See Chapter 3. For a different perspective on the situation of orphan diseases in Brazil, see Biehl and Petryna (2011).

¹⁸ Usually a drug, but sometimes also an intervention such as a health service, medical device, or type of information.

withholding it from another group, which receives only an inert placebo. Within the blinded trial, neither the patient nor the doctor and all other people involved in the study know who is taking the active treatment. The goal is to create an experimental condition where the only difference between the two groups is the intervention being studied. Described as “the ultimate means of applying the scientific method to the practice of medicine” (Chalmers 1981:325), and commonly referred to as the “gold standard” method for generating biomedical knowledge, the clinical trial is much more than just a research methodology but rather an epistemology (or way of conceptualizing the world) unto itself—one that undergirds the shift toward evidence-based medicine, the industrialization and rapid expansion of pharmaceutical development, and a vast institutional apparatus for regulating which drugs can be sold and on what terms. Importantly, the central claim of this paradigm is its purported objectivity; by ostensibly removing the influence of biological, molecular, and social variables, the trial claims to isolate and measure an unbiased—and therefore supposedly “true”—treatment effect within a cohort of patients. The claim is that (if done properly) the clinical trial enables a “clean” interpretation of any differences observed between two study populations, free of the “noise” of everyday life.

The current pre-eminence of the clinical trial in turn floats in broader philosophical currents within biomedicine. Dumit (2012), for example, discusses how the roots of the trial’s popularity and credibility can be located in the 1950s shift toward statistics in biomedicine, and the emergence of a post-war public health model that moved from vaccinations and “public health education” to the identification of “populations of increased risk” and the reduction of “risk factors,” which could be measured using biomarkers such as cholesterol and high blood pressure. During the latter half of the twentieth century the industrialization of clinical trials occurred as drugs were paired with risk factors for potential future events, such as heart disease,

stroke, and cardiac arrest. The shift toward standardized, evidence-based medicine—the paradigm which currently dominates much of biomedical practice in the global North today—emphasized the use of mathematical models of risk, benefit, and harm to inform clinical decision-making, evidence that is most reliably derived from randomized trials (Timmermans and Berg 2010; Sackett et al. 1995; Weisz et al. 2007). At the same time, regulatory frameworks in industrialized countries emerged to control the safety, purity, and manufacture of drugs by restricting their sale in the marketplace to those treatments on which clinical trials had been conducted. These regulatory imperatives emerged in the wake of episodes such as the thalidomide disaster of the 1960s, in which thousands of women worldwide gave birth to children with severe congenital malformations after taking the drug to treat morning sickness.¹⁹

These and other factors have ensconced the clinical trial as both the principal means of knowledge generation in biomedical research, and the footing of a pharmaceutical industry whose size is staggering, with prescription drugs now accounting for 10 percent, or \$203 billion (of a total \$2 trillion) in health care expenditures in the United States alone (in 2011) (Dumit 2012). More than 2.4 million Americans participated in clinical trials in 2006, and the industry is rapidly expanding to markets such as India, China, and Russia, as the recruitment of treatment-naïve trial subjects in North America and Western Europe becomes more difficult and costly (Ernst & Young 2006; Lakoff 2006; Peterson 2004; Ecks 2008; Rajan 2010a; Petryna 2009; Fisher 2008). Paradoxically, the trial functions simultaneously as both the enabling and impeding factor that a company must surmount if it wishes to commercialize and sell a new treatment in an industrialized country. Though recent policy changes in the United States,

¹⁹ The COX-2 inhibitor rofecoxib (Vioxx) is a more recent case cited as evidence of the need for regulatory oversight of pharmaceuticals. The drug is estimated to have caused some 60,000 deaths before it was removed from the market in 2004 (CMAJ Editorial 2005).

Canada, and Europe have created pathways for accelerated or conditional approval of “breakthrough” therapies in serious conditions where treatments are lacking (Sherman et al. 2013), a company still has to meet the traditional benchmark for approval by demonstrating the safety and efficacy of a new drug, ideally in “at least two adequate and well-controlled studies, each convincing on its own” (FDA Center for Drug Evaluation and Research 1998; Temple 1982). Regulators have been criticized for a lack of transparency and consistency in how drugs are approved (Downing et al. 2014). However, since new treatments for rare diseases are often novel molecular compounds without precedent that intervene in genomic processes, they have a higher potential for unanticipated safety issues and/or toxicity (Kesselheim, Myers, and Avorn 2011; Orfali et al. 2012) and regulators tend to evaluate them conservatively and cautiously.²⁰

As a genomic “revolution” gathers steam and the pharmaceutical industry looks to rare diseases to fill its pipeline, a growing number of investigational treatments are being translated for rare diseases. The current moment is therefore one in which the scientific, industrial, and marketing logics of a well-established pharmaceutical industry are sweeping over the varied and unique terrain of rare diseases, generating both hybrid models for research and drug development, and a set of unique problems. The United States *Orphan Drug Act* of 1983, which offered seven years of marketing exclusivity and various other incentives to spur industry to develop new treatments for orphan indications, has led to the approval of 442 new drugs for diseases historically neglected since its passage (Thomson Reuters 2013; Thorat et al. 2012).²¹

²⁰ This is in part a legacy of the early days of gene therapy during the 1990s and early 2000s. In 1999, an American patient named Jesse Gelsinger died while participating in a clinical trial testing a gene therapy for ornithine transcarbamylase deficiency, an X-linked genetic disease of the liver. In 2002, 4 of 9 infant patients undergoing gene therapy for SCID in France developed leukemia. Both of these events led to regulatory moratoriums on gene therapy research.

²¹ There is presently no comparable legislation in Canada.

But it has also done little to address the unique conditions in which trials for rare diseases are carried out, nor the high cost of treatments once they come to market, which are priced by industry in the hundreds of thousands per patient per year (Biehl and Petryna 2011; O’Sullivan, Orenstein, and Milla 2013).

The *Orphan Drug Act* also left in place the same requirements for demonstrating efficacy and obtaining approval for new drugs in rare diseases as for common ones, despite the fact that the clinical trial was initially developed for infectious and acute diseases—where an intervention such as an antibiotic or antiretroviral could have an immediate and easily measurable effect on a disease process (Bhatt 2010). When a disease is common and a particular outcome (such as a patient recovering from an infection) occurs frequently, clinical questions can be answered relatively straightforwardly and with a high degree of scientific validity. Applying the clinical trial in the setting of rare disease, however, creates a number of problems. Among them, definitive answers are much harder to come by in diseases with smaller populations, where it is often difficult or impossible to recruit sufficient numbers of patients to perform trials that are adequately (statistically) powered. This means that often “trials cannot detect or exclude clinically worthwhile differences between treatments with standard levels of statistical confidence” (Lilford, Thornton, and Braunholtz 1995:311). This problem is exacerbated when testing mutation-specific personalised medicines, which require the stratification of already-rare populations defined by a phenotype (in this case, Duchenne muscular dystrophy) into smaller genotypic cohorts (discussed in Chapter 3, see also Keating and Cambrosio [2011]). Many rare diseases also exhibit a high degree of phenotypic variability between patients, and a broad range of symptoms that often involve multiple body systems at different stages in disease progression. A lack of research means that there are large gaps in existing knowledge with which to design

and plan clinical trials (including information on the “normal” natural history of a disease), and a paucity of validated outcome measures and biomarkers with which to measure treatment effects. Trials are also extremely expensive to run, with a recent study conservatively estimating the average cost is \$26,000 per patient (Stewart, Whitney, and Kurzrock 2010). There are “opportunity costs” measured in both dollars and lives as resources are devoted to expensive and long term trials which are ultimately unsuccessful, and as patients die or progress while taking placebo and/or waiting for new treatments.

In short, the existing model in which clinical trials for rare diseases are carried out is widely regarded as poorly suited to their unique clinical and epidemiological characteristics. Various authors have critiqued an overly bureaucratic regulatory system, a lack of flexibility on the part of regulators to account for the unique constraints of rare diseases, and a lack of consensus or clarity about how what constitutes both an acceptable benefit from a new treatment, and an ethically tolerable risk in pursuit of it (e.g. Stewart, Whitney, and Kurzrock 2010) (see Chapter 6). Today, the average translation time between discovery of a molecular target and approval of a new drug sits at 13 years, with a failure rate exceeding 95%, and an estimated cost per successful drug that is often claimed to exceed \$1 billion (Collins 2011).²² With the cost of new personalised medicines now commonly in the hundreds of thousands of dollars per individual patient per year, and with little correlation between the drugs brought to market and the diseases with most pressing medical need (Bartfai and Lees 2013),²³ the system in which

²² The figure of \$1 billion includes accounting for the cost of failed drugs. Though often cited, this figure is disputed. “The industry often throws around the figure of \$1 billion as the cost. Yet this figure is often questioned, even by one of their own; last year, GSK’s [CEO] Andrew Witty called the \$1 billion figure ‘a myth.’ Other organisations have proved that it’s possible to develop new drugs for significantly less than \$1 billion, and have no patents or high prices attached.” (Balasegaram 2014).

²³ This point has been made widely in relation to both rare diseases and neglected diseases of high prevalence in the global South, such as malaria, tuberculosis and tropical diseases (e.g. Farmer 2005; Balasegaram 2014).

drugs are developed is widely regarded as lumbering, broken, and unsustainable (Novas 2009; McGuire 2011; Cohen and Raftery 2014).

Finally, there are a bevy of problems with the trial itself that are applicable to both common and rare diseases. Among them is the issue of whether participants in trials are truly providing free and informed consent (Bosk 2008; Faden, Beauchamp, and King 1986; Appelbaum, Lidz, and Meisel 1987)—a notion that, as I show below, appears rather lofty in the hope-laden sector of terminal rare disease. The main ethical premise on which clinical research currently operates is the distinction between research and care, which are (supposedly) firmly demarcated as separate activities governed by different and often conflicting ethical obligations. Clinical medicine is governed by the principles of beneficence and therapeutic non-maleficence, which compel physicians to practice medicine with the primary goal of improving the health of individual patients. In short, therapeutic decision-making (what treatment to administer, when, and how much) in medical care is directed toward the individual patient and what is best for them. Clinical research, in contrast, is not a therapeutic activity designed around the personal needs of individual patients, but rather to answer scientific questions and to generate knowledge about *groups* of patients (cohorts). Decisions about which treatment is appropriate are made in the service of this goal and not necessarily with an individual patient's best interests in mind. Confusion between the separate and bounded domains of research and care has been labelled the “therapeutic misconception” and has been noted to occur on the part of patients and investigators alike (Appelbaum et al. 1987; Miller and Brody 2003). However, as this dissertation shows, it is unclear whether this distinction carries any meaning “on the ground” in which trials are conducted, and in which the boundaries between research and care are often blurry for both patients and clinicians alike.

The line between research and treatment and the ethical obligations of care providers has led to a long and heated debate about the ethical acceptability of placebo-controlled trials, along with the settings and conditions in which they are justifiable. The concept of clinical equipoise emerged in the late 1980s as the dominant framework through which clinical trials could be ethically performed (Freedman 1987). According to this widely-adopted principle, placebo-controlled trials are ethical so long as there is genuine uncertainty on the part of medical professionals as to which intervention is best, thus leading to a similar and balanced chance of success in each arm of the trial. Though the notion of equipoise has been critiqued from various quarters for its selective application (Petryna 2005), its ignorance of socioeconomic and political disparities in access to basic health care (Farmer 2004b; Farmer 2013), and its incoherent philosophical roots (Miller and Brody 2003), it remains a crucial concept within prevailing bioethical frameworks governing clinical research, where it is frequently invoked by Institutional Review Boards (IRBs) and regulatory agencies; in theory it is only when equipoise is satisfied and there is a balance between the risks and potential benefits from each arm of the trial that the clinicians' dispensation with her ethical obligations to her patient's personalised care becomes justifiable (Miller and Brody 2003).

1.4 Argument, Contribution, and Significance of the Dissertation

If the clinical trial operated in the manner in which it is conceptualized by bioethicists and Institutional Review Boards (IRBs)—that is, if research and treatment were indeed separate and neatly bounded domains, and the state of equipoise a carefully balanced condition of genuine uncertainty in which the trial is undertaken—we might expect there to be a peaceful orderliness around the performance of clinical research (Collet, personal communication, May 20, 2014).

Patients would have little concern about their treatment assignment and their exposure to an investigational drug, since no one should expect to benefit from their involvement in the trial. Having offered their informed consent, patients would be aware of the investigational nature of clinical research and might participate in it for altruistic reasons; clinicians too, would be comfortable in managing their dual roles as investigators and care providers.

Instead, I show in this dissertation how we see an entirely different picture when we examine the social arena in which medical research and clinical trials are conducted for rare diseases. Therapeutic research is fraught with the hopeful anguish of parents of terminally diseased children and the fervent desire on the part of both parents and professionals that investigational medicine will provide a “ticket off the train of despair” that is Duchenne muscular dystrophy (as one mother described it to me, see Chapter 3). There is an entire community and culture that structures patients’ approaches to clinical research, their moral conceptions of their obligations to enrol in it, and their biosocial connections in seeking to advance it. In short, there is a social and cultural reality “on-the-ground” that I explore in this thesis, a reality fraught with the tension, emotion, and messiness of everyday life which does not appear in medical journals or industry press releases, and which unsettles the neat and tidy conceptions of “clinical research,” “treatment,” and “efficacy” described in them.

With this dissertation I set out to examine this terrain anthropologically. I explore the antecedent conditions in which parents develop their understandings, expectations, and experiences prior to engaging in clinical research, and the ways they make sense of their experiences as experimental subjects. For obvious reasons, parents—especially those coping with a new diagnosis and those of younger children, for whom a treatment is likely to be more effective—see themselves in a race against time (Stockdale 1999). As I discuss throughout this

monograph, they describe living with an agonizing sense of anticipation, as they watch their child deteriorate knowing that scientists can cure his disease in the mouse, the dog, and perhaps the human,²⁴ but that no effective treatment for Duchenne is yet approved or available (Condin 2005). In rare diseases, genomic technology is today both ubiquitous and untranslated.

This dissertation examines the gap between the promise and reality of genomic technology, where we find a rich set of illness experiences, moral and ethical dilemmas, and social and cultural changes that I aim to unpack. In doing so, my principal aim is to contribute to a need for scholarly research on how patients' lives are altered by both the prospective potential of genomic treatments for rare disease, and increasingly, by their direct experiences with its creations as participants in investigational trials. The connection between parents' (and their children's) expectations, hopes, and experiences with experimental medicine, and the qualitative dimensions of their lives (what anthropologists refer to as "the everyday") have received comparatively little scholarly attention and are at present poorly understood.

We can gain a clearer picture of them, I suggest, by approaching the topic using the interpretive tools of ethnography and narrative theory. This approach to illness examines the ways that people emplot and tell stories out of their experience. Narrative and story-telling are now firmly established as fundamental ways that humans order, memorize, give meaning to, and communicate our experiences with each other (Good 1994). That is, we use stories to understand concrete events that require relating "the inner world of thought-feeling to the outer world of observable actions and states of affairs" (Garro and Mattingly 2000:5). The collection and analysis of narratives as a source of scholarly data has a long and extensive history in both

²⁴ Though not curative *per se*, there is present controversy about whether recently obtained trial results with the exon skipping drugs eteplirsen and drisapersen demonstrate meaningful therapeutic advances in children with the disease (Hoffman and Connor 2013; McSherry 2013).

anthropology and medical anthropology (e.g. Kleinman 1988; Mattingly 1998; Mattingly and Garro 2000; Frank 1995; Hyden 1997; Mishler 1995; Labov and Waletzky 1967). In mainstream biomedicine as well, the narratives of patients, care providers, and other actors in health care are now increasingly recognized as a key source of data for developing more patient-centred clinical approaches (Pope and Mays 1995; Giacomini and Cook 2000).

I approach my topic from this perspective and ground the dissertation in the claim that, for scholars seeking to understand and improve how clinical research is carried out “on the ground,” parents’ narratives can serve as a rich source of useful information. After elaborating the Actors, Methods and Research Design in Chapter 2, I turn in Chapter 3 to an examination of the narratives parents tell about their illness experience with Duchenne, and the stories of waiting they construct as they watch their children decline in the absence of an effective treatment. This experience unites parents in communities of practice (Lave and Wenger 1991) in which they are playing increasingly important roles advocating, collaborating, and demanding attention and resources for their children’s disease (Rabeharisoa 2006). In coming together and developing connections with each other in both “real life” and using social media, I explore how parents are at the same time constructing moral ideals about effective parenthood, caregiving, and research participation. Finally, I examine how the emergence of personalised genomic treatments is contributing to reconfigurations of social relationships of support within patient communities by identifying patients with “lucky mutations” and those not so fortunate. In this chapter, I introduce the theoretical concepts of “Lost Milestones,” “Duchenne as Culture,” “Stories of Waiting,” and “Lucky Mutations” to help frame my analysis of the settings in which parents

travel prior to their experience as clinical trial subjects, and I advance scholarly discussion of biosociality (Rabinow 1996b; Rabinow 1996a)²⁵ by pointing to both its nuances and its limits.

In Chapter 4, I develop and elaborate a typology of parents' connections to clinical research and examine the various stakes and forms of capital families invest in scientific development. Building on my findings from the previous chapter, I suggest that these connections are likely to play an important role in how parents approach the trial and frame their experiences within it. The typology I develop is likely to be applicable in other rare diseases as well.

In Chapters 5 and 6, I turn my attention to the clinical trial experience itself, and examine what parents' narratives can tell us about how they navigate and make sense of their experience as mothers and fathers of trial subjects. I invoke the concept of liminality to frame how the trial unsettles taken-for-granted social roles, constraining clinical relationships and leaving parents to construct the significance of an experimental treatment in the context of limited information. In coping and responding to these conditions of uncertainty, I suggest in Chapter 6 that parents assemble and tell "narratives of efficacy" while administering the study-drug to their children, drawing on their own observations and those made by others. In introducing and developing this novel theoretical concept, I show that though parents' narratives are often dismissed as mere anecdote, they can also offer insight for developing more personalised approaches to clinical research and outcome measurement for rare diseases, by restoring focus on the nuance, individuality, and context of families' experiences with investigational treatments.

²⁵ I define and elaborate this theoretical concept in Chapter 3.

The findings of this dissertation are of immediate practical importance. Understanding parents' experiences is important because patients and parents are demanding quicker access to new therapeutic advances for rare and other diseases, and at present there is considerable uncertainty about how to respond to their public advocacy. They are also enrolling in therapeutic trials in growing numbers, often with the goal of obtaining access to cutting-edge experimental medicines not yet commercially approved by regulatory authorities. As a group, parents have been noted to express a high degree of tolerance for assuming medical risk—importantly, this risk is borne by their children—in their pursuit of treatment (Peay 2013). There is a shortage of medical evidence about the efficacy of supplements and off-label drugs, and a surplus of charlatans and unproven therapies, from stem-cells to electrode stimulation. Many families are mortgaging their homes to seek unapproved and/or potentially dangerous treatments outside mainstream biomedicine (often internationally) in the absence of effective treatments offered by mainstream biomedicine (e.g. Cook 2004; see also Song 2011). The result is escalating tension between the demands and expectations of parents for new drugs to treat their child's disease, and the current politico-economic system in which new treatments are developed, marketed, and regulated.

Finally, I aim to contribute with this dissertation to ongoing scholarly discussion about the nature of the clinical trial and its use in the setting of rare diseases like Duchenne. The clinical trial and its attendant methods of blinding, randomization, and placebo control, are research strategies aimed at creating a controlled environment. But they are also epistemological claims that apply a particular lens to understanding patients and their bodies. However, as this dissertation shows, some of the claims of this paradigm are problematic, in part because (as I demonstrate) the trial captures only part of the picture, and because value judgments about what

constitutes improvement or degradation in one's lived experience are irreconcilably subjective, personal, and idiosyncratic. What is "good" for one patient, may be "bad," or at least less important, for another. Moreover, patients often have entirely different expectations for treatment than those imputed to them by clinicians, regulators and policymakers—a theme that recurs throughout this dissertation and in the rare disease arena more generally.

Pressing questions then, currently confront patients, clinicians and regulators alike in an emerging pharmaceutical era for orphan diseases: What, exactly, constitutes *treatment*? Whose definition of *benefit* should prevail, and how should it be assessed? This dissertation seeks to contribute to scholarly discourse in this area by shedding light on the significance of experimental medicine and clinical research for patients, and on the ways that these meanings are connected to their own personal biographies and illness experiences. I conclude by suggesting that these dimensions of patient experience are likely to be rendered invisible when we focus only on the statistical significance of new medicines—that is, on quantifiable, measurable, and statistically significant improvements in function—to the exclusion of more nuanced and individualized ways of understanding their *everyday* significance (that is, their meaning and impact on patients' lives). Consequently, an overarching argument of the dissertation is that qualitative research has a vital role to play in understanding the significance of experimental treatments in patients' lives. If the goal of treatment is to cause improvement in the quality of life of an individual and not just in quantitatively measurable outcomes, then it follows that the assessment methodology should fit the goal. This is, I suggest, a moment at which qualitative health research and medical anthropology have much to contribute to efforts to make drug development for rare diseases more responsive to the needs of patients—who are, after all, its greatest stakeholders and its ultimate constituents.

Chapter 2: Actors, Methods, and Research Design

I begin this chapter with an overview of the main actors in the dissertation, and more generally in the arena of medical research for Duchenne muscular dystrophy and other rare diseases. I then turn to a description of the methods used in the dissertation and how the study was designed.

2.1 Parent Patient-Subjects

The views and experiences of patients, or in this case their parents, form the bulk of the data reported in this dissertation. Their voices are those of mothers and fathers who are (no matter how long it has been) constantly adjusting to, processing, and reeling from the devastating diagnoses in their sons. Though the impact and shock of this initial diagnosis recedes over time, it never really goes away. Chronic illness, as a now voluminous body of research shows, is an experience of constant and perpetual biographical revision as parents modify their personal narrative and expectations for the future, and as a child's disease waxes and wanes between periods of acuity and stability (see, among many others: Mattingly 1998; Bury 1982; Becker 1997; Kleinman 1988; Garro 1992; Murphy et al. 1988). In some families, there is more than one affected child, since children with DMD are usually diagnosed between the ages of 3-5 years and parents may find themselves with a younger son or sons already born or *in utero* who must now be tested for the disease.²⁶ Additionally, in children with Duchenne muscular dystrophy

²⁶ DMD's x-linked pattern of inheritance means that a male child born to a female carrier has a 50% chance of inheriting the disease and a 50% chance of being unaffected. A female child born to a mother who is a carrier typically has a 50% chance of being a carrier herself, and a 50% chance of being unaffected. Most female carriers

over 30% have associated cognitive and behavioural disorders, and there is an increased incidence of autism. Families with one, two, or even three affected children face an extremely high burden of care, and those with associated diagnoses are all the more complex.

After receiving their child's diagnosis, most families in North America find themselves subsumed in a vortex of doctors' appointments, laboratory tests, physical therapy, and later, appointments with school officials. Typically, they are referred in their diagnostic odyssey to the nearest tertiary Children's Hospital where care is increasingly delivered by multidisciplinary neuromuscular care teams (Bushby et al. 2010a; McMillan, Campbell, and Mah 2010). Children are usually seen under the care of a pediatric neuromuscular physician, and have regular reviews with an extensive team of health care providers—this includes respirologists, cardiologists, orthopedic surgeons, geneticists and genetic counsellors, endocrinologists, physical therapists, occupational therapists, respiratory therapists, orthotists, dieticians, social workers, physiatrists, home ventilation team palliative care physicians, and others. Often, these visits take place over the course of two or three days in hospital, usually as an out-patient. The long list of care-providers is quickly overwhelming for parents and children alike. Regular clinical visits tend to be exhausting, as parents process an overwhelming amount of clinical information. In the United States, dealing with insurance companies and/or state-provided Medicaid to determine one's eligibility and coverage can become a central, time-consuming and stressful preoccupation. While basic medical insurance is not an issue in Canada, parents in both the US and Canada face limited coverage for medical devices, prescription medication, and behavioral, physical,

do not manifest symptoms of the disease, with the exception of around 10% who may show mild cognitive delay or cardiac issues. The dystrophin gene is the longest gene found in nature, containing 2.4 million base pairs (MBP), and is thus prone to mutation. Approximately 40% of DMD cases result from a *de novo* mutation (i.e. the mother tests negative for the mutation and there is no prior family history of the disease) (Bushby et al. 2010a; Seemann et al. 2011).

occupational and psychological therapy, respite care, and counselling. The absence and/or inadequacy of such services places many parents on an exhausting treadmill researching and trying to obtain support and services for their child (Miller et al. 2009; Ray 2003). Discussing the present context of neoliberal health care policy for those with disabilities in the US, Rapp and Ginsburg (2001) point out that if paid, family caregivers' labor would cost over \$200 billion per year in the United States alone (Langone 2000),²⁷ and while health insurance typically covers the routinization of high technology health care, an estimated 21 billion hours yearly in family caregiving goes unpaid by public funds (Johnson 2000).

At home, families struggle with how to maintain marriages, friendships, and family relationships in the face of a major diagnosis. Many describe changes in their social networks as their lives are increasingly occupied by the tasks of co-ordinating care, and later, coping with mobility and emotional issues as their preteen child begins to lose muscle function and the ability to walk. Parents also struggle with learning about their son's diagnosis and many devote considerable time to computer research and fundraising activities. As we see throughout this monograph, much of the illness experience revolves around parents' struggles to maintain hope and optimism and to cope with anxiety about their child(ren)'s future.

I describe the illness experience with Duchenne in more detail elsewhere in the dissertation, but here I wish to point out that most of the patients in this study were also participating (or considering participating) in medical research by enrolling their sons in clinical trials testing an experimental compound. In doing so, they occupy a hybrid space, whether they realize it or not. Parents—as their child's primary care providers and medical decision-makers—

²⁷ Notably the figure quoted is from 2000 and would equate to approximately \$280 billion in 2014 dollars.

are simultaneously mothers, fathers, guardians, patient supporters, patients, and research coordinators. The clinical trial experience can place strains on relationships with both care providers and other families; parents must balance these often opposing roles, all while managing their expectations and hope for an experimental—maybe even curative—treatment.

2.2 Patient Advocates

The current era of social networking and electronic information has contributed to the formation of patient communities around most identifiable disorders. In the process, a vibrant, eclectic movement of patient advocates has emerged, most of whom are affiliated with non-profit charitable organizations. As prominent and vocal actors in the biopolitics of experimental research, leaders and prominent members of these groups lobby for greater attention to their illness experience on the part of the public, regulatory and policy decision-makers, industry and clinicians, as well as for increased investment in research and care (e.g. Rabeharisoa 2003; Callon and Rabeharisoa 2008; Novas 2006; Gibbon and Novas 2008; Novas 2009). Where in the past these groups were limited primarily to fundraising and social support, today they are a strong political force in a contested domain, engaged in a diverse array of activities: lobbying, strategically investing in industry and academic research, accumulating biocapital in the form of patents, tissue repositories, and patient data registries, as well as using documentary filmmaking and creative technology to communicate their message.

Rare disease non-profit associations are also increasingly important sources of financial capital, offering grants for research and clinical development to labs and companies willing to focus on their disease. Relationships with patient-groups also enable pharmaceutical and biotech companies' access to capital in the form of knowledge about the illness experience that can be

invaluable for designing a clinical trial. For instance, choosing and developing an outcome measure for a disease that is relevant to patients is much easier with their input, and relationships with patient groups can be invaluable when recruiting patients to clinical trials.²⁸ This has enabled patient advocates to amass considerable influence as gatekeepers of access to patients' bodies for clinical trials. Several patient groups have also entered the patent-game, purchasing the rights to outcome measures, animal models, and devices in order to advance drug development and generate revenue. Some patient-groups exchange a form of genomic capital with companies and academic labs, as they begin to collect, bank, and ship cells, blood, and tissue samples for experimental research.

Seeing the potential for advancing their programmes, biotech companies working in rare disease have taken great pains to make inroads and grow their links to patient advocacy groups. For example, representatives from pharmaceutical companies attend and sponsor conferences, fundraisers and gatherings organized by non-profits, including, in the case of Duchenne, those of groups like the Muscular Dystrophy Association (MDA), Parent Project Muscular Dystrophy (PPMD), CureDuchenne, and other patient-advocacy groups. Such interaction may involve informal discussions about the disease experience, and more formal research, including pilot studies, surveys, and lab research using tissue donated by patients.

As with any community of people with varied backgrounds, perspectives, subject positions and experiences, there are frequently differences of opinion within the Duchenne

²⁸ Patient input into outcome measures and trial design is increasingly mandated by United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) under the auspices of Patient-Focused Drug Development (PFDD). In the US, this approach has been mandated in the 2012 Food and Drug Safety and Innovation Act (FDASIA). Though a similar program of renewal is underway at Health Canada under the title of Health Products and Food Regulatory Modernization, this program has yet to result in substantive legislative or policy change (see CIHR 2011; Health Canada 2012).

advocacy movement regarding which areas, activities and/or strategies should be prioritized, and parents may express affiliation with a particular group over others. Allegiances in the patient-advocacy sector raise questions of biosociality and citizenship in a genomic era. I explore the Duchene patient advocacy movement further in Chapter 3.

2.3 Clinicians and Site-Investigators

This research draws on formal interviews with four physicians who treat patients with DMD (and informal interactions with many others). Most of the clinicians who care for and perform clinical research on Duchenne patients are sub-specialized pediatric neurologists.²⁹ Though there are various paths to qualification, these doctors train initially as MDs before enrolling as residents who in Canada spend two years in general pediatrics, then three years in pediatric neurology and subsequently complete a fellowship or further training in neuromuscular disease. Some have additional training in genetics, whether formally or by clinical experience treating diseases increasingly recognized as having a strong genetic component. Some have also pursued additional PhD training in neuromuscular biology, and oversee active research labs or programmes in addition to their clinical work.

For the majority however, the practice of pediatric neuromuscular medicine is primarily a clinical sub-specialty. A shortage of neuromuscular specialists means that their services are in high demand, and waitlists for clinic appointments can be in the order of months or even years.

²⁹ Recent improvements in the lifespan of children with DMD mean that adult neurologists are increasingly important health care providers in the care of young adults with Duchenne muscular dystrophy. In the past, a pediatric patient would see an adult neurologist only when they could not access a sub-specialized pediatric neuromuscular physician. Clinicians untrained in this disorder were frequently criticized for providing inadequate care. Today, they, along with physiatrists, are being integrated into multidisciplinary care teams as many clinics try to establish protocols that improve continuity-of-care for children reaching adulthood (and thus ineligibility for pediatric care) (Abbott, Carpenter, and Bushby 2012; Schrans et al. 2013; see also Miller et al. 2009).

The result is that many pediatric neurology specialists are over-worked and challenged by multiple demands on their time. Most lament a lack of psychosocial supports for their patient-families. Since these disorders are serious and life threatening, neurologists tend to follow and develop relationships with families and children over long periods of care. They also share in common other challenges delivering care to patient-families for a complex disease. One neurologist remarked to me,

It is often very challenging to communicate with families; most parents have only a rudimentary understanding of medical issues, about a disease that is really very complex. It requires a great deal of background knowledge in genetics, muscle biology, and the human body to really understand. It really affects all of the muscles in the body, so I often find myself trying to explain how the disease is manifesting in different systems—like the digestive system for example. Most of my patients with the disease have weakness in their bowels, in terms of moving food through the digestive tract, and so diet becomes a really key element of taking care of these kids' health, especially when they are more susceptible to weight gain with being on steroids. So I often find myself explaining how, for instance, a muscle disease manifests itself in the digestive tract, or in the lungs, or the heart, and sometimes this makes me more of a generalist than I think people realize, or even than I would have thought when I first started my training.

In a sense then, neurologists are both highly sub-specialized clinicians and general care practitioners for Duchenne patients, since much of their work with patients involves explaining how test results and symptoms from various parts of the body are connected. They are hybrid practitioners who must work across many medical disciplines and specialized clinical dialects while interacting with their patients.

Since very few treatments for neuromuscular diseases existed even a decade ago, clinical trials are a relatively new phenomenon in pediatric neurology. As they become more common, clinicians are faced with the challenges of an additional form of professional hybridity. Those carrying out research (that is, Principal- or Site-Investigators) must balance the demands of their

patients for a clinical relationship, with those of the clinical trial for a detached, objective and consistent approach to interactions with research subjects. I describe this tension in their work further in Chapter 5.

Neurologists are also increasingly facing demands to “get into” research and to act as site investigators for clinical trials. For most, this emerging responsibility involves new relationships with trial sponsors, regulatory agencies, and other personnel. One neurologist described this shift in how he sees his practice and his responsibility to his patients vis-à-vis what constitutes “good care.”

I mean, you genuinely as a person want to provide hope around [the disease]. ... My role, I feel it's now my responsibility to just provide them [patients/parents] with the opportunity to be involved in those kinds of things, like trials, if they want. ... Because I think there's two parts of it. I mean one is ... helping them understand that this is still an experimental process. But even *that* offers some hope for people. And so, the way I think about it [is] I try not to get too excited one way or the other about the drug. I mean PTC is gonna work, or it's not gonna work. But I still think there's an intangible benefit to people to even be a part of a clinical trial. I mean that is very real. Like there are lots of people [who] want that experience, and that opportunity.

So ... in Canada, I'm trying to create an environment, where companies will consider Canadian patients for clinical trial opportunities. ... I think, regardless of what happens, I want to be able to provide for my patients an opportunity at least to consider those things and up until now ... Canada probably hasn't been considered really the spot to really get your data. And so I view that alone as a bit of a victory for our patients.

Several neurologists remarked to me that their entry into the world of clinical trials for Duchenne also entailed navigating the medico-legal implications of this type of clinical work. Under current regulations, site-investigators retain full medical-legal responsibility for their clinical decisions made with or on behalf of patients in the trial, and they often continue to care for patients after the trial has ended. However despite retaining this liability, they describe

having little or no input and control over the design of clinical trial protocols, which is carried out by the trial sponsor. This can lead to dilemmas for the site-investigator, who has ethical and legal obligations to not only implement the trial protocol, but also to manage care for their patients in a study. For example, if a safety issue arises in a trial that could potentially have a deleterious health outcome for a patient (an abnormal urinalysis result suggestive of kidney damage, for example), the clinician has a responsibility to report any adverse events and to follow the guidelines outlined in the trial protocol to deal with them, but they also retain full liability for managing such events appropriately and ensuring that the long-term health of their patient is not compromised. Such incidents can blur the line between the supposedly separate domains of research and care, and place neurologists in the difficult position of reconciling conflicts between their ethical obligations as site-investigators (to carry out the trial and ensure that it remains blinded) and their medico-legal obligations as care providers (to protect the long-term health of their patients). Though I do not explore this topic in depth in this dissertation, questions about how neurologists navigate such dilemmas, and how they engage with trial sponsors in responding to them, are worthy of further examination.

2.4 Research Co-ordinators

This study involved field observations and interactions with several hospital-based research co-ordinators, and formal interviews with two. These individuals are typically employed by a hospital's neurology department and handle the day-to-day activities of the clinical trial. Often, they act as liaisons between the Principal-Investigator, patient-families and the trial sponsor, making them the first and most frequent points of contact with families during the trial. Their responsibilities include ensuring the completion of applications for hospital,

ethical and regulatory approval to conduct the trial, scheduling and co-ordinating patients' study visits, overseeing the randomization and treatment assignment process, collecting, storing and shipping tissue samples and test results, and organizing the documentation and filing systems (research charts) for the trial. Since study visits with patients often last more than one day, the research co-ordinator is likely to be the main point of contact for families as they navigate through different areas of the hospital. Like clinicians and other care providers, they are blinded (if it is a randomized, double blind, controlled trial) to the individual treatment assignments of trial participants. Research co-ordinators usually have backgrounds at the bachelor's level in nursing or the biological sciences, though a surprising number are international medical graduates with MDs in their home countries.

Research co-ordinators often find themselves balancing a key tension in their work: they work closely with families and often develop caring relationships with them; however these relationships must be balanced against their professional obligation to maintain the integrity of the trial by ensuring that the study remains blinded and that subjects are treated consistently. This means that they are often constrained in how they can communicate with patients. For example, they must often refrain from providing detailed clinical information when parents ask whether their son's muscle function is improving in a trial, and to answer questions in vague or general terms that do not reinforce or give clues about which treatment a patient is receiving. Many describe a professional tension between "caring about" what happens to their patients, a desire to support them and answer their questions more candidly, and the need to approach their clinical relationships dispassionately (see also Fisher 2006). Since their contact with families is occasioned by the clinical trial, it typically ends when the trial is concluded.

2.5 Trial Sponsors

“Trial sponsor” is a rather vague term used in therapeutic development to refer to an entity (usually a biotech or pharmaceutical company) seeking to bring an experimental compound to market by demonstrating its efficacy and safety in clinical trials. The trial sponsor retains legal responsibility for administering the trial in accordance with regulatory requirements, manufacturing and providing the experimental compound to clinic sites, and overseeing data collection. Traditionally, the few trials carried out in rare/genetic diseases were run by small to medium-sized biotech companies started (or “spun-off”) by academic principals with the goal of commercializing a compound or scientific discovery. The industry is increasingly crowded, however, by large-cap companies entering the sector as a new wave of investment in orphan drugs materializes.

PTC Therapeutics fits in the former category, though its size has grown substantially. Currently it is a publicly traded entity with a market-capitalization of \$993 million.³⁰ The company was initially founded by academic scientists Stuart Peltz and Allan Jacobson to commercialize a system for screening small-molecules that interfere with RNA decay, which they developed at the Robert Wood Johnson Medical School at Rutgers University. In simplified terms, this ability to modulate RNA expression amounts to a kind of switch, enabling researchers to control gene expression by turning a gene “on” or “off.” The control of gene expression through RNA and other means—broadly referred to as epigenetics—has opened a frontier of curative possibility, animating scientists, investors, and families in hopeful discourse about its potential application for a long list of incorrigible diseases (Good et al. 1990; Hamburg and

³⁰ As of August 22, 2014. Figure obtained from NASDAQ.

Collins 2010; Feero, Guttmacher, and Collins 2010). Ataluren and other drugs that modify gene expression are currently both “hot topics” in medical science and the subject of billions in capital investment. Their appeal stems from their potential to modify disease processes “at the genetic level” without the technical difficulty of correcting the genetic mutation itself, as is required in gene therapy.

It is important to note that trials are often sponsored by more than one company working in partnership. Typically, a biotech company such as PTC will bring new molecular compounds through pre-clinical and animal testing. However, the high cost of human trials means that biotechs must often partner with a larger entity with deeper pockets. In the past, it was common for small companies to sell their assets, shares, and technology to a larger industry player via merger or acquisition prior to carrying out pivotal trials. However, in an era of capital fluidity and company outsourcing, it is today more common to partner with larger pharmaceutical companies through licensing deals. These arrangements offer a larger pharmaceutical company with substantial capital reserves the right to market a new drug once approved, in exchange for investment and/or technical assistance in its clinical development. Transfers of capital between the two partners usually take place upon the achievement of pre-specified “milestones” (called “milestone payments”), such as selecting a molecular compound to move forward into clinical trials, completing a trial, or mounting an application to regulatory agencies. The agreements are structured to incentivize progress, however they usually provide each party with the ability to back out or terminate the partnership if plans change, or if data are not as positive as hoped. Partnerships in pharmaceutical development are thus transitory, ephemeral, and contingent, and nearly always under threat of extinguishment if a clinical trial fails.

In the case of the trials discussed here, PTC Therapeutics entered a partnership with Genzyme, a much larger pharmaceutical company specializing in rare diseases, prior to initiating their Phase 2b pivotal trial. Under the agreement, PTC was to commercialize and sell ataluren in North America, while Genzyme obtained the rights to do so in the rest of the world.

These developments raise a number of key anthropological questions relevant to the present project and beyond. Foremost among them are the power-relations inherent in relationships between trial sponsors, patients (or in this case, their parents), and patient-communities. Companies entering the rare-disease arena wield influence by virtue of possessing the technological wherewithal to cure and relieve families of their disease burden.³¹ Patients and families, whose interpretations of medical science and therapeutic possibility are entangled with the burden of coping with a fatal disease, are deeply hopeful for cure. This can make them vulnerable to exploitation, disappointment, and the promotion of false hope by trial sponsors and/or academic scientists promoting their products or research, which may be unproven or untranslatable, and may never come to market (Dubowitz 2002; 2004).

The overpowering desire on the part of parents, the financial stakes involved, and educational disparities between scientific “experts” and patients with a lay-understanding of disease biology, give rise to questions of equity. As I suggest throughout this dissertation, there are important, unresolved questions about the extent to which patients are truly included as partners in the drug development process, whether they are adequately consulted and heard in the design, testing, and approval process for new drugs, and whether their voices are sufficiently acknowledged in steering scientific projects in which they are penultimate stakeholders

³¹ Arguably, this can be conceived of as a form of symbolic capital, though I do not pursue a Bourdiesian approach here.

(including decisions about whether to move a compound forward or to abandon its development).

And yet still, things are more complicated. As I show in Chapters 3 and 4, The well-trodden—and all-too-common and commonly justified—narrative of “big pharma” ignoring the wishes of a passive and powerless group of patient-consumers in its pursuit of profit, does not map neatly to the rare disease arena; such renderings can overlook a great deal of nuance and agency on the part of (some) patients and patient-advocacy groups. In some instances, the biopharmaceutical company is as dependent on the patient or the patient-community, as vice versa.

2.6 Others Involved in Research

Finally, there is a bevy of other hospital staff members who are instrumental to the performance of the clinical trial, but whose perspectives may not appear in narratives about or reports of clinical research. In the case of Duchenne, this includes physiotherapists and occupational therapists who administer muscle function, strength, and flexibility testing as part of the trial, clinical secretarial staff, hospital-based travel co-ordinators, pharmacists, nurses and paramedical staff (including imaging technicians, for example), pathologists, and similar professionals. Though I had the chance to observe some of these providers—mainly as they undertook the activities of neuromuscular assessment—their perspectives on the clinical trial process are not explored in depth here and would be a fruitful area for future research.

2.7 Data and Field-Sites

This dissertation uses a qualitative, field-based and multi-sited approach to investigate what parents and children with DMD experience as they seek an experimental treatment for a rare disease. A qualitative approach is best suited to examine the issues surrounding families' understandings of their child's disease, genetics, and medical research, because it captures the complexity, contingency, and dynamic change that are part of families' experiential accounts. Additionally, a qualitative research approach helps us to better understand the relationships, experiences, values, and morals through which parents build their understandings of, make decisions about, and tell stories of their participation in clinical trials (Bernard 2006). The dissertation adopts an ethnographic approach. The main methods used are in-person interviews and field observation, which are well-established as the most direct scholarly tools a researcher can use when seeking to access the lived experience of research participants (Giacomini and Cook 2000; Pope and Mays 1995; Pope, Ziebland, and Mays 2000). Secondly, the dissertation is supported by my own extensive collection of published media, online social discourse, and popular literature pertaining to Duchenne muscular dystrophy, experimental research, and rare disease.

I obtained my ethnographic data through research activities that were conducted from 2009 through 2013.³² During that time, I conducted formal, semi-structured interviews with 29 parents from 21 separate households (16 mothers and 13 fathers), three young-adult men with DMD, four neurologists, two research co-ordinators, and three laboratory-based scientists. These formal interviews took place in Canada and the United States, in both home and hospital

³² The bulk of the ethnographic data collection for this study was carried out during 2009-2010. Data analysis, follow-up interviews, and write-up took place in 2011-2013.

settings, and were supplemented by other informal discussion, mainly at patient conferences (see below) and by telephone. I also accompanied 10 families at two hospital sites as they participated in medical procedures and appointments (usually over two full days) related to both research and regular clinical care. These latter experiences enabled me to better understand the routines of research participation, its relational and communicational constraints, and the physical environment (i.e., the tertiary-care pediatric/children's hospital) in which clinical trials take place. My experiences and observations in the hospital setting were supplemented by semi-structured interviews with parents that were conducted in their homes. Together, the interviews and observational methods enabled me to see the impact of the clinical trial on the lived experience of parents and patients both within and outside the walls of the hospital.

In addition, during my fieldwork I attended six patient advocacy conferences (five in the US and one in Canada) where I had the opportunity conduct informal interviews and observe, interact and develop relationships with many parents, advocates, clinicians and industry professionals. At these conferences industry professionals, academic laboratory scientists, and physicians (mainly neurologists but also geneticists)³³ present the latest research findings and medical knowledge about Duchenne. Regulatory professionals also attend and present information about how drugs are developed, evaluated, and approved to an audience of parents with diverse backgrounds and varying levels of experience with the disease.

Parents interact extensively with each other at these conferences in both formal sessions and informal social settings. They build friendships (or just as often, solidify previously-made

³³ In Canada, the United States and other Northern countries, neurologists are typically the main specialist care-providers for DMD patients (McMillan, Campbell, and Mah 2010). Clinics are usually based at tertiary-care hospitals. In the United States, most pediatric neuromuscular care is provided by clinics sponsored and funded by the Muscular Dystrophy Association (MDA). It is estimated that 7-10% of children under the age of 18 in the United States do not have access to medical insurance or regular medical care (Kominski 2013:44).

digital connections online) and share their experiences and advice concerning how they cope and adapt to living with their child's disease. Increasingly, boys and men with DMD play key roles in the conferences by presenting their perspectives and experience with the illness to other families, most of whom have younger children. Attending the patient conferences enabled me to develop my understanding of the science and community around DMD and to learn more about what families go through with the disease. I was also able to pose questions to parents and researchers, and to develop my own analytical queries about the social and political arenas in which biomedical research and drug development for rare diseases are carried out.

Finally, two other field experiences contributed to my understanding and thinking about Duchenne. In the first case, I was hosted for an extended visit and tour of the Wellstone Muscular Dystrophy Center at Children's National Medical Centre in Washington, DC. While there I was able to interview lab-based researchers about their work and to observe them performing basic and therapeutic research in both tissue-culture and animal models. Among other topics, I spoke with them about their perceptions of and interactions with patient-families, and what motivated them in their work. I also attended a clinical conference in Italy during which a small group of neurologists, endocrinologists, geneticists, and parents from North America and Europe met to establish guidelines for treating some of the endocrine problems caused mainly by the use of steroids to treat the disorder (including obesity, delayed puberty, osteoporosis, and short stature)—issues that are of growing importance to DMD patients in the global North.³⁴ During this conference, I was able to observe and interact with specialist

³⁴ These symptoms have always been part of the natural history of Duchenne. However, they are increasingly prevalent as a result of widespread use of corticosteroid therapy, which has recently become standard-of-care for Duchenne patients. In addition, a shift has also occurred among neuromuscular practitioners in conceptualizing Duchenne as a "treatable" disease whose symptoms can be actively and aggressively managed, rather than a fatal disorder that should be managed reactively.

clinicians working within an evidence-based model of health-care, as they sought to develop consensus guidelines in an area where virtually no evidence existed (that is, in the use of hormone therapy in Duchenne patients) (Bianchi et al. 2011). The challenges of applying evidence-based approaches to care and treatment—a paradigm, it should be noted, on which the entire drug development project is based—in a rare and historically neglected disease where large-cohort and natural history data is severely lacking, creates an enduring tension in the field of neuromuscular medicine, and more generally in all orphan diseases. Attending the conference enabled me to see clinicians in dialogue as they sought to incorporate and account for patients' requests for non-evidence-based treatment, while still adhering to a perceived ethical obligation to practice evidence-based medicine and avoid harming their patients.

2.8 Ethnography

Ethnography is the core research method used by anthropologists, and the subject of a rich, extensive and spirited literature regarding its production and aesthetics (e.g. Geertz 1973a; Clifford and Marcus 1986; Behar and Gordon 1995; Scheper-Hughes 1995; Gupta and Ferguson 1997a; Hammersley and Atkinson 2007; Puddephatt, Shaffir, and Kleinknecht 2009; Maanen 2011). I suggest here that ethnography is an appropriate methodology for this research because of the critical role that social and cultural factors play in the meaning and performance of investigational medicine. Ethnography permits a micro-focus on detail and nuance in individual cases. This can be especially illuminating when addressing research topics that are emergent—where the cultural categories, roles and relationships are still being worked out (as in this case). Beeson (1997), for example, has argued that an ethnographic approach is uniquely suited to the study of genetics (and by extension, gene-based drugs) because actors with diverse backgrounds

interact using language and concepts that are technical, unstable, and changing rapidly. As a research method, ethnographic investigation allows the researcher to develop first-hand knowledge of what patients and other actors experience when making sense of investigational therapies in real time. Real-time observation of clinical encounters and social interactions (for example, in hospitals and at patient advocacy conferences) enables observation and analysis of the different ways in which meanings emerge, converge and conflict, even when these processes are not explicit or apparent to the research participants themselves.

As the extensive literature (cited above) on ethnographic practice demonstrates, effective ethnography requires careful attention to our own subjective perspectives as observers and interpreters of our research data.³⁵ In carrying out and writing this ethnography, I have tried to adopt a critically reflexive perspective that accounts for my own interpretive framework, personal history, and subjective experience (Good 1994; Marcus 1998; Maanen 2011). I approach my data as a qualitative researcher seeking to better understand the experiences not only of the patient-families with complex chronic health conditions, but also the various professionals who care for them and who work on developing new treatments. I also approach my data as a father myself of two young boys. When analyzing the narratives collected in this study I have strived to maintain a dispassionate approach, while also shedding light on the visceral, experiential, and emotionally fraught dimensions of the terrain in which I am working.

³⁵ To some extent this is also true of other forms of scientific research, though it is less often acknowledged (e.g. Latour and Woolgar 1979; Latour 1987; Rabinow 1997; Hacking 1975; Hacking 1990; Gibbons et al. 1994; Bowker and Star 1999; Ioannidis 2005; Tsilidis et al. 2013; Button et al. 2013; Fujimura 1996; Franklin 1995; Martin 1998).

2.9 Semi-Structured Interviews

Most of the data for this project come from interviews with various actors connected to drug development for DMD. I relied primarily on semi-structured interviews conducted in the homes of the respondents, although I also carried out informal interviews in conference settings and while interacting with parents and children in hospital. The semi-structured interviews were based on an interview guide (i.e., a written list of questions and topics to be covered during the interview). However, the interviews were loosely structured in order to enable respondent(s) to pursue new leads, spontaneous thinking, and unanticipated connections in the course of speaking about their experiences. This technique achieves a balance between consistency in the questions and topics covered across cases, and a more unstructured approach that gives control to the respondent in developing their answers to questions and leading the interview toward the subjects and issues that are most salient to them. A narrative approach was used as part of the interviewing, and a variety of probes were employed to elicit lengthy and detailed responses to questions. These techniques yielded a dataset that is grounded in the direct experiential accounts of interviewees. As noted above, most of the semi-structured interviews were conducted in participants' homes.³⁶ However, in cases where this was not possible or when interviewing professionals, interviews took place in a quiet office, a hotel meeting room, or a patient examination room. Interviews generally lasted between 90 minutes and three hours in length, and all interviews were digitally recorded and transcribed.

³⁶ Sankar (1986) discusses how home-based interviews can elicit more detailed information about respondents' everyday lives than hospital-based ones, partly due to the effect the physical environment and social conventions of the clinic can have on respondents' impressions of what constitutes "relevant information" to the interviewer.

In order to avoid third-party-present effects—and considering the sensitivity of the topics under discussion—I conducted most of the interviews without children present.³⁷ However, in a few cases where adolescents and teens with Duchenne expressed an understanding about my research and a desire to be involved, they also participated in the interview. These interviews provided valuable insight into the attitudes of young men with Duchenne toward therapeutic research, and their reasons for participating in it. However, there were not enough cases in my research sample to conduct a rigorous analysis of these young men as a separate group, and so their perspectives were used mainly to supplement the information provided by their parents. Since this study focused on parents’ attitudes toward Duchenne and clinical research, I did not seek to interview young men or children with Duchenne without their parents present.³⁸ In the cases just described, it is possible that the presence of these young men at the interview affected their parents’ responses to questions and their willingness to share information. However, in my experience the families who chose to have their children present tended to communicate openly about Duchenne with their son(s).

2.10 Direct Observation and Accompaniment

In addition to interviews, I also carried out direct observation in several field settings, including conference settings, informal social events, families’ homes, laboratories and hospitals (as described above). I used these opportunities to learn more about the practices and perspectives of the different actors in my research, and to evaluate how various actors

³⁷ Including the burden of care posed by the disease and parents’ efforts to improve their sons’ quality and length of life.

³⁸ As this dissertation shows, such research is urgently needed in order to better understand the perspectives of children, adolescents, and adults with Duchenne (and other rare diseases) regarding their illness experience, treatment and research.

communicate in different environments (e.g. in hospital versus home versus conference settings). I was also able to connect my interview data with my own direct observations of parents, especially when accompanying them in hospital and during clinical interactions. This allowed me to see which aspects of families' everyday experiences and narratives were discussed and/or addressed during clinic visits, and which parts were deemed "private" or unworthy of discussion with clinical staff. I was also able to observe the practical routines of clinicians, ancillary health service providers, and laboratory-based neuromuscular scientists.

Observation in hospital was primarily carried out at two sites. During these visits, I accompanied parents and their children during their two-day study visits and/or during appointments for regular clinical care. I walked with them through the hospital to their various appointments with specialist clinicians and other service providers, I sat with them in waiting rooms, and I watched as they completed various tests and procedures, including muscle biopsy, lung function testing, physiotherapy, and MRI. Field observation enabled me to develop a better sense of what trial participation entailed, and to engage families in informal discussion about their experiences. During clinical interactions, I observed quietly and conducted myself as would a resident or medical student; indeed, I often observed alongside such trainees. In order to avoid even the remote possibility that my presence might affect the randomized, double-blinded placebo-controlled Phase 2b study, direct observation of study visits was carried out only with families who were engaged in the open-label Phase 2a extension trial.³⁹ These families had already developed some experience with the clinical trial and were aware of their treatment

³⁹ In fact, parents found my presence entirely unremarkable since they were used to having trainees and residents passively observe their interactions in clinic (see below).

assignment. In an abundance of caution, interviews were carried out after hospital study visits in order to ensure parents' reflections during our interaction did not affect their responses to questions and questionnaires carried out as part of the clinical trial itself.⁴⁰

2.11 Multi-Sited Design

I designed this study as a multi-sited ethnography of the medical research enterprise for DMD, as it has manifested in the US and Canada. The multi-sited ethnographic model entails a methodological shift in terms of how the research field is conceptualized (Gupta and Ferguson 1997b; Hannerz 2003; Marcus 1995). Unlike traditional approaches that focus on one geographically-bounded community or culture, the multi-sited method seeks to account for the ways that ideas, meanings, and people travel through time and space.⁴¹ Its popularity has coincided with a shift in the anthropological gaze toward problems “at home,” and to work in the de-exoticized cultural settings of “the West” (Gupta and Ferguson 1997a; Martin 1998; Nader 1972; Appadurai 1986).⁴² The method is appealing because it combines ethnography's traditional strengths (e.g. the grounding of interpretations in “thick description” [Geertz 1973b]) with a focus on broader historical and social contexts (Marcus 1998). It also enabled me to address a research problem that would otherwise be impossible to examine using traditional

⁴⁰ As I discuss below, in retrospect these concerns were overwrought. Later in the dissertation, I also describe how parents are constantly reflecting on their experiences in the trial as it overtakes everyday life. My interviews were only one of several occasions in everyday life where such contemplation and communication occurred.

⁴¹ Traditionally, ethnographies focused on explaining the lifeways of bounded—usually far-away—groups of people who share a particular “culture.” In this approach, culture often served as a proxy for geographic locale, in that study groups were often defined by virtue of their shared location of residence, and their cultural homogeneity taken for granted.

⁴² These changes have paralleled a broader re-orientation in terms of how the discipline conceptualizes its main unit of analysis—that is, the concept of culture. As a bounded, homogenizing and unifying concept, culture has come under increasing pressure when called upon to explain the globalized, fractured, and multiply-embedded subjectivities of the post-modern world.

ethnographic methods, since individuals with rare disease are just that—rare—and scattered distantly across geographical space. Families participating in clinical research for DMD are even rarer, being a subset of an already small population, a fact which necessitated a multi-sited design in order to make the research feasible.

One shortcoming of the multi-sited approach is that axes of commonality and difference in the groups being studied are often overlooked or poorly defined (Bernard 2006). I have tried to articulate the commonalities and differences between cases throughout this dissertation by adopting a comparative approach while at the same time maintaining critical distance. While carrying out the study, I tried to reflect continually on whether my research design was capturing an accurate representation of how the various groups were composed and arrayed. It is often said that no two boys—and no two families—with Duchenne are alike, given the clinical variability of the disease; I tried not to take for granted the generalizability of the cases presented here, nor to make assumptions about what families share, and what they do not.

2.12 Recruitment

Participants in this study were recruited using a targeted sampling method. This method aims to reach potential study participants with attributes of interest to the researcher—in this case, those experiencing Duchenne muscular dystrophy as parents, or those who work with the disease in an occupational or professional capacity. Targeted sampling aims to identify participants who come from particular social locations, cultural backgrounds, or who have personal experience that is relevant for answering a particular research question. The objective is to maximize diversity within the sample in order to account for the breadth of human

experience and perspectives on a given topic.⁴³ In the present study, families who were enrolled or who considering enrolling in clinical research were of particular interest. These families were recruited primarily via patient rosters at three clinical trial sites. Families who met the inclusion criteria were invited by a research coordinator to participate in a home-interview. Where feasible and appropriate, parents were also asked if they wanted to be accompanied by myself during their appointments at hospital.⁴⁴ Those who expressed interest in the study were referred to me, and I was able to follow-up, discuss their participation, and explain the study prior to obtaining their consent.

One potential issue with the sampling method I used is that prior to my reaching them many parents in this study had already enrolled in a clinical trial via the study-site. This introduced a source of potential bias, given that research staff at the trial centre had already applied their own eligibility criteria in identifying a particular child as a candidate. The sampling methods used in clinical trials are often designed to minimize variability and recruit a homogenous population, while I was seeking to account for diversity by identifying people with a variety of backgrounds and experiences. However, selection criteria for the trial were focused primarily around medical and biological (as opposed to biographical) features of trial participants, including their age, genetic mutation, and medication history. In the end, my final group of participants contained a healthy range of families with different ages, abilities, places-of-residence and backgrounds.

⁴³ This is in contrast to some quantitative sampling methods, and in particular those used in the controlled clinical trial, which use randomization, restricted eligibility criteria, and in some cases stratification, in order to minimize within-group variance in a sample. I discuss this further below.

⁴⁴ In order to avoid influencing data-capture during the Phase 2b trial, only families participating in the Phase 2a open-label study were observed in hospital (see “Direct Observation” above).

However, it is important to point out that a population of research participants cannot be assumed to be representative of the Duchenne patient-population as a whole. The former have already been identified as having “lucky mutations” (see Chapter 3), and their experience with the disease is likely to be substantially different than those whose genotype offers less hope for treatment. Additionally, in many cases these families were already obtaining clinical care at a premiere neuromuscular centre. Such centres tend to be located in urban areas and accessed (particularly in the United States) by families with the health insurance and social capital required to obtain specialized care. Thirdly, families who participate in trials are likely to be particularly motivated and exhibit a higher level of understanding about their son’s disease, and these families also tend to have both the means and flexibility to bear the onerous burdens and time commitments of trial participation (see Chapter 4). Finally, I cannot exclude the possibility that trial staff employed their own informal selection criteria in identifying patients they deemed “suitable” for participation in the trial. For example, I discuss in Chapter 4 how some children are more likely to be offered a trial spot than others. As such, it should be emphasized here that the experiences of the parents whose stories appear in this dissertation may differ in significant ways from those of more “typical” Duchenne families.⁴⁵

I cannot exclude these potential sources of bias; however, I did take steps to mitigate them. In addition to recruiting through clinics, I recruited families in person at patient advocacy conferences. In order to provide cases for balance and comparison, I also recruited several families from different cultural backgrounds, as well as families that were either ineligible or chose not to participate in the ataluren trials. I made use of snowball sampling techniques and

⁴⁵ To the extent that such typical families exist, for this category too, is an abstraction of convenience given the individual variation in how the disease presents and is experienced.

conducted inquiries with both my own research participants and with patient advocates, in order to identify families whose experiences were particularly unique or who might not have been captured through my existing recruitment channels.

Despite these efforts and with a few exceptions, the group of families who ultimately participated in this research is predominantly Caucasian, and most participants come from a middle/upper-middle-class socioeconomic position. All but two of the families recruited for this study spoke English as their primary language. I suggest that the under-representation of families from low-income and visible minority backgrounds in this study stems in part from an underlying inequity in access to experimental therapies and high-quality care for such patients (e.g. Ford et al. 2008). It is also reflective of an inherent selection bias common to much social science and health services research, which often suffers from a conspicuous absence of minority perspectives (Epstein 2009).⁴⁶ This is indeed a pressing issue, and though anthropologists have been instrumental at adding underprivileged voices to the records of public and scholarly discourse, this research—by virtue of the topic it considers and the population it samples—follows more appropriately in the tradition of Laura Nader’s notion of “studying up” (Nader 1972).

Finally, I should note that professionals interviewed and/or observed for this study were identified for their expertise and contacted directly.

⁴⁶ Still, one of anthropology’s greatest contributions has been its success in accessing and giving voice to people in marginal and disadvantaged social positions. To cite but a few classic examples, see the works of Farmer (1999; 2004a), Scheper-Hughes (1992), Bourgois (2003; 2009) and Biehl (2007).

2.13 Ethics and Access

Readers may have questions about the relationship between this study and the ataluren clinical trials. This research was designed and conducted independently of the clinical trials, and was not funded or affiliated with PTC Therapeutics in any way. This independence was important, and I repeatedly emphasized this fact to all of my participants and interviewees in order that I would not be seen by them as a representative of either Parent Project Muscular Dystrophy (PPMD)—the non-profit organization that funded my research via an independent grant—or the trial sponsor. I concerned myself with establishing a relationship of trust and transparency with my research participants, and I was careful to ensure they understood that any information they shared with me was part of my own study, that it would not form part of the clinical trial dataset, and that it would not be shared directly with either organization.

This was important for two reasons. First, I wanted to ensure that parents felt comfortable speaking candidly about their experiences with medical research and its impact on their lives. I was aware of the possibility that if research participants perceived me as being affiliated with PPMD or PTC Therapeutics, they might be less forthcoming or willing to participate based on their impression of these organizations, or alternatively that they might tailor their responses to express support for them. I emphasized in both my interactions with parents and in discussions around informed consent that participation in my study would not affect a child's eligibility or enrollment in any other study.

Secondly, I wanted to ensure that parents' participation in my research did not affect the clinical trial they were participating in. I was aware of the possibility that, for instance, extended reflection precipitated by the interview process, or my presence during clinical encounters, might

affect how parents answered questions asked of them by research staff (such as their responses to Quality-of-Life questionnaires, or to questions asked by their clinicians).

I believe I was successful at ensuring that my research did not affect the clinical trial itself—and in turn, at ensuring the fidelity of my own results—for several reasons. First, my impression was that parents understood my independence from the clinical trial and my scholarly impartiality as an academic researcher. During the consent process, I took considerable time and asked several questions to verify their understanding of this point. Most of my interviews also covered topics which parents were already being asked about by others in their social networks, and about which they were already thinking deeply and discussing among themselves (especially given the all-consuming nature of the clinical trial experience). Although my research may have affected how parents storied their experiences and ordered events temporally when communicating with a specific audience (i.e., me, the anthropologist), I consider it implausible that recounting their experiences to me altered their perceptions of the investigational drug in any significant or enduring way, since they were already grappling with many of the issues addressed by my research prior to discussing them with me.

That said, I took extra precautions, including scheduling interviews after (rather than before) study visits had already been completed. I was also careful not to offer my own opinion during interviews in order to avoid reinforcing or granting legitimacy to parents' impressions of the drug, its effects, or its impact. On the few occasions in which parents posed questions about the medical aspects of the study or about DMD more generally, I declined offering an opinion by demurring and clarifying my own position as that of a researcher and not a physician with medical expertise. Similarly, I was careful during interviews not to share comments related to

me by other families in an effort to avoid offering social legitimacy to parents' idiosyncratic experiences and impressions.

Regarding my presence at clinical appointments and the potential for introducing bias, I took care to ensure that my observations were passive rather than participatory. Families seemed comfortable with my presence in the same way they are used to residents, student nurses, and other care providers observing their clinical interactions (and indeed, many of these same individuals came and went during the time I spent with families in hospital). I carefully explained my role and my research during informed consent sessions prior to observing clinical interactions. Out of an abundance of caution, I did not observe study-visit assessments for patients participating in the Phase 2b placebo-controlled trial, and instead restricted my observations of research-related visits to families engaged in the open-label Phase 2a extension-study.

Finally, in planning my research, I anticipated the possibility that parents might share adverse events while on the study drug with me which they had not shared with their care providers. In such a scenario, a child's safety could be of concern. In an extreme case, there could be a potential ethical dilemma if a parent's refusal to disclose appeared to be jeopardizing the health of his/her child. Accordingly, when parents described side effects or unexpected concerns with me during interviews, I asked them casually whether they had already discussed these with their clinician. In all instances, parents reported that they had discussed these experiences with their neurologist prior to their meeting with me. In the end, I felt comfortable that my interaction with parents did not influence their willingness to disclose adverse events, nor did it precipitate any disclosures that might not otherwise have been made.

For its part, PTC Therapeutics was aware and supportive of my research, offering (to their credit) an all-too-rare opportunity for independent access to an ongoing clinical trial by a medical anthropologist, during a pivotal period in their development as a small company. I initially began my research by approaching representatives of the company and asking if they would be willing to permit access to their clinical trial participants. I expected—in an era of litigious protectionism in the pharmaceutical industry and beyond—that they would politely decline the offer.

I was surprised when representatives of the company (including senior management) expressed an interest in my work, a desire to learn about and improve support for families contributing to the development of ataluren, and a genuine curiosity about the questions I was asking. Many of these points were related to issues they were grappling with themselves. For example, an enduring problem in drug development is how to systematically document the qualitative and idiosyncratic dimensions of one's experience with a drug, along with its significance and impact on quality-of-life—dimensions of human experience that can be difficult to measure and anticipate.⁴⁷

Initially, I had planned to also interview and follow company representatives and site-investigators, to include a detailed ethnographic account of their experiences developing treatments for DMD. However, as the project moved forward, company representatives expressed concern about being involved with this aspect of the research, since they were uncertain how such a study might be received by regulatory authorities. The decision was made to focus on the experiences of families, and to maintain a strict boundary between the ataluren

⁴⁷ This issue is especially vexing in the context of rare diseases, where there is often a high-degree of clinical variability between patients, where clinical trials are often being conducted for the first time, and where outcome measures have not yet been developed.

clinical trials and my ethnographic study. In designing and carrying out the research, representatives at PTC remained supportive of my concerns about independence and eager to ensure that I retained my autonomy. The company did not contribute to the planning of my research, nor did it place any restrictions on the publication of my findings.

This research was funded by an independent academic research grant from Parent Project Muscular Dystrophy (PPMD). Principals at PPMD, including its President Pat Furlong, provided valuable insight into the study design and the questions it poses, as well as logistical support by introducing me to parents within the Duchenne advocacy community. Like PTC Therapeutics, PPMD did not place any restrictions on the publication of this study.

This study received ethical approval from the Institutional Review Board (IRB) and/or Research Ethics Board (REB) of all sites from which patients were recruited.

2.14 Strategies for Data Analysis

All interviews were audio-recorded and transcribed verbatim. Fieldnotes were organized, reviewed for content, and coded to retrieve relevant sections. Interview transcripts and notes were then imported into ATLAS ti 6.0 (a qualitative data analysis software package) for assistance, but not reliance, in organizing the analysis. When I returned from each field trip, I conducted an initial, cursory data analysis to compare interviewees' comments and my field observations in an effort to discover the places where research subjects' accounts converge and diverge. This allowed me to generate analytic questions for integration into subsequent fieldwork and interviews.

As the data accumulated, thematic analysis was used to develop an initial set of codes indexing themes observed in both parents' comments and my own fieldwork observations across

cases. These codes were then used systematically to tag sections of transcripts, fieldnotes, and other texts in which a particular theme appeared. This process transformed the raw transcript and fieldnote data into a database broken down by themes of interest, which I could then query analytically. This method also enabled me to retain the links between themes and the broader narrative texts from which they emerged.

Database queries were used to identify individual cases of content in the themes of interest. This facilitated an ongoing process in which cases were located and compared in order to generate hypotheses about the relationship between the themes being analyzed. This analysis was carried out alongside data collection in an iterative fashion.⁴⁸ Hypotheses were developed and tested in later fieldwork in order to determine whether they adequately explained the phenomena being observed. The list of themes (codes) and their relationship with each other was refined as the study progressed and as new data “challenged” the explanatory model being developed.

In addition to thematic analysis, I also approached my data by focusing on narrative and discourse. In examining narrative, I was particularly interested in the ways that different groups ordered events temporally when representing their experiences (Labov and Waletzky 1967), and in the genres of stories told by members of the various groups (Frank 1995; Hyden 1997). I wondered whether different sets of actors would have different ways of ordering and framing the events in the clinical trial process (and their roles within it), and I anticipated that they would use different vocabularies and reference points to represent their experiences. I also compared accounts in an effort to determine how parents managed the uncertainty of the trial experience.

⁴⁸ Iterative cycling between phases of data collection and analysis is conventional in qualitative research, in contrast with quantitative approaches where these phases are conducted separately.

Finally, my analysis focused on the functions of narrative, including the different kinds of “work” that stories do for articulating self-identities and roles. I tried to be attentive to the kinds of stories my research participants told in different contexts (e.g. the clinic, the support group/conference, the home, online), and the various audiences they tell them to. As I claim throughout this dissertation, it is through the circulation of stories that particular representations of “what treatment is,” “what illness involves,” and “what the clinical trial entails,” are communicated by various actors. Moral, ethical and cultural ideals about how best to cope with the disease, how to parent one’s child(ren), and how to manage uncertainty and respond to medical risk, coalesce around these representations (e.g. Dumit 2012; Lupton 1992; Beck 1999; Becker 1997).

At the outset, I wish to draw attention to the immense diversity in families’ experiences with DMD. Factors such as cultural background, class and social position, family structure, educational background, coping strategy, and individual personality create uniqueness and idiosyncrasy in families’ narratives that mirror variability in how the disease presents clinically. Though common themes emerge from parents’ narratives, I argue that we must resist the temptation to see the collections of stories here as universally representative of all families. Qualitative methods, including the open-ended semi-structured interviews and direct observation methods used in this research, are an effective way of capturing this diversity, but like other research methods, they provide only a partial window into the everyday lived experiences of research subjects.

Chapter 3: Study Setting and Context

In the first two chapters, I introduced the research, the main actors, and the methods used in this dissertation. In this chapter, I examine the context for this study in finer detail. One of my objectives is to give the reader a sense of the illness experiences of the families who participated in this study, as well as the social, political, and technological settings in which they are lived. These illness experiences are important because they are the backdrop against which parents develop their perspectives on experimental medicine and make and narrate their choices regarding treatment and research participation. Despite this obvious contention, these connections often remain unexplored in scholarly discourse and policymaking. In those arenas, anthropologists and others have critiqued a tendency to focus on questions around informed consent and to de-contextualize and separate decisions about treatment and research participation from their experiential reality—that is, from the contradiction, multiplicity, anxiety and ambiguity that characterize how illness is experienced as “present in a life” (Good and Good 1994:841; on this point, see, among others Kleinman 1997; Kleinman 1999; Farmer 2004b; Bosk 2008; Sherwin 1992; Hoffmaster 1992; Turner 2008). One result is that many parents feel their experiences are unrecognized, undocumented, and misunderstood within abstracted discussions of “risk/benefit,” “therapeutic misconception,” and “informed consent.” A key contribution of this dissertation is therefore to articulate these connections between everyday life and experimental science using ethnographic methods.

In the next section, I use the case of Carol Williamson to begin our discussion of this background illness experience—a discussion which continues throughout the dissertation. I then introduce the concept of “Stories of Waiting” and present the case of Garrett Petersen to describe

the experience of parents waiting for an experimental drug, and the impact of this waiting on everyday life. Next, I turn to a description of the cultural significance of the disease's progressive destruction of muscle function, by introducing the concepts of "Lost Milestones" and "Reversed Teleology," and explaining their connection to personhood in "Western" culture. Finally, I describe the biosocial⁴⁹ and community context in which therapeutic research for Duchenne is carried out, by introducing the notion of "Duchenne as Culture," describing the patient advocacy movement, and highlighting the ways that genomic research is introducing new configurations within rare disease patient communities. I label these changes "New Contours" and "Lucky Mutations," and in describing them I argue that they offer insight into emergent forms of biosociality that are precipitated by personalised medicine. I suggest that these changes both extend our understanding of biosociality, and draw our attention to its limits.

3.1 The Duchenne Illness Experience: The Case of Carol Williamson

Carol lives in the suburbs of a Midwestern American city. She is mother to Avery, who participated in the original Phase 2a trial of PTC124. "He's a pioneer," she tells me as she leads me through her home and introduces me to her son who sits watching TV on the couch. Avery is recovering from his fourth surgical muscle biopsy as a result of his enrollment in the trial. This time Avery's doctors have removed a small strip of muscle tissue from his foot to test for the presence of dystrophin. Avery's arms and other foot bear scars as well. Carol and I retreat to the backyard where we sit beside her modest swimming pool built for Avery's physical therapy. "We built this whole house for him, to be wheelchair accessible, to have the pool, it's all on one

⁴⁹ I introduce and define the concept of biosociality below.

level,” she tells me. Her house is decorated with wood-carved letters, photos, and engravings of the words *Hope* and *Believe*, which remind her to “stay positive.”

She describes how when Avery was a toddler, she and her husband Peter started to wonder about his development.

We didn’t know there was anything wrong with him, but then right away we noticed, just because of his development. The doctor kept saying, no he’s developmentally delayed. He’s a boy. Blah blah blah. But finally when he was a year and a half and wasn’t walking, they sent us to a neurologist and started testing.

She continues,

We didn’t find out for 6 months. That he actually had DMD. But we found out one night, the doctor called and said “has he fallen recently?” We said “why? No.” And she said “because his CK level was so high,” and I said, “well what does that mean?”⁵⁰

And when she said, “muscle disease or disorder,” then I said “like what?” And she said, “like muscular dystrophy.” I just [sigh]

Carol pauses, tearing up remembering the moment. “I fell apart. You never think that your child’s gonna have [a disease]. And it’s true.”

The first doctor they saw at Children’s Hospital was, she says, frank.

He said, um, go out and do everything you ever wanted to do, right now, because this child will not walk, when he’s five years old. And this child will die, when he’s 17 or 18 years old. And of course, after being devastated, we wouldn’t take that for an answer, and that’s when we found [our current neurologist]. Our life saver. And Parent Project. Honestly [chuckling]. And we went from there.

⁵⁰ CK, or creatine kinase, is an enzyme found in muscle tissue. Elevated CK levels indicate muscle breakdown and are used as a diagnostic marker for muscle disease.

I asked Carol how Duchenne has affected her life, and she responded,

It's been hard. Quite an impact.

The first thing that bothered me of course was the other kids playing and him not being able to keep up with the other kids. When he was little. And not being able to do what they could do, and trying to keep the kids playing with him. Even though he couldn't do everything they could do. That was hard. And plus, he was a very withdrawn child.

If all the kids were running in the yard and playing tag. And Avery can't run. He'd try. I mean, he can walk, you know, [he can] kind of walk a little faster. But, he could not run. And they're playing a little whiffle ball game and he would never even join. He wouldn't even try. You'd try to get him to try, just you know, because, even if he can't do it, like they do, maybe it could still be fun. And they all ride bikes. And scooters, you know, even the little kids. We did get him to ride a bike though. The doctors told us he would never ride a bike. And he rode a bike. We have pictures of him riding a bike.

She continued,

People don't know, the anguish you feel when your child can't be a normal kid. Every day, [pause] I see another kid doing something and wish my child could do that. Even though I know he's happy um, you know, I, "what is he feeling? Does he feel that all the time?" You know what I mean? I hope he doesn't. I don't want him to feel that way. So you know, I would never say that to him, but it's [her voice quiets], ... it's hard.

There was a neighbour in our old neighbourhood. This will live with me forever. And to show you that people don't understand. I never thought she was a very compassionate type of person anyway. She was never like, nurturing to me. I never saw that side of her. And she has three children. And Avery was six, maybe seven. And he couldn't keep up with the kids. And I said, "you guys, wait for Avery. He wants to come with you and he wants to swing and I'm gonna push him" and, she said, [pause] "Why don't you have, him play with his own kind?"

When she told me that... You know I. How could you say that? How could somebody say that?

Carol's description gives a sense of the way that Duchenne is more than just a physical diagnosis but also a marker of difference and "other-ness" for parents and children alike, setting them apart

from friends and neighbours in their community. Parents and children often describe being the objects of stigma attached to their disease and disability (“cast-off,” as Carol describes it below), and narrate a desire for mere normalcy (Goffman 1963; Murphy 1987). Socially, Carol found that many of her friends stopped calling after her son’s diagnosis. “People just didn’t know how to handle it, and you also lose touch with friends if their kids are doing stuff that your son can’t do. It’s difficult, but I know who my real friends are now.” As a result, she and her husband have devoted their energies inward, to helping Avery succeed at school and make friends for himself. Avery has experienced some cognitive symptoms of the disease, which are sometimes a bigger issue than those related to muscle weakness.

Avery had learning problems. He had attention deficit hyperactivity disorder. We had him go through a whole battery of tests at Children’s [Hospital] when he was five, because he was havin’ such a hard time at preschool. And we kept him, held him back, in kindergarten, because he just wasn’t learning.

The disease has affected her family in other ways too, Carol says. Avery has broken several bones, a result of what she describes as osteoporosis “in his bloodline” that is exacerbated by the side effects of his corticosteroid regimen.⁵¹ Avery has always had a hard time getting around, and his parents have wrestled with his supplement regime, as Carol explains.

We found out when he was two, so he was about two and a half, three, and, let’s see, he started steroids when he was five. Because he was having a hard time sort of pulling himself up steps. You know, then all the supplements, you know just, that we’ve heard of, from other people. Should we give him calcium? Should we

⁵¹ Individuals with DMD often have reduced bone density that is also exacerbated by the side effects of corticosteroids, which disrupt bone metabolism (Söderpalm et al. 2007).

give him CoQ₁₀? As soon as he got on the steroids they put him on Fosamax.⁵² But we just found out later, he's broken, several, several bones. Besides his, two femurs, he's broken ankles. He broke an ankle when he was two, two and a half. Just, he was trying to crawl up the one step, he slipped and fractured an ankle.

As Avery approached 8 years, he was getting weaker and starting to need considerable assistance. Avery was relying more and more on his scooter, needed help to get dressed, and could only walk short distances with a distinct waddling gait, characteristic of boys struggling to remain ambulatory. His mom requested that he be dismissed early from all of his classes so that he wouldn't be trampled in the hallway. Carol and Peter also realized that their 2-storey house would not work for a son who could not walk. Like many families with Duchenne, they spent most of their savings to build a new single-level house to prepare for Avery being in a wheelchair. The family has recently moved into the home, which has extra-wide entranceways, kitchen and bathroom spaces to accommodate a mobility device. Although they have not installed one yet, there is room for a lift-track system to run along the hallway and bathroom ceilings if Avery gets too heavy to carry. These are preparations for the future that Carol is uncertain she will need, because she is hopeful a treatment will emerge in time to stabilize Avery's disease.

At the same time, Carol relates how she and her husband became closely connected with Parent Project Muscular Dystrophy, a patient-advocacy group raising money for Duchenne research. Carol and Peter began holding dinners and gatherings to raise awareness and funds, and asking questions about their son's disorder. They went to a few conferences to learn more

⁵² CoQ₁₀ is a nutritional supplement thought by many in the Duchenne community to have a beneficial effect for muscle, but for which limited evidence exists (Spurney et al. 2011). Fosamax (alendronate) is a drug for osteoporosis sometimes administered off-label to patients with Duchenne.

about the disease and connect with other families. It was at these meetings that Carol found support and understanding.

They [other parents of boys with DMD] understand. You're angry, you're tired, you're frustrated, you're [pause] you're hopeful, or you wouldn't be at the conference. Or you wouldn't be, you know, talking about it, because the other ones just, kinda hide away. They're compassionate. They know what, they know everything that you've had to do. You've had to give up a lot of your own personal time. Much of your personal time to be a caregiver. They know the sadness that you feel that, because your children can't do what, you want them to be able to do, what all these other kids are doin'.

You want, you drive past a baseball game, and you, you get a tear in your eye, thinkin' you know, "my child never got that, or um, [pause] [sigh]. The whole gamut of emotions you go through. [pause] The love that you feel for that child. The love and [pause] never stopping trying whatever there is out there, to, to help him. Wishing that, other people could understand what that child is going through.

I don't care if they say something about me, [but] don't put my child in some horrible category. Like he is a cast off. Because he's, a regular kid, that just happens to have a muscle disease. You know, they [other parents of children with Duchenne] know all those things because they feel, all those emotions that you do. It's hard, but they share, [by asking each other] "What do you do? What have you tried with your child? What's helped you? Who do you talk to? What do you do when you're frustrated about this?" ... You get all these ideas, too, to help you try something you never thought of. You know? And it's that understanding of where every[one], we're all on the same, boat. ...

You know we all know more about this disease than we ever wished to, and we never heard of it before our child was diagnosed with it. Never knew there were 40 kinds of muscular diseases. And, never wanted to know that, you know? [chuckle]

Still, it was at these conferences that Carol hardened her resolve to "fight" Avery's illness. They were not going to passively "sit back and accept the diagnosis." "It just wasn't an option that was even considered. We thought, there's no way we're losing, you know, you can't be right. I

don't know," she says, her voice trailing. "Stubbornness. I think that instinct as a mom takes over."

Carol points out that she has a "particular personality" that colours her approach to DMD.

You know it's, it's hard for me to answer because I don't understand the other side. I don't understand the people who close themselves in their houses, and, accept, "okay, this is how it's gonna be. You're gonna be in a wheelchair. We're gonna just, you're gonna die and I'm not gonna fight." You know. I don't understand that, and not having that, in you. And maybe that's a personality [trait] ... I don't know. I guess it's, um. I just never thought to do different. I mean it would be easy. It would be really easy to do that, and I guess sometimes you do. There are times where you think, "I can't take this anymore." You know, when you're standing in the shower and you cry. And um, and I do. But, I don't know...

Carol and Peter learned about the trial through their connection to Parent Project Muscular Dystrophy. They were "trying everything," various supplements, steroids, and proactive care at a premier neurology clinic, and when the trial came up, they responded enthusiastically,

Well anything we could hear about through PPMD that would help and I would always call Pat. Pat, what should I do? You know, should I give him, prednisone? Should I give him deflazacort?⁵³ Which we can get [i.e. import], from England. You know. What's the best? And we would go to the conferences that Parent Project had and, you know what are you giving your son now? What are you trying? We've tried everything. We would try, whatever, and, when we found out that he had this particular nonsense mutation and that there was a study coming up, well we jumped right on it.

It "wasn't really a choice," she says. The trial, in essence, just "happened."

CJC: Did you feel at all when you started it, that it was a decision? Was it a choice that you were making?

⁵³ The steroids deflazacort and prednisone have recently become standard-of-care for DMD, and are now more widely prescribed. Children take these drugs long-term on one of several regimens; they cause a variety of difficult side effects, including weight gain, difficult behaviours, and changes in appearance.

Carol: There was no choice. It was just, we were doing it. We looked at the risk factors. I take that back, I guess it was, a little bit. We looked at the risk factors. But I don't know if the risk factors were much, you know. I don't know where the line would have been. Yeah, I really don't. Since he was one of the first ones [to take the drug]. But in the animal studies, you know, they said [the drug was safe], and so and he was one of the first ones and everything was good, and so we were so, excited. And excited to be one of the first. They kept telling him in the hospital, "you're making history Avery," you know. "You're the first one to take this," and that made him feel really good. But I think we looked at the risk factors and there was no choice.

3.2 Stories of Waiting

Nearly universally, parents of kids with DMD (and other debilitating and progressive diseases like it [Wästfelt, Fadeel, and Henter 2006; Stockdale 1999; Biehl and Petryna 2011]) view themselves in a "race against time"; they tell compelling "Stories of Waiting" for a new treatment.⁵⁴ In situating themselves within this narrative they invoke redemptive meanings of science as salvation, expressing their hope that the therapeutic enterprise will produce a treatment "in time" to rescue their son from his decline. This hopefulness can be a source of strength and optimism that parents often use to adapt and cope with their child's diagnosis (Browner 2010; Simpson 2004; Good et al. 1990; Samson et al. 2009; Wiles, Cott, and Gibson 2008; Mattingly 2010). For parents waiting for a treatment that will possibly—hopefully—offer a "ticket off of this train of despair" (as one mother described it to me), the slow pace of research progress can be agonizing and frustrating. And yet in a bio-genomic era where a growing number of treatments are "in the pipeline" for rare diseases with high unmet medical need (but are not yet available clinically), and where a burgeoning, inefficient drug development regime

⁵⁴ There are exceptions to this view that can be read as resistance to the pressure, anxiety and suffering that comes from "living in the absence of treatment." I discuss an example of such resistance in Chapter 4 ("The Actively Unconnected Parent").

grinds the pace of scientific progress, “waiting for science” has become a defining feature of the North American illness experience.

In reconciling their child’s diagnosis, parents must learn to negotiate the uncertain space between untreatability and therapeutic possibility. Existing treatments for the disease are severely lacking, but the tantalizing possibility of a scientific breakthrough—of potential relief from the burdens they face—paradoxically creates both a space for hopefulness and a deep anxiety. Children with Duchenne are neither treated nor untreatable. Parents, especially in the early stages of the disease, must learn to discipline and manage their hopes and expectations for treatment; in other words, they must learn to wait *effectively*, without “going crazy.” This process involves a great deal of emotional and cultural work. For example, in my previous research I discuss how information about scientific progress is layered with emotional meaning and can produce tremendous unease (Condin 2005). Parents often find themselves developing strategies to manage the flow of scientific information into their everyday lives and to process their emotional reaction to both positive and disappointing news. This background experience of “waiting for cure” is familiar to most families living between treatability and its lack.

Parents who gain access to the clinical trial are both excited at the prospect and relieved, because it seems—for a moment at least—that the wait is “over” and that they have realized their objective of obtaining a breakthrough treatment not yet available to others.⁵⁵ Still, many parents in the current study found themselves unprepared and disappointed to learn that, even in spite of their eligibility for a cutting-edge trial, their lives as experimental subjects would involve a great deal of waiting as well, as the trial sponsor obtained IRB approval at each of the trial sites,

⁵⁵ Only those children with “lucky mutations” amenable to genetic intervention are eligible for trials, a point I return to below. For those assigned to the placebo-control arm of a trial, access to an experimental treatment is not immediate but is anticipated to come during the open-label extension trial afterward.

ramped up production of the drug, negotiated research, non-disclosure agreements, and payment provisions with hospital sites, and ensured strict packaging and labelling requirements were met⁵⁶ before sites began screening patients and enrolling them into the trial.

In the section to follow I will examine how parents experience and narrate these periods of waiting, and the effect of waiting on their illness experience with Duchenne by examining one case study in close detail. The case shows how stories of waiting are anchored, emplotted, and re-told against the backdrop of disease-time, measured in lost milestones and reversed teleology (discussed in the subsequent section), and rooted in the visceral experience of watching their child struggle each day with a disease that slowly removes him of his physical capacities. The disease is relentless, always progressing, and parents do not see their child as having extra time to spare. The agony of waiting is compounded by the reality that a treatment is only likely to be successful if administered when a child is young—before the disease progresses, replacing potentially recoupable muscle cells with irreparable sclerotic and fatty tissue. Parents’ stories of waiting are thus dramatic and painful. As I suggest below, these stories also have significant implications for ethical deliberation, policy, and research.

3.3 Waiting for the Drug: The Case of Garrett Petersen

Garrett Petersen lives in the United States, works as an entrepreneur, and is father to Adam, who was 16 years-old at the time of our interview. Adam is no longer ambulatory, but was a participant in the initial Phase 2a trial and later in the open-label extension. Accompanied

⁵⁶ At present, institutional review policies, labelling, and packaging requirements for investigational drugs are mandated by each country’s regulatory agency, and differ from country-to-country. An investigational drug’s packaging and label are also reviewed by the local IRB at each site, which may request changes to conform with institutional policy. Variations in policy, duplicate review processes, and challenges in working in different languages can lead to delays in clinical trials getting underway.

by his family, Adam was attending at Valleyview Children's Hospital for a study visit, clinical check-up, and to have his post-treatment muscle biopsy as part of the trial. I attended Adam's biopsy and watched as his mother held his hand while, under local anaesthetic, an orthopedic surgeon excised a small strip of muscle from his upper arm.

As Adam recovered from surgery, I sat down with Garrett in an empty hospital room for an interview. We began by discussing how when Adam (his eldest son of three) was diagnosed with DMD as a young child, Garrett poured himself into learning more about the disease and started networking extensively with scientists and clinicians in the US.⁵⁷

We got through lots of things and, [it's been] really tough for me too. Actually I'm an optimist and I always felt that I can move mountains. Well, he was sick, and I was very devastated of course, but then I said "we have some time [but] we're not gonna rely on time. I'm going to be very active. I've got to [start] understanding the genetics that's behind it and trying to come up with solutions."

Garrett sees it as his role to be a networker. As a father, he tells me, his role is to maintain relationships with leading scientists, clinicians, and pharmaceutical companies in order for his son to receive the best care. In pursuit of this goal Garrett began bringing his son along with him on business trips, flying to various neuromuscular centres across the US for assessments and clinical care. When Adam was young in the late 1990s, Garrett began making side-trips to network with researchers on the US Eastern-seaboard, even going so far as to provide some of Adam's biopsied muscle tissue to a research lab in Washington, DC. It was through these connections that Garrett became aware of PTC Therapeutics, then a small biotech startup working on stop-codon suppression. After learning that Adam had a nonsense mutation, Garrett

⁵⁷ Mr. Petersen could be accurately described as a "Connected Parent," using the typology I describe in Chapter 4.

became interested, began to speak more regularly with representatives of PTC and with other scientists, and became hopeful that he would have a chance to enrol Adam in the initial Phase 2a clinical trial. Garrett and his family followed PTC's preclinical research programme, and a parallel one testing gentamicin in Columbus, OH, from the beginning.⁵⁸

It's kind of [like] living a nightmare in a slow, [pause] way. It's still a nightmare, but you live it every day. So it's kind of, an anomalous life that you just, kind of go step by step. You just learn to live step by step. And I just think that then as the time goes on, [you have to] work on adjusting your, whole, hopefulness. [pause] With the reality. And you just go and keep living. And you survive.

Because as time passes, goes on, you struggle more, in finding a realistic place where you can get your hope. Like where to attach your hope. ... You always have to balance it. You always have to balance, but the more time that passes, the less easy it is, to really keep your hope realistic. So then you start losing it. But again it's that, [pause] [sigh]. I think the magic is the time, because it's gradual. You think on it every single, day. But your mind is adjusting.

As Adam approached his preteen years, his disease began to progress. Garrett describes how Adam's walking was getting worse; Adam was nearly off his feet and close to stopping walking completely. At considerable expense, Garrett and his wife Salima travelled with Adam to several prominent neuromuscular clinics in the US in order to get him "on the list" for a potential clinical trial and to seek extra advice regarding his care. Garrett and Salima resolved that when a trial spot opened up they would try to get Adam into it, despite the fact that this would potentially mean commuting or relocating some distance from their home. "We had [extended family closer to the trial site] that we could use as a base, you know, and nothing was happening near [our home], and so I felt that it was really something we needed to do." Adam,

⁵⁸ The antibiotic gentamicin has been observed to promote similar readthrough of premature stop codons. However, gentamicin can be toxic when administered in high doses and/or over long periods (Malik et al. 2010). I discuss the drug further in Chapter 6.

for his part, was a relatively pliant traveler, despite his declining mobility and his growing dependence on a wheelchair.

Having established a care-relationship with a neurologist at one of the three main trial sites, Garrett and Salima were able to obtain a spot for Adam as one of the initial 38 boys to try the drug in the Phase 2a trial. Adam was among the first to receive it. At the time, Adam was beginning to lose his ability to walk and relied on a wheelchair nearly full-time. In the 28 days that he was administered the drug, his parents noticed that he was more energetic and experienced an increase in his muscle strength.

You know I mean if I carry somebody and they just hold on me, sure everything [is easier when] all the muscles work together and they are helping to hold on to you. That's the feeling we had at that time, when we'd been with him for the 2a you know. I just felt and not right away, and I knew it's okay. It was about two weeks later when I had to move him from the wheelchair to the toilet, it got, got easier. He was pulling, working with us a little bit. He was working more.

One of the reasons Garrett and Salima enrolled Adam in the trial was the promise of an extension. Boys who were in the original 2a trial were entitled to roll into an open-label extension trial and to receive the drug for at least one year. They were unprepared, however, for an intervening period of more than 2½ years while the company laid the groundwork and obtained the necessary approvals for the extension trial.

Sometimes I just think too much time passes. It's an orphan drug. And there's been so much good news about it. I thought after the 2a that we would get access to it shortly after. To have to wait more than two years, I would have never thought. I'm realistic. I know how things get delayed if you file something with the FDA ... but two, three years it's a long, long time.

Parents tell stories of their child losing function as they wait for a trial to begin. Their child is getting older and declining. Some children are in the process of “coming off their feet”

and becoming non-ambulatory. As the disease progresses, the children oscillate between periods of relative stability and periods of acuity in which the disease overtakes life—a cardiac arrhythmia, a broken limb, a respiratory infection—which requires treatment and occasionally hospitalization (on oscillations in the chronic illness experience, see Kleinman 1988; Mattingly and Garro 2000; Murphy 1987; Bury 1982; LaDonna 2011).

For Garrett, such moments are all too real. He describes a particularly harrowing acute episode in which Adam nearly died. The problem was a persistent pneumonia—which can be life-threatening for Duchenne patients whose respiratory function is compromised due to both muscle weakness and the immune-suppressing effects of corticosteroid therapy. Respiratory infections are a frequent occurrence in children with Duchenne, and during this particular episode Adam had been admitted to hospital.

The most devastating thing was last March, when he got the second pneumonia in a row. And he was in the hospital. And he's a smart guy, he said "I wanna go to the hospital, to a neurologist just to be on the safe side." And she took an x-ray and everything and said "everything looks fine. You have a little bit of a lung infection but nothing bad. [You can] stay around two days, we'll give you the antibiotics, and things will be fine."

The second day, I visited him because his mother was with him in the hospital. And to me, it didn't look good. I mean it was just developing all of a sudden. I mean, there was no medical error there actually, and they were trying to do the cough assistance with him.⁵⁹ And, it was just that he developed spontaneously so much fluid in his lung. No one was realizing, and as they did the cough assist it kind of concentrated in the middle, and all of a sudden he was just sitting in the bed, and he told me, "I can't breathe I'm dying."

And at that moment he turned blue, his eyes didn't move any more. His pulse got down to zero. The oxygen level in the blood, I saw everything dropping.

And, [pause—wiping tears] that was hell.

⁵⁹ CoughAssist is a mechanical device that assists with removing secretions from the lungs in patients with an ineffective ability to cough (otherwise known as a mechanical insufflator-exsufflator).

For Garrett, this episode was harrowing and traumatic. The nurses tending to Adam called a code blue, and Garrett watched in desperation as the respiratory technicians swept into the room, intubated Adam, and tried to aspirate the excess fluid from his lungs. Eventually, Adam was revived. “It was a big relief, you know, when we got him back,” Garrett tells me, no doubt understatedly.

DMD boys often develop severe respiratory infections, and occasionally these cause acute respiratory distress. For Garrett though, this event is not only attributable to the “natural” progression of the disease—to Adam’s weakened lungs and to a relatively common complication of the disease in non-ambulatory patients—but also to the slow pace of research.

[I feel that this could have] been avoidable, yes. If things [the drug development programme] would have happened earlier, you know, then maybe his lungs would not have been in a weakened state. It’s desperation, desperation. I am not mad at anybody actually, you know. It’s not any one person’s fault, or anything like that. It’s just desperation. And that shook me. That was so traumatic that I barely was able to recover.

Images of Adam “dying on the hospital bed” still haunt Garrett. “I still get these images in my head. And they’re so persistent,” he says. Garrett’s eyes swell as he describes how he keeps getting visions of his son.

It’s like I keep seeing my son dying again and again, you know, and the impression is so strong, that there is no room for thinking, in that moment when these images come. I’m really living that moment, and there’s nothing around, and I’m just reliving it. You know, it’s crazy. I know it’s crazy.

For Garrett, this traumatic episode is layered with different significances. As a father, he still feels guilt that his son’s disease has progressed to the point that it has, and that he hasn’t

been able to intervene more effectively. Despite all of Garrett's efforts networking and advocating to get access to treatment, he wonders if it is already too late to coax Adam's muscles into producing dystrophin. This sense of guilt is heard often when speaking with parents of children with Duchenne. Garrett is struggling to maintain hope in his family, and is exhausted balancing his work and career responsibilities with his "second job," first trying to secure a treatment spot for his son, and more recently, as a transnational trial participant.

I think I've done better in the past, but once his condition deteriorated and I, I think psychologically it was a lot more of a burden for me than I ever realised.

I realised that actually, I started to be a lot less pleasant at home. You know, there was no room for other problems. Every little problem filled up the glass fully, you know. And I didn't want to hear of any other problems. I didn't have any more room for anything. [sigh] I think I got a little bit better now but being so active, it's hard for me. And I got to the stage where I wanted everybody to do what I'm doing. You know being my brother or my wife.

CJC: To be helping Adam you mean?

Interviewee: Yeah, yeah and of course they do. But to me, I became angry. It was like everybody should have as much energy as I have. Everybody should be working 24 hours for that cause [to find Adam a treatment] ... I think I got to be an unpleasant companion. Yes, I got to be a difficult person without having a difficult core I think.

... I think I'm in the, in the breaking point, like [last year], I was very hopeful. This year I'm less hopeful. [It's] very, very tough. Because ... now the tough part is like, we don't know [if this drug is working], and what will happen next. So then you start to get concerned, focusing more on, what will it be like if the hope is not there [because the treatment is not working]? How tough it will be? And that, tears us more apart, like, as the hope goes down, the concern for the future goes up. Of course. And, you just get scared of how much, will you suffer?

Garrett's case is remarkable on its own as an example of the suffering and torment that parents experience waiting for an investigational treatment. "Stories of waiting" are constructed

and re-told not just as part of the background illness experience, but also in the context of bureaucratic delays in getting clinical trial and extension programmes underway (Reith et al. 2013). As the disease waxes and wanes, parents are coping not only with the destruction of muscle tissue and the loss of functional abilities discussed earlier; they are also experiencing acute episodes that have traumatic and lasting and lingering effects, which in Garrett's case take the form of nightmares and disturbing memories of his son nearly dying. Parents' stories of waiting provide us with insight into the ways that "urgent medical need" and the absence of treatment are lived, as a form of suffering, every day by families experiencing rare disease.

Garrett's story can be used to suggest that the slow pace of research has deep and everlasting psychosocial effects upon parents and families that remain largely unexamined. These sequelae occur in families, caregivers, and communities. They are independent of statistical indicators used to assess how "well" medicine is doing at treating patients with a particular disease, including outcomes like survival, morbidity, and mortality. Statistical assessments of medical progress can overlook the ways that unmet medical need caused by delays in research programmes are *lived* by families in ways that go unrecorded, creating, as in Garrett's case, ever-present feelings of guilt about whether one is "doing enough" for their child, a deep and overwhelming anxiety about whether a treatment will arrive in time, and pervasive stress about whether unnecessary delays will lead to an adverse outcome or death in the absence of effective intervention. These downstream and extra-corporeal symptoms of the disorder (in the sense that they are experienced not only by an affected patient but his caregivers as well) are frequently unremarked in academic discussions of disease burden and policy. Parents rarely receive psychological support in coping with them, despite their prominence in family narratives of their experience with DMD. These aspects of families' experiences often go unrecorded in

statistical assessments of the burden of disease and evaluations of benefit and risk, which tend to focus only on disease outcomes in individual patients.

Parents' stories of waiting also provide insight into how, for the experimental subject, the illness experience becomes *re*-framed. Acute episodes and disease progression are not (or not only) happenstances along the natural history of the disease: they are also failures of scientific and therapeutic possibility. For Garrett, the dominant schema through which he has come to view Adam's pneumonia is that *it might not have occurred if the treatment had been here in time*. For families eligible or accepted into a clinical trial programme, the fact that a treatment for Duchenne is "so close" means that the progressive decline of the disease and acute episodes that occur along the way, are given meaning within a context of scientific lack. Garrett's case illustrates this phenomenon. He attributes his son's functional deterioration and near-fatal respiratory distress not (or not only) to the disease, but also to the intervening delay in obtaining a treatment that might have preserved his condition. For many Duchenne parents, the current moment is one in which the illness experience is being reframed: progression is today not only an outcome of the natural history of their child's genetic disorder, but of its technological history as well.

Garrett's case also suggests that the experience of waiting for an investigational treatment (especially when delays occur after a family is made aware of or accepted into a clinical trial, such as those between initial screening and dosing, or between controlled trials and open-label extensions) may affect parents' perceptions of a study drug and/or their decision to participate, by increasing the stakes. In the course of my ethnographic research it was common to hear parents remark that one cannot "turn back after having come this far." Such comments raise the possibility that parents' stories of waiting may actually impede their (supposedly) free and

informed choicemaking regarding trial participation by burdening such decisions with the guilt of having “waited this long and worked this hard” to get their child into a clinical trial. The role of guilt and parent/patient self-advocacy, and how they configure in decision-making about research and treatment, remains largely unexplored (Gaudine, Sturge-Jacobs, and Kennedy 2003). Parents’ stories of waiting raise questions about how urgency is defined in the field of medical research practice and clinical research oversight, and the extent to which policy and practice account for the psychosocial and traumatic sequelae of living delays in medical innovation.

Taken together, the cases of Carol Williamson and Garrett Petersen give a sense of the Duchenne illness experience. Parents are constantly in the process of adjusting to their child’s diagnosis and his changing care needs. They must re-modify their own personal biographies and adjust expectations for their own lives, as they grieve a terminal diagnosis in an adored child. Carol Williamson describes how all-encompassing the illness experience can be, as DMD colours everything from her social relationships with friends and family, to the house they are able to live in. Decisions about supplements and treatment are all-consuming and often overwhelming, and many parents devote considerable energy to learning about the disease and options to manage it. Both cases also show how maintaining hope and optimism, managing relationships with care providers (and increasingly for some parents, research scientists and biopharmaceutical companies), and “learning how to wait” are now major aspects of their experience, even for parents who are offered an experimental treatment as part of a clinical trial.

3.4 Lost Milestones and the Reversed Teleology of Childhood

*“When you were one,
you were learning to walk.
You fell down on your knees.
You fell down on your nose.
You fell down on your bottom.*

*You kept trying and trying, and then—
you did it!
You learned to walk!
Yes! You did it yourself.*

*When you were two, you were learning to
talk.
You made up funny words.
You made up funny noises.*

*You kept trying and trying, and then—
you did it!
You learned to talk!
Yes! You did it yourself.*

*When you were three,
you were learning to ride a trike.
You crashed into the house.
You crashed into the tree.
You crashed into the cat.*

*You kept trying and trying, and then—
you did it!
You learned to ride a trike!
Yes! You did it yourself.*

*When you were four,
you were learning to dress yourself.
You put your clothes on backward.
You put your clothes on inside out.
You put your shoes on the wrong feet.*

*You kept trying and trying, and then—
you did it!
You learned to dress yourself!
Yes! You did it yourself.*

*...You will keep trying and trying,
And you will keep learning and learning.*

*And you will do it!
Yes! You will do it yourself.*

*-You Did It!, a short children’s reader by
Jan McPherson and Rachel Conner (1996).*

In their seminal studies of parenthood across cultures, LeVine and colleagues have argued that in spite of vast cultural variation in parenting strategies, parents across the globe share in common a set of universal goals for their children. These include survival and health, subsistence competence, and social and moral appropriacy (LeVine 1977; LeVine, Miller, and West 1988). While the particular competencies emphasized in each culture vary—Italians, for example, have been observed to rarely praise their children for intelligence, instead emphasizing their even-temperedness and *simpatico* (sympathy), where American parents tend to praise

intelligence and cognitive ability—there is likely also, I suggest, an additional commonality in childrearing that transcends cultural variation. Universally, childhood is “supposed” to be about the *accumulation* of milestones and accomplishments. As children grow, they gather new skills: these include linguistic and cognitive abilities, physical strengths, emotional attributes and knowledge. It is a time of *expanding* horizons, increasing independence, and growing personal autonomy. It is also teleological—that is, children are “growing-up” and advancing toward maturity and adulthood, a process that entails multiple changes in social status over time (Turner 1969; Shostak and Nisa 2000; Fishbane 1995). Though the experiences of childhood and the practices of childrearing exhibit an almost unfathomable cultural diversity, it is arguably a core feature of humanity that parents live vicariously through their children’s accomplishments—experiencing joy, pride, and excitement at the accumulation of their new competencies.⁶⁰ A child’s attainment of culturally valued milestones, whether as a hunter, a weaver, a reader or a baseball player, are occasions for celebration.

For the Duchenne parent, things are more convoluted. Duchenne parents, for example, celebrate their children’s birthdays in customary ways, but they are often occasions of grief and anxiety as much as happiness. They symbolize another year passed without a treatment, another year of progression, and another year of advancement to what parents know (even if they are not able to speak it) is the ultimate outcome of their son’s disease. Parents are known to experience bouts of depression around an affected child’s birthday, as expressed by Janet Sanders, mother of 17 year-old Thomas.

⁶⁰ Here, I should clarify that I do not wish to present an idealized vision of childhood and parenthood. Of course, both children’s achievements and parents’ experiences of them are constrained by the realities, demands and stresses of everyday life, including families’ often vulnerable subject positions within economies, political systems, and (labour) markets. The experience of illness and disability also brings its own contradictions. Case studies include Scheper-Hughes (1992); Solomon (2012); Brown (2011). See also Harkness et al. (2000).

Our outlook was, and Dr. Neurologist as well, when Thomas was four and was diagnosed he told us, you know, he has high hopes. That in Thomas's lifetime there will be a cure. Well, you know, ... every average family celebrates birthdays. We celebrate Thomas's, but we actually really don't *like* Thomas's birthdays. It's actually a very sad time. Because, that's one more year we haven't heard anything. And one more year that has gone by. And with Duchenne, with the shortened lifespan, is, you know, is [pause, struggling for words], it's factual.

In a similar way, developmental milestones—the ability to walk, to ride a bike, to catch a ball, to perform complex tasks—are not steadily accumulated as a child grows and the disease progresses. Rather, they are delayed, occasionally never met, and eventually lost. The Duchenne illness experience, therefore, is primarily marked by repeated and cumulative moments of regression and *lost* ability, a characteristic of the disease that is often described colloquially in the Duchenne community as “*death by a thousand cuts*” or a child “*dying many little deaths*.” For example, a child gains the ability to walk (often for boys with Duchenne, this occurs much later than their peers) but retains it only for a few years, and only with much difficulty. In the process he struggles to stride without falling, to keep up to his siblings and friends, to gird himself and master his gait against his progressive weakness. I know of one boy who learned to catch a ball at age 6, only to lose this ability at age 8; others are able to swim only for a few years before muscle loss makes this impossible.

For the Duchenne parent then, the very developmental teleology of childhood is reversed.⁶¹ That is, the cumulative acquisition of ability from childhood to adulthood is disrupted, upheaved, and turned back upon itself. Children grow initially as normal but are delayed—both physically and often cognitively—reaching milestones later than their peers. In

⁶¹ Teleology (from Greek *telos*, “end”; *logos*, “reason”) is a term with a long history in philosophy (often traced back to Aristotle). Here, I use it to refer to the directional expansion of ability as a child grows from beginning (infant) to a culturally emphasized “end” (adulthood).

terms of physical ability and strength, they “peak” around age 8, before the disease takes hold of their bodies.

The result is that there is never any certainty that a child will be able to perform an activity or task for long, and achievements are always celebrated with the vexing question in the back of parents’ minds: “How long?”; “how long will my child be able to do this?”

Because he, he was always delayed, like I said, he was always behind. Like at thirteen months he wasn’t even crawling. Like, he just started crawling at thirteen months. I mean I could put him on the floor and he’d stay there. At exactly eighteen months old, he started to walk. ... He had no interest in it and then all of a sudden at eighteen months ... and the doctor wasn’t concerned. He said “you know, he’s just delayed, he’ll eventually do it.” ...

Now, every day leads us to something new and every year ... One time we went [to the playground], and he’s on the jungle gym, he’s climbing the monkey bars, and I had to walk away because I’m going, “I can’t handle this,” because he’s, he’s scaring me, because he could never do this and all of a sudden he’s hanging on it and I’m like, I had to totally look away. He was just barely hanging there. And he could only do that for a little while, and only barely, if that. It didn’t last long.

Rather than a steady accumulation of milestones met then, the Duchenne experience is instead a relentless reversal of the very teleology of child-development. It is a reversal embodied in the pubescent changes of adolescence, changes that are often delayed, suppressed, or entirely skipped in boys with the disease—a symptom of both the disease itself and a side effect of the corticosteroid therapy now considered standard-of-care.⁶² Many “boys”—actually teenagers—with Duchenne have short bodies, cherubby skin unaffected by facial-hair, and voices that have

⁶² Long-term use of corticosteroids in children leads to growth inhibition and suppression of puberty, among other effects.

not yet deepened. They are, in a sense, “arrested developers” in that the disease has frustrated their ability to reach and hold on to the milestones of childhood.

Of course, this presents a tremendous emotional burden to both parents, whose children are losing abilities at the same time their friends and peers are gaining them, and to the boys themselves, who are given a taste of boyhood competencies, only to have them taken away.⁶³ The reality is that a Duchenne parent does not know “how long” a competency such as walking (on a hike), lifting (a ball or toy), getting dressed, climbing on a playground, or tying a shoe will last. One mother wrote in her journal of her experience raising two boys with Duchenne,

Suddenly, I realized, life goes very quickly and in the flash of a moment, it is gone. The world moves on, hardly notices the incident. My sons have a progressive genetic disease, described as slow, although it seems they just learned to walk and in the blink of an eye, that ability was gone. As feeding themselves became an art, capability vanished. Just when they learned to tie shoes, in an instant, their dexterity vanished. It is apparent that [some day] their life will be over and the world will not stop—just mine.⁶⁴

Parents’ awareness of this fact leads to an abiding sense of liminality⁶⁵ and uncertainty—nothing is for sure, in Duchenne—accompanied by a feeling of urgency. Universally, DMD parents describe their strong desire (and often, pressure) to squeeze every last moment out of childhood, and they report an almost-obsessive focus on the present.⁶⁶ This experience also appears to have engendered a particular view on parenthood. In their studies of parenthood across cultures, Harnkness and Super (2006; 1996) have argued that each community has its own

⁶³ Parents devote considerable energy to modifying the activities, sports and spaces of boyhood to create a space for their son to play. However, their efforts to do so are often constrained by non-accommodative policies and built environments in schools and communities.

⁶⁴ Shared with permission.

⁶⁵ Liminality is a social state of ambiguousness or “limbo”—often observed during rites of passage—when the role obligations and expectations of an individual are unsettled and altered, resulting in uncertainty and often anxiety. I define the term more fully in the opening pages of Chapter 5 (see also Van Gennep 1909; Turner 1969).

⁶⁶ See also Condin (2005); Bregman (1980); Webb (2005).

“ethno-theory” of parenthood to refer to community-specific, dominant, and widely-shared beliefs about “the right way” to raise a child. For Duchenne moms and dads, this concept captures nicely the ethos of childrearing that arises in response to the disease’s reversed teleology: “maximizing the time we have” is not only a parenting philosophy among Canadian and American Duchenne parents, but also a moral imperative, one that dovetails with an emphasis on stimulation and “quality-time” that is now a staple of popular ideals about parenting in North America. This perspective was described to me by one mother of a 6 year-old boy.

You know and, and it still makes me cry sometimes to think about it, but yeah it has changed... my outlook, on his life, and what it’s gonna be like. Because, and especially now with the divorce, because I’m thinkin’, you know “I can’t do this by myself.” You know, but, even though I don’t let myself think about the future of him being in a wheelchair or on breathin’ stuff, or whatever, in the back of my mind it was always there.

And now it’s almost like, maybe it does give me, the ability to [believe], it’s not gonna happen. You know, because there’s hope. Because of this research, because of this trial he’s involved in, there is hope. And, that’s what I focus on. I don’t focus on, the negative side of it. You can’t. When you’re a parent with a child who has any kind of illness, whether it’s cancer, muscular dystrophy or anything that’s fatal, you can’t think about the negative side. You have to think in the positive. You have to, focus on that child, what his needs are today, enjoy every minute that you could spend with him. And make it as pleasant and, active, and meaningful to those kids. Because that’s what’s important, you know?

Parents’ narratives collected in the course of my research also suggest that the burden of reversed teleology for Duchenne families is compounded when set against popular Western ideals that emphasize childhood achievement as a moral imperative. In an age of attachment parenting, maximizing opportunities for personal, physical and intellectual enrichment is seen in contemporary North American as a defining moral obligation of parenthood (Ochs and Kremer-Sadlik 2013; Hays 1996; Warner 2006). This point is illustrated by Newman, who argues (in

relation to breastfeeding) that “intensive mothering” has become a dominant mode of motherhood in middle-class North America. She describes this ideology as

A belief system that demands that mothers provide unlimited amounts of care, attention and affection to their children. This dominant discourse of motherhood has been described as one that sees mothers as “selfless” and “sacrificial.” That is, mothers are expected to focus primarily, if not exclusively, on their children’s needs rather than on their own desires and needs. Furthermore, mothers are increasingly being held responsible not only for the health and well-being of their children, but also for their cognitive and intellectual development, and their overall short-term and long-term success in life. (Newman 2010:133)

This cultural shift creates an implicit (and implicitly able-ist) notion of childhood development through milestone achievement and accomplishments in sports and school, against which parents of children with Duchenne struggle. The following excerpt from the journal writing of the same mother of two boys quoted above, poignantly illustrates this point,

My neighbor approached my car this afternoon. She complained of fatigue due to spending so much time at the baseball field. She was unsure when she had cooked the last meal for her family. Life is hectic, if only she could rest. My thoughts raced, how should I react here? How could I feel any connection to this life? My own children are dying. I would give 10 years of my life to have this opportunity, if only for one minute to observe my own child running from first to second base. It would exhilarate me to sit in the heat and watch my small brown-haired child smile as the ball magically left his bat into the air and see that little leap of joy as he began the journey to his first home run. I could almost feel my own heart accelerate and the scream that might escape ... These are the things I had imagined my life would hold ... I am jealous. These are the things I had dreamed of, now completely out of reach. Now you know why my mouth fell open and nothing happened.

In Euro-western culture in particular, “little deaths” are about much more than just lost milestones and abilities. This is because achieving competencies in ambulation, cognition and physicality are not merely benign acquisitions of new skills, but are rather deeply symbolic

markers of a child's "normalcy" and, by extension, his personhood.⁶⁷ Milestones are not only celebrated in the houses, hospitals and schools of North America—they are measured, plotted (on growth charts and school-assessment instruments, for instance), emplotted (as stories told to grandparents, family, and friends), and circulated as matters of maternal or paternal pride ("Gina scored her first goal in soccer today"; "Amrit took his first steps"). They are markers of a child's growing independence, and in a digital age they are tweeted, blogged, posted, and shared online.

Arguably, this circulation of narratives around achieved milestones is all-the-more common and significant in an era where the intensive parenthood described above collides with social media; posts on Facebook, Instagram, and Twitter are often symbolic markers not only of a child's development, but also of a parent's worthiness as mom or dad. The effects of a profound and growing cultural obsession with milestones on families and children with Duchenne—from whom they are taken relentlessly—remain poorly understood in scholarly research. Despite their obvious importance in forming the cultural context in which parents make treatment decisions and choices about experimental medicine, they are also curiously elided from academic and regulatory discussions of risk-benefit, informed consent and clinical research participation.

3.5 The Duchenne Community and "Duchenne as Culture"

DMD is like many other rare diseases which have experienced a renaissance in community-building and patient advocacy over the past two decades (Rabeharisoa and Callon

⁶⁷ This argument is amply demonstrated in a vast disability-studies literature. See, for example Ingstad and Whyte (1995); Davis (2006); Wendell (1996); Murphy (1987); Rapp and Ginsburg (2001); Landsman (2003; 2009). Much of this work traces back to Goffman's work on stigma (1963), in which he discusses at length the "blemishes of the body" and how these are not only physically but also symbolically defined.

2002; Rabeharisoa 2003; Rabeharisoa 2006; Gibbon and Novas 2008; Novas 2006; Novas 2009; Aymé, Kole, and Groft 2008). They join a global current of political activism by patients with more common diseases like HIV/AIDS and cancer demanding and fundraising for better research, treatment and care, and attention to their plight (e.g. Epstein 1996; Kaufert 1998; Rapp 2000; Heath, Rapp, and Taussig 2004; Rapp and Ginsburg 2001; Nguyen 2010; Barbot 2006; Landzelius 2006; Terry et al. 2007; Winkler and Finegold 2008; Aymé, Kole, and Groft 2008; Panofsky 2011). The origins of this movement lie in the reclamation of patient autonomy and self-determinism from a paternalistic biomedicine, in liberalist claims to equity made by the civil rights and disability movements, in the democratization of medical and scientific knowledge, and in the rise of web-based social media and networks. Today, patient groups connect across disparate geographical, linguistic and cultural barriers to share their stories of disease with one another, to seek support, exchange knowledge, and to demand changes in regulatory policy and legislation. Epstein (1995; 1996) has argued that this movement can be explained in part by changes in the kinds of knowledge we deem credible. Patients (and in this case, their parents) have acquired authority, credibility and power in the eyes of scientific researchers, clinicians and policymakers. This has corresponded with an erosion of faith in expert scientific knowledge in Western settings (on this point, see also Collins and Evans 2002; Beck 1999; Foucault 1994; Foucault 1975; Prior 2003; Bourdieu 1984; Habermas 1984; Wynne 1992; Callon 1986). Today, patient groups are instrumental players in the biopolitics of research and therapeutic development for rare diseases (Rabeharisoa et al. 2014).

The origins of the modern “Duchenne community” are often located in the telethon efforts of the Muscular Dystrophy Association (MDA) (“The Jerry Lewis Telethon”) in the US, and the *Association française contre les myopathies* (AFM, or French Muscular Dystrophy

Association) in France (on the latter, see Callon and Rabeharisoa 2008; Rabeharisoa 2006).⁶⁸

However, despite raising hundreds of millions for neuromuscular research, the galvanization of an organized political movement in the United States did not occur until the early 1990s when two mothers from Ohio and New York met and found themselves exasperated at the lack of treatment options available for their children. Mothers Patricia Furlong and Donna Saccomanno worked together to form a small organization that was ultimately branded the “Parent Project”; later, they were joined by Elizabeth Vroom, a mother who started a similar group in the Netherlands. The group began holding annual conferences to which they invited prominent neuromuscular researchers and clinicians. Initially the scientists came only reluctantly and with trepidation about speaking to parents, who often made “desperate” and emotional demands for a treatment for their sons. However, over the next two decades PPMD expanded its influence and grew to anchor a broad community that now encompasses many actors. Pat Furlong described the composition, structure and scope of this community to me during an interview.

So it's all encompassing to me. So it starts off at the research community. I don't mean start off in terms of a hierarchy, I mean the researchers are part of the group. The clinicians are part of the group. The families are part of the group. The boys are part of that group, other foundations. So I see it as all inclusive. I see, the community as very broad. [There are] parents, clinicians, researchers, scientists, pharmaceutical professionals. There are Congressmen and Senators who are champions for the disease, people who have given their public persona. So I see it as broad. I see the runners [people who run in marathons fundraising for Duchenne research]. I see their friends. I see the families. And I see the grandparents who, sometimes have double heartbreak in a certain way, watching their child, suffer, or have suffered, not in terms of physical suffering, but, the heartbreak of having a catastrophic illness. And then watching your grandson and feeling a little peripheral to that, to being able to get down in there and roll your

⁶⁸ The Jerry Lewis Telethon has been critiqued by disability studies advocates and scholars for its representation of people with disabilities (referred to as “Jerry’s Kids”) as passive, piteous actors in defective bodies. For more, see Smit (2003); Phillips (2001); Devereux (1996); Kemp (1981). Jerry Lewis’ tenure as host of the telethon was unceremoniously terminated by the MDA in 2011 (Wiener 2011; Stanley 2011).

sleeves up. So I see the community as being broad.

Today, PPMD commands an annual budget of \$6 million. The community as a whole has leveraged over \$500 million in US government spending for muscular dystrophy research (PPMD 2013),⁶⁹ gaining considerable recognition in the wider rare disease advocacy movement. In 2001, parents successfully lobbied the US government to implement legislation appropriating funds and oversight for DMD research and care (called the MD Care Act),⁷⁰ which established a network of Centres for Excellence for muscular dystrophy research throughout the United States. More recently, members of PPMD have been prominent discussants, advocating for increased patient involvement in regulatory decision-making as part of public consultations by the National Institutes of Health (NIH), European Medicines Authority (EMA) and FDA on regulatory and research policy, and as this dissertation goes to press, the group has successfully launched the first patient advocacy-initiated draft guidance for a rare disease to the U.S. Food and Drug Administration (FDA) in the hope of accelerating development and review of potential therapies for the disorder (PPMD 2014a).

The organization has succeeded in these initiatives by uniting a range of disparate groups into a network focused on DMD, creating a community of parents who interact online to offer support, circulate medical knowledge and parenting strategies regarding DMD, and co-ordinate fundraising and advocacy. Online social networking has become a key source for parents to

⁶⁹ In Canada, charities focused on Duchenne muscular dystrophy include Muscular Dystrophy Canada and Jesse's Journey. These organizations have been influential in funding care and research in the Canadian context, but exist on a smaller scale than their American counterparts.

⁷⁰ Among other requirements, this historic legislation mandated federal oversight and investment in further research, epidemiological surveillance, and data collection on muscular dystrophy on the part of the US Centres for Disease Control (CDC) and National Institutes of Health (NIH). A co-ordinating committee was also established to oversee the implementation of an MD Action Plan. The Act is widely regarded as having catalyzed attention toward DMD and was successfully re-authorized in 2008. Efforts are currently underway to re-authorize it again.

acquire information about their child's condition, make decisions about treatment, and develop expectations for research. In a digital era, medical information is widely disseminated, making parents less dependent on their clinicians for information; many consult the internet regarding their child's condition before seeing a physician or having a confirmed diagnosis (cf. Radin 2006).⁷¹

From an anthropological perspective, the parent advocacy movement can also be argued to centre a *community of practice* relating to the disease, drawing on the influential work of Lave and Wenger (1991) on community organization and participation. Members of the community share (to various degrees) a particular outlook and cultural orientation to the illness that is structured both by the particularities of the disease experience and the range of practices that parents learn and share within the community when coping with DMD. In other words, despite considerable diversity within the community of parents (who as mentioned come from a variety of social and geographic locations), members of the North American Duchenne community can be argued to share a set of cultural practices, narratives and schemas relating to the disease.

One can observe this cultural orientation, for example, in the shared patterns of interaction on display at any group gathering of Duchenne parents. I illustrate this point by quoting from my fieldnotes, taken at the PPMD Connect Conference in 2009.

At conferences there is a real mix of parents. Some are veterans, with older teenagers who have been coming to these conferences for many years. But others are new to the disease, having just been diagnosed, and are entirely shellshocked at what they find. Many are truly overwhelmed, and it's not uncommon to see mothers, fathers, and couples sharing tears in the hallways, or sitting with their heads in their hands at the back of the room. Parents go up and down the elevators to take a break from the flood of information and to process what they're learning.

⁷¹ Of course, this brings its own set of problems, since the quality of medical information online is variable and often difficult to judge.

There's a certain disposition and culture here, through which parents communicate to each other their shared mixture of despair, desperation, hope, strength and even (sometimes) enthusiasm for their sons' futures. New parents are mentored into the community during the first sessions of the conference, where veterans share words of support and encouragement, repeating variations of the refrain that "knowledge is power." I am sitting in a circle around the outside of the meeting room, while Pat Furlong and a few other moms and dads speak in the centre. Many are pale and rigid, and you can feel the despair in the air. But words of encouragement and support are the norm. "What you'll find here is people who understand what you're going through, that it will be hard, but that there is hope, there is reason to be optimistic," says one mother whose child is well-known in the community. There is a shared sense of camaraderie here that develops as the days wear on.

Duchenne parents have a particular way of greeting each other. They carry photos of their children tucked with them into their name badges. When one meets a new parent, they share these photos with each other as a way of establishing a bond in common. Some bring business cards to circulate with their contact information. When introducing oneself, it is customary to ask first for the name of one's son. After exchanging names, parents identify, firstly, as "Anthony's mother," or "Charlie's father." The usual greeting proceeds with a patterned exchange of how old one's children are, and then—with trepidation—the question "is your son still walking?" Here, parents are establishing the extent to which they share a disease experience in common, since the issues faced by parents of older, non-ambulatory children and teenagers are substantially different than those of younger children who are still walking. And they are also constructing and reaffirming the loss of ambulation as the key milestone of disease progression. For parents coping with a new diagnosis or in the early stages of the disease, speaking to parents of wheelchair-bound children can be emotionally difficult, and this can often be a major impediment to mutual interaction and friendship. In the course of early conversation, talk usually turns to an exchange of genetic information as parents wish to learn whether their children also share in common a particular genotype or mutation.

In addition to such shared patterns of interaction and language, many parents of children with Duchenne also share a particular outlook and perspective "on life," as described above. For example, parents frequently comment on how their child's diagnosis has caused them to better appreciate the limited time they do have with their children and to try to maximize their moments together. The phrase "don't sweat the small stuff" is a commonly held dictum for life usually

described in terms of “what’s important, which for families includes an emphasis on family time and a focus on the present.

Mother: You know what, I don’t think much about [the future] and I’m sure that other parents [don’t either]. I’ve heard some say “you know, one day at a time right? Live day by day.” If I was to sit here and think about the things that he’s going to go through, I would be a mess. I might as well just kill myself because I would be a mess. [Laughter] Like seriously, I couldn’t imagine anybody being able to deal with it. So you live one day at a time. You live, you know, this week. We’ve planned this week out and we just plan it out to the maximum amount of fun we can have, you know, without overdoing it. So, yeah, you’re living for now, you’re living for the present.⁷²

In exploring Duchenne as culture, we can say that despite their idiosyncrasies and differences, families also share in common the practical routines occasioned by accessing care for the disease, including obtaining health care and ancillary services such as physiotherapy, occupational therapy, support at school, and, later, medical devices, surgery, and the like.⁷³ These experiences are major intrusions into daily life and are often overwhelming; they consume a significant amount of time, labour and emotional energy (Ray 2003; Miller et al. 2009). Supporting children through school, dealing with a child being teased by other students, performing physical therapy and stretching (which are often prescribed as daily exercises), and nutritional proscriptions to carefully manage caloric and fat intake, are also common dilemmas faced by parents. Later, as a child loses ambulation, families must figure out how to move a

⁷² This perspective has been noted in other research with patients with chronic illness and their families, because the experience occasions a rewriting of one’s personal autobiography and a re-examination of what’s important. Among many examples, see Bury (1982); Mattingly and Garro (2000); Frank (1995); Becker (1997).

⁷³ Of course, many families—particularly in the United States where universal health insurance is not widely available—are unable to access health and extended health benefits for services like physiotherapy and devices such as wheelchairs, orthoses, and, later, cardiac and respiratory apparatuses. In both Canada and the US, these are often not covered by state-sponsored and private plans and must be purchased out-of-pocket or with charitable support. There is also considerable inter- (and even intra-) jurisdictional variation in which services are provided through the school system. Thus, there are likely to be location-specific subcultures based on the availability of services (including between Canada and the US), though I do not take up this thread here.

child through space in a stroller, power scooter, or wheelchair, how to get him dressed, and what to tell him about his disease.

All of the above are frequently discussed topics within the community, where advice circulates on how to approach these issues. Parents exchange information about best care practices, how to communicate with children about their disease, how to advocate for one's child (for example, within the school system), and how to manage the stresses of everyday life. Such knowledge is highly valued by community members and exchanged with gratitude for its usefulness. The scholarly literature also suggests that patients who are “educated” about the options for care, and who have support and recognition of their experiences with a fatal disease, are likely to have improved outcomes and report higher quality-of-life (Epping-Jordan et al. 2004; Bodenheimer et al. 2002; Angelmar and Berman 2007).

However, in examining the notion of “Duchenne as culture,” we must also note that in the discursive exchange of such knowledge, the Duchenne community is also a site for the development of subject identities and the circulation of moral proscriptions about parenthood and coping with the disease. In other words, parents do not only exchange knowledge to support each other, they also exchange and construct moral notions of what makes a “good” mother or father (and by extension, a good biological citizen [Rose 2006]) of a boy with Duchenne. As parents advocate and connect (both online and in person), they are also consuming and creating a culturally patterned view on parenting a child with a chronic and terminal disorder—one that comports with neoliberal notions of self-management, care and the mitigation of health risk (Dumit 2012; Biehl and Petryna 2011; Tulloch and Lupton 2003).

According to this moral framework, when aiming to be a “responsible” parent, one should not *only* attend at the doctor regularly and follow her advice. Rather, the ideal North

American parent of a child with neuromuscular disease should also pursue the best multi-disciplinary care available (despite its often great distance and cost), evaluate and seek treatments and supplements for efficacy, and engage in fundraising and political advocacy to the extent one is able. One should seek to understand the shortcomings of research and learn to critically evaluate the credibility of information about unproven treatments, whether at conferences or in the course of personal investigation. Various organizations and groups offer advice and information to improve parents' skills at evaluating medical and (pseudo-)scientific claims, seeking out services and self-advocating for one's child, and holding fundraisers.

Of course, such moral notions of caregiving and citizenship are a deliberate feature of many disease advocacy movements, bound up in the commonly-repeated phrase "*knowledge is power*" and promoted by mentors to apprentices in an effort to empower parents as patients. They contribute to a greater purpose of educating parents about their child's illness and assisting them in managing its impact on their lives, and they provide parents with a greater sense of meaning when coping with the disease. As but one example, fundraising has been noted to instill a broader sense of purpose and identity when coping with a new diagnosis, in addition to generating capital to advance a shared social good in the form of research into new treatments and cures (described by Novas [2006] as the creation of "biovalue" [see also Hughes 2010; Anand 2006; Terry et al. 2007]).

And yet, the moral framework that underpins "Duchenne as culture" (as I refer to it here) brings its own complexities and dilemmas. For example, parents often struggle with the question "how much is enough?" in searching out the boundaries of "good parenthood" and moral

caregiving.⁷⁴ Mothers in particular are often exhausted and overwhelmed; many describe overextending themselves in trying to be a “good parent” to their affected child(ren). They quit jobs, mortgage houses and travel across countries, borders and oceans to attend premiere neuromuscular clinics, to participate in clinical trials and conferences, and to seek out potential treatments.⁷⁵ Many also experience guilt for “not doing enough” to secure a therapy for their sons, as in the case of Garrett Petersen described above.

One outcome is that the limits of the moral proscriptions of Duchenne as culture—of the notion that “knowledge is power” and “you are your son’s best advocate”—are increasingly difficult to pin down. Balancing the activities of advocacy with the vicissitudes of everyday life can pose its own dilemmas. How far does one go in pursuit of knowledge, treatment or care for one’s child? As we rode on a bus together at a parent conference event, one American mother described how she travels across the country every three months to obtain care at Cincinnati Children’s Hospital (widely regarded as a premier centre for neuromuscular care), despite the fact that she lives near a well-regarded neuromuscular clinic in a large city on the US Pacific coast.

Lately, she has been flying with her son, who is 13 and now nearly full-time in a wheelchair, to Cincinnati every 3 months, as he is evaluated for scoliosis surgery. She is also participating in an MRI-study in Florida, which requires visits for imaging every 3-6 months clear across the country. When I asked her how much each trip to Cincinnati costs (those to Florida are covered by the MRI clinical trial), she replied in the ballpark of between \$3,000 and \$5,000 per trip. The bulk of this is not covered by her husband’s employer-sponsored insurance, which pays

⁷⁴ In many ways, the struggle to pursue the moral ideals of good parenthood mirrors both a wider dilemma experienced by North American parents more generally, and the recent popularity of “attachment parent culture” noted by social scientists over the past two decades (Faircloth 2013; Lee, E.J. et al. 2014; Senior 2014).

⁷⁵ Many of these treatments are deceptively promoted by charlatans. Despite little or no evidence of efficacy and considerable risk of harm they are often represented as cutting edge therapies not yet sanctioned by mainstream biomedicine. As in the case with stem cell therapies offered abroad, they pose vexing ethical dilemmas for parents and care providers alike. See for example Song (2010); Bharadwaj (2012; 2014); Einsiedel and Adamson (2012); Murdoch and Scott (2010).

only for care at her local clinic. They are a firmly middle-class family; her husband works in IT and she stays at home. They have re-mortgaged their house to pay for their son's care, and he's missed big chunks of the school year. "We do it because we think it's important," she tells me. "He's getting more there than we ever received with his previous neurologist and she [the neurologist at Cincinnati] is so amazing. We think it's worth it and we know he's in good hands."

-Fieldnotes, July 2009

And, as is recognized within the community, there is a flow of participants, with newly diagnosed families entering its ranks, and parents whose children "age out" of the community (and eventually die) becoming less involved as they cope with a near 24/7 burden of care. In a compelling image, one father of an older and non-ambulatory teen likened the Duchenne advocacy community to a giant sausage-making machine; the machine is replenished with new and hopeful parents entering at one end and exhausted, older parents falling out the other.

Because ...the research and fund raising community is like a sausage machine. You go in one end, and you're all [chuckle] idealistic, naïve, and enthusiastic. And you come out the other end, and you're consumed, and a bit rubbed out. That's how it works... people come into the organization, and work really hard, and then, [they get] pulled away.

Here then, I have introduced the notion of "Duchenne as culture," and used it as an analytical framework to examine the practical, experiential, moral and cultural schemas that parents—and particularly those connected to the parent-advocacy community—construct and share to various degrees. Theoretically, I have argued that this community can be conceived usefully as a community of practice, in which parents move from being peripheral learners and participants to become integrated as they process and respond to their child's diagnosis, consume knowledge online, and (in many but not all cases) begin to interact with other parents. Finally, I have pointed to some of the ways that notwithstanding the substantial benefits that flow from the

social support, knowledge, and political advocacy such communities provide, participation within this community of practice poses dilemmas for parents by setting out a moral ideal of parenthood that can at times be difficult to achieve, and which can present its own challenges in trying to do so. In an era of information flows, globalized health care and patient self-care, a defining struggle for Duchenne families is to pin down the boundaries of chronic-illness parenthood and to balance it with an overwhelming array of other demands in everyday life.

3.6 Personalized Medicine and Segmented Patient Communities

Many of the investigational treatments for Duchenne are at the forefront of a much prophesied “new era” of personalised genomic medicine where treatment will be individually tailored to a patient’s specific genetic mutation (Hamburg and Collins 2010; Hedgecoe 2004; Guttmacher and Collins 2003). In 2009, the potential (and as yet largely unrealized) value of this market was estimated to be \$232 billion in just the United States alone, with projected growth of 11% annually and a near doubling in size to over \$450 billion by 2015 (PriceWaterhouseCoopers 2009).

Such *mutation-specific* therapies are only applicable to those with the genotypic mutation for which the therapy is designed. Ataluren, for example, is only of potential use to patients whose disease is caused by a so-called *nonsense mutation* or *premature stop codon*, which is estimated to represent 10 to 15 percent of the DMD population worldwide (Finkel 2010). In the case of exon skipping (another treatment modality currently in Phase 2-3 trials), the first compounds to be advanced to clinical trials are potentially applicable only to individuals with

mutations correctable by skipping exon 51, estimated to account for only 13 percent of Duchenne patients (Kinali et al. 2009).⁷⁶

This feature of personalised medicine is especially relevant to the present study, as I illustrate below. Others have examined how personalised medicine fragments disease *markets* into ever-smaller groups, thus raising questions about the potential return-on-investment (ROI) for pharmaceutical companies investing in this disease space (e.g. Olivier et al. 2008; Smart and Martin 2006). This fragmentation of already-small rare disease populations compounds the challenge of recouping the high investment costs of therapeutic development for orphan indications; it is also offered as justification by pharmaceutical companies for the extreme costs of medications that do make it to market (McGuire 2011). However, one under-examined aspect of mutation-specific treatments is their effect upon social configurations within patient communities. Over the past two decades, these communities have become increasingly close-knit and important for families with rare diseases, particularly in North America, Europe and Australia. As I discussed above, they are now key sites from which many (but not all)⁷⁷ parents with DMD obtain much of their information about their child's disease, make contacts and friendships with other Duchenne families, and access support from other parents. In the case of DMD, despite the fact that no mutation-specific therapy has yet been approved for clinical use, the shift toward personalised medicine has nevertheless had a considerable social impact.

I begin by exploring some pre-existing social contours within the patient community. It is not uncommon to hear parents remark that interacting with other parents (for example, during social gatherings, in patient-support groups, or at patient-advocacy conferences) is therapeutic

⁷⁶ See also the Leiden Muscular Dystrophy Pages (2014).

⁷⁷ See Chapter 4.

because, as one parent put it, “they are the only ones who understand what it is like” to have a child with Duchenne. Family members and friends who do not have a child with a serious illness “can never really understand” this experience, and this can make relationships with other families in the disease community especially valued for some parents.

However, an overly essentialized view of Duchenne as a shared culture and perspective is also a limited horizon, as it causes us to overlook complexity and difference in patients’ experiences. Like all communities, there have always been contours, sub-groups, and fissures within the Duchenne parent-community. The formation of social networks here are subject to the same vagaries of personality, time, space, and common experience that influence the formation of all human relationships.

Prior to the introduction of mutation-specific therapies, these tended to be a function of the disease experience itself. The sequential events in the disease’s natural history include distinct phases, including the loss of ambulation, the requirement for respiratory and/or cardiac support, and later, for full-time care. For example, it is difficult to organize local support-group meetings for parents overwhelmed with the care burdens for a disease that affects mobility and consumes much time and energy. This was described to me by the parents of 13 year-old Kyle, Martin and Mary Roberts. They struggled to organize a chapter for fundraising and social support in their local community.

Mary: We raised a lot of money in three years. But we also found that it’s a community of individuals who are all, you know, having their own struggles with it.

Martin: Right, being a physical disorder, it’s just really, just getting to a meeting. Just bringing people together is a huge obstacle.

Mary: Uh huh. We were at the point of you know, like for eight months of the year, it's either wet or freezing. So you know, it was a struggle. So the chapter folded after three years. And then we just continue to, sort of, hunker down and do our own thing.

Another mother of a younger child remarked,

So it's hard because there's just basically a little group of six or seven of us [in our local area]. So it's hard because nobody comes out, [especially] the kids who are older and [who are] in wheelchairs, because they feel that there's nothing for those kids, you know, their kids are in wheelchairs already, there's nothing they can do, that's it. But it's like, it doesn't have to be that way, so it's hard.

Significantly, it appears that as the burden of care increases, factors related to mobility and time become barriers to social organization at precisely the moment when parents are most in need of support—that is, during the middle and later stages of the illness when children with DMD require a great deal of care, including feeding and ventilation. In the current neo-liberal context of diminished ancillary health services, there is a profound lack of respite care in most health jurisdictions (Ray 2003; Rapp 2000; Rapp and Ginsburg 2001). Some parents—particularly those with older children whose care burden is highest—are simply unable to access specialized respite or nursing care required to “get a night off” to attend support and social meetings in person.

The emotional and psychological challenges of coping with a terminal childhood illness also affect how parents congregate and interact. As discussed earlier, parents are engaged in a constant struggle to maintain a semblance of normalcy in their lives, to keep a “positive outlook” on life, and to avoid the disappointment of “false hopes” (Condin 2005; see also Simpson 2004; Mattingly 2010). Many described seeking connections and support with other families who

share a similar outlook to their own (here labelled “attitude”) regarding the possibility of a new treatment or cure.

Martin Roberts: As the saying goes, you know, like it’s ninety percent attitude kind of thing. So that’s kind of where it is for us. And I think we’ve done enough and we also know when we talked to people pretty quickly [i.e. whether they are coping optimistically and hopefully] ... [This influences] how much we will share. And it’s very, probably the first minute or two of a conversation, you just kind of know who you’re talking to.

Mary Roberts: Well and what’s funny is that Martin and I are very positive in our day to day. We just keep trucking along and, people sometimes look at us and think ...”you know they must be doing so great. Kyle must be doing so great.” I mean nobody really has a clue what you deal with day to day. But we just don’t want to be wallowers. We don’t want Kyle, like we always tell him, “self-pity is not a thing that goes on around here. Right? There’s no feeling sorry for yourself.” So we just really try to tough it out at this house. But we found that talking to other families [in the local chapter] and stuff, like we just get caught up in the negative. And you get caught up in negative experiences and, um, we’re always there to care, and to support other people. It’s not about that ... you know, but, but you gotta do what’s right for you.

Finally, disease stage is one variable that affects social organization within the DMD community. Duchenne is a progressive illness that presents different issues in different stages of the disease. For example, children in the early-ambulatory stage of the disease tend to have comparatively few medical issues, whereas children who are non-ambulatory require an array of interventions, assistive care, and both mobility and respiratory devices. In interviews, parents have remarked on their observation that families within the community tend to congregate in groups where children are of similar ages and ambulatory ability. This silo effect can be reinforced by the emotional difficulty of confronting the future and “seeing what’s in store” for one’s child when interacting with families in a more advanced stage of the disease, as illustrated by the following description by a patient advocate and mother.

Interviewee: I think it's "walking" / "not walking" fragmentation [in the community]. That's one fragment. I think that's the line and then, it's [based on genetic] mutation [*ed: discussed below*]...

CJC: Is it hard for families?

Interviewee: They think they're here [gestures, indicating: where the child is walking], right? You don't want to go there [where the child is not walking]. [They think,] no, I'm not gonna be there [because there will be a cure]. I don't need to talk to you. Right? That's why, you know, in the past when wheelchair vendors would come to patient conferences and show their stuff, parents wouldn't visit them.

You know predominantly at the conference we have people, so we have two groups [those who are walking, and those who are no-longer ambulatory]. So there's no reason for a wheelchair vendor to be there necessarily, right? If the boys are in wheelchairs, they have them [already]. The boys who aren't in wheelchairs, aren't going to need one [because the disease will be treatable]. So [the thinking goes] "Why would I visit those people?" Right?...[they feel] "I'm not, my son hasn't stopped walking, right?" That's the view.

So, I mean, one year we had one of those Belding chairs [a power-assist chair that looks more like a typical wheelchair than an electronic one]. And so we took it to the conference. So I found ... we had people who were asking him about, "tell me about your chair," right? But it was the safe way to ask. They weren't asking these other boys in these gigantic machines with the headrests. They weren't asking about those chairs [but the more conventional style ones, parents felt safer talking about]. It's heartbreaking, right?

Another father of an older, non-ambulatory young man elaborated on this divide.

So parents of the ambulatory, and babies through ambulatory boys, you know they're very [pause] optimistic and idealistic about research. And they think that everything's gonna change overnight. And that their sons will never go in a wheelchair and all this stuff. And then, as you, the kids get older, and it just unfolds and you realize, "it's not so bad when they get to a wheelchair." And then, you get involved with trials, or research, like I have. And you get a bit more cynical. And you realize that even a wonder drug is gonna take four or five years, to go through the process. More than likely they'll start things, and they will blow off, and won't come to anything. We've seen that so many times. So, I think that parents of older kids, are not so idealistic, and not such a fun group actually [chuckle] as the younger parents. So it's natural that they would split up.

For me, I'm less involved [now], just because I have to spend more time with my son [who has more intensive care needs] and less time to be involved. So it almost takes care of itself.

Taken together, the above quotations illustrate some of the pre-existing social contours within the DMD patient community, and some of the factors influencing the development of support groups and relationships. These are primarily a function of disease stage, symptoms, and physiology, as well as the coping strategies and attitudes parents develop toward it. Within the community, these factors may act as barriers to the transmission of knowledge (for example, about how to cope with the disease) from “older” and more experienced parents to newly diagnosed families with younger children. These factors also present a challenge for advocacy organizations seeking to empower parents and young children through mentorship and shared experience.⁷⁸ It is, of course, extremely difficult adjusting to a diagnosis like Duchenne, which precipitates a profound biographical and personal rupture in one's identity as a parent, and one's vision of their future.⁷⁹ However, we can also see that although one's attitude toward the diagnosis and possibility of a cure is one factor influencing whether parents see commonalities with others and/or a potential for relationship of mutual support, the role of technology and treatment has not (until recently) been determinative.

⁷⁸ Organizers of patient advocacy conferences such as PPMD's annual Connect Conference have approached this challenge by offering conference sessions where older men with Duchenne and their families share their experience directly with younger children and their families.

⁷⁹ Some parents, it should be noted, don't “cope”; the phrase “you never really adjust” is a part of the DMD lexicon, and all parents have moments of “not coping” with their son's disease.

3.7 New Contours and “Lucky Mutations”

I now turn to new contours in the community that have resulted from the shift toward personalized medicine. I examine how this therapeutic strategy stratifies the patient population in new ways. Perhaps most saliently, the mutation-specific nature of these treatments means that some patients may be eligible for drugs such as ataluren and exon-skipping compounds (in the event these treatments are approved by regulatory agencies), although those with the “incorrect” mutation are not. One outcome of this reality is that in the context of rare disease, experimental personalised treatments are remodelling patient communities by creating new social categories. These changes are of growing importance as the value of the orphan drug market surpasses \$80 billion, with a compound annual growth rate of 25.8 percent (Thomson Reuters 2012). I focus here on the emergence of one category in particular, which I label “lucky mutations.”

It has recently been recognized that genotypic variation in Duchenne is of clinical and therapeutic importance (Phimister, Feero, and Guttmacher 2012; Boone, Wiszniewski, and Lupski 2011). One implication is that many families are seeking genetic testing in order to learn their child’s specific genetic mutation. Recently published care guidelines also call for genetic testing to be offered to all patients as standard-of-care; however, there remains wide variation in the provision of this service in both Canada and the US (Bushby et al. 2010a; Mah et al. 2011). Biopharmaceutical companies have also urged care organizations (such as MDA in the US), legislators, physicians, and insurers to provide increased access to testing in order to identify new customers and expand markets. Some have even funded such testing directly (Sarepta Therapeutics Inc. 2013).

However, not all mutations are created equal. Some mutations are described by families as being “luckier” than others, because they are more amenable to therapeutic approaches

currently under development.⁸⁰ In the event these experimental compounds reach the clinic, children with these mutations are thus likely to have a treatment option before others. Maria Pauling, mother of 9 year-old Larson, describes the moment she found out that her son has a nonsense mutation (the type of mutation which ataluren is designed to address).

So she [the neurologist] wrote off the letter [to obtain public funding for genetic testing] and got the results back. And she said, “wow.” She says, “this is a first, they said yes” [and approved provincial insurance coverage for the genetic test]. And so that’s what happened, and when we got the results ... I was ecstatic, I was ecstatic because, from everything I had read about what was out there [for patients with nonsense mutations]...

Discovering that one’s son has a lucky mutation is viewed as a “silver lining” when dealing with a difficult diagnosis. Dawn McNeil described her reaction to her 7 year-old son Bradley’s genetic diagnosis as follows.

And, okay, yeah, it’s a bad thing but you know what, we’ll deal with it. But then when we found out, then I had him tested. Because we never really had his blood tested to find out actually what it was, because my genetic counselor always said in our family they could never find what it actually was that they were missing, or like the delusions [deletions] or what it was. And I’m like “well, nowadays with what’s going on they should be able to find out.” So I said “okay, you know what, just do the blood work I want to know what it is.”

So it took us probably about two years because they said they had to go through a lot of testing to find what it was, because it was a hard one. ... And then when we did, it was like, okay, this is what we have, and they were already doing tests on that [nonsense] mutation. So it was like, “okay, you know, maybe we’re lucky.” So then when we got called for this and only ten to fifteen percent of boys have this stop codon mutation, and it was like, okay, I think now I just feel that I guess we’re luckier than the ones that [have other mutations]. You know, he has Duchenne, and it is a bad thing, but I think we’re lucky because I think we have a

⁸⁰ As knowledge develops about the connection between genotype and phenotype, it is likely that some mutations will also be identified as “luckier” than others because they have a milder clinical course. Moreover, though a patient’s mutation is thought to be determinative, it is increasingly apparent that the dystrophin gene is but the most well-known among a set of other genes and genetic modifiers that interact to produce the DMD phenotype (Lock 2013; Pegoraro et al. 2011; Flanigan, Ceko, et al. 2013).

chance at getting something. Because now they're doing this trial drug so I just, I don't know, I have hopes that there's something for him in the future.

Lucky mutations are a source of hope because they mean that a treatment is a possibility. They provide a basis for forming a vision of what the future may be like, as described by Carol Williamson, mother of 12 year-old Avery.

'Cause I have hope everywhere. 'Cause that's always been, our thing here. We have hope. We're one of the lucky people, that does have some hope. Because there is something happening. ...There's always hope. Anything could happen. You know, you never know. Don't tell me my child's gonna die, you know... because I don't believe you. There's hope that he'll beat the odds and, show us all different. So.

For many parents, receiving a genetic test result is akin to a second diagnosis. The information provokes reflection and offers a frame for determining therapeutic possibility—for addressing oneself to the question, “how likely is it that a cure may be possible in his lifetime?”⁸¹ For some, a genetic diagnosis marks the beginning of an odyssey seeking treatment. Genevieve Martinez (whose child is not eligible for the ataluren trial) describes what she did next after learning her son has a deletion for which skipping exon 44 may one day prove beneficial.

Interviewee: So I said, “I will do whatever is in my hands, until the level that is physically possible.” So what I did, in fact I came here [moved from one country to the United States], and after him being diagnosed I found [out] “where is the research and the pipeline?,” and then I saw that Dr. Neurologist [a clinician-

⁸¹ Several neurologists remarked to me that parents have a tendency to focus on the genetic aspects of their child's condition, including his mutation and its implications for the severity and treatability of the disease. Neurologists observed that this emphasis on genes may cause parents (and arguably researchers and policymakers) to overlook the profound effect that “environmental” variables that have on a patient's disease course, including care, diet, physical therapy, surgical management of spinal deformity, and respiratory and cardiac interventions. Here, we might draw parallels with the case of cancer, where genetic risk factors have attracted considerable attention, resources and hope for treatment, despite their relatively minor contribution to cancer susceptibility in comparison to “environmental” variables (Lichtenstein et al. 2000; Kamangar, Dores, and Anderson 2006).

researcher in the UK] was doing the exon skipping [research], and he was skipping exon 44.

CJC: I didn't ask yet what his mutation is.

Interviewee: It's a deletion of exon 43. So it's *an excellent one*, and I kind of tried to understand like where, where are they doing that? And then I went and traveled to London. So I went to see Dr. Neurologist and I kind of just, wanted to make sure like if there's a, trial, whatever, for exon 44. [I said to him] "tell me what you need, whatever you need, if I need to move here, to London, like I will move." I just wanted to know. [italics added]

Parents also expressed humility regarding their child's genetic diagnosis. One mother whose sons were diagnosed before the advent of genetic testing described her concern for those whose children do not have "lucky mutations" (estimated to be roughly three-quarters of the patient population).⁸²

I just feel bad for the have-nots. The ones that aren't walking. [Those who] have a duplication, or have a mutation that doesn't fit in. I wonder how heartbreaking it must be, to hear all this... and sit there and think "it, it won't be for me." Right? So I feel for those parents, because keep in mind 25 years ago, there was nothing, right? So I had to listen to people tell me, there's nothing, there's nothing, there's nothing. And I didn't accept it. But I had to, I had to listen to it. ... I just think that there is so much pressure on families.

Genetic technology reveals new information, and as anthropologists have argued in various settings, this knowledge is never neutral and may have unpredictable effects that transcend the mere clinical implications of knowing one's mutation (e.g. Cox and McKellin 1999; Cox 2003; Finkler, Skrzynia, and Evans 2003; Richards 1996; Rose 2006; Rabinow 1999; Rapp 1999; Hallowell 1999; Rapp, Heath, and Taussig 2001; Franklin and Roberts 2006). In the case of DMD, many parents have remarked that the last decade's shift toward genetic diagnosis

⁸² I obtain this figure by adding the estimated prevalence of the mutations for which drug candidates have advanced to Phase 2/3 trials, that is ataluren (12-13%) and drugs targeting exon-51 (13%) (see den Dunnen 2014).

and treatment has fragmented the patient population. Those with lucky mutations are first in line for a disease-modifying treatment. Many parents have come to see their relationships with other families, and their allegiances with disease-advocacy and research fundraising groups, through the prism of their child's genetic test results. One father involved in patient advocacy describes this point.

What has happened is that now that we have the internet, and now they know about all [the various types of mutations] the exons and the duplications, deletions, and nonsense mutations. The first thing we saw is parents breaking up into groups as to what kind of genetic fault that they had. So you have people with duplications that are very frustrated, 'cause it's a difficult problem to solve, and they know that. And there's some, maybe not overt, but there's some sense that there's resentment between them and a group like the nonsense mutations, which [appears now to be] the easiest thing to solve. And it seems like there are some drugs that are becoming available just because that was the easiest one to fix. So the duplication people are lobbying for more funding for research specific to them. And the nonsense mutation people are saying, "well, all boys will benefit from the breakthroughs with these boys cause it will lead to breakthroughs in other areas." ... You also see parents supporting the charity [i.e. patient-advocacy group] that they think will fight hardest for a treatment for their son's mutation.

Comments like these show that the genotype is simultaneously an axis of shared identity and a social fissure in this rare disease patient community, and perhaps other communities as well. The emergence of "lucky mutations" within patient groups has occurred as the paradigms of genomics and personalised medicine are applied to rare diseases like DMD. Genomic research is shedding light on genotypic variation within disease categories that were previously grouped together because they shared the same genetic locus and/or phenotype. This has led to segmentation of what were previously considered to be homogenous clinical genetic categories into genetically heterogeneous subcategories. The labels of Duchenne muscular dystrophy, cystic fibrosis, and breast cancer are increasingly giving way to the new classificatory language

of genomics: nonsense mutations; G551D mutations; BRCA1/2 mutations. As I showed above, my ethnographic research suggests that a child's genetic mutation is an increasingly important factor in how parents view themselves, their connection with other families, and their position in the patient community as a whole.⁸³

Crucially, these changes in the social arrangements within the Duchenne community are not apolitical, nor are they solely the result merely of “scientific progress” so often heralded within the medical literature and popular press. Instead, they can be viewed as social outcomes of the political arrangements in which drug development currently takes place—that is, as outcomes of a market-based system which privileges some mutations over others based on whether they offer a sound rationale for bringing forward for development. Certain mutations are technically simpler to treat, offer a clearer regulatory path to approval, and have larger patient-populations and thus larger potential markets. Patients with more common mutations are also easier to find and recruit for clinical trials, thus reducing costs. These factors in combination mean that some mutations (presently nonsense mutations and those amenable to exon 51 skipping) are brought forward for clinical development before others. The result is a shifting kaleidoscope of social connections within clinical research for Duchenne that is (in part) shaped by the logics and needs of industry.⁸⁴ Parents are coming together to participate in clinical trials and advance research for their own mutations, at the same time that they are fragmented from other parents of children with different mutations, or who are not eligible for any of the current (limited) menu of personalised therapies. There are simultaneously occurring

⁸³ Interestingly, this uptake of genetic identification among parents is occurring at precisely the moment that researchers are beginning to learn more about the *extra*-genomic effects—the roles played by other genes, epigenetic and regulatory factors—that influence the disease process in DMD.

⁸⁴ Industry actors might point out that they are in turn responding to the logics and needs of regulators.

processes of collectivisation and division as personalised medicine paradoxically fragments patient populations at precisely the same moment as it establishes new genotypic connections between parents. Anthropologists have examined the new forms of collective identity that are revealed by biotechnology primarily by expanding upon Rabinow's seminal concept of biosociality (Rabinow 1996b; Rabinow 1996a), which refers to the formation of social relationships and the production of identity based on genetic or biological conditions. The data presented above show how a similar process is occurring in the North American DMD community. Viewed from this perspective, the shift toward widespread genetic testing within the Duchenne patient population, coupled with the market, technological, and scientific considerations that propel therapeutic development for personalised therapies—forces which place mutations with a higher prevalence and molecular feasibility at the top of the list for commercialization—are leading to the emergence of new forms of biosociality and genetic citizenship (Heath, Rapp, and Taussig 2004; Rose 2006) within the Duchenne sphere. Analogous processes have been observed in other settings as well (e.g. Gibbon and Novas 2008; Wehling 2011; Petryna 2002; Rose and Novas 2008) and were predicted by Rabinow in his original formulation of the concept.

However, my ethnographic research also shows that genetics does not tell the whole story, since parents view their connectedness and differences not only in terms of genetic *diagnosis*, but more complexly based on where their child's mutation *fits* within the matrix of market-driven biopharmaceutical development—on whether, and to what extent, their child's mutation is one of the “lucky ones” amenable to capital investment and commercialization. The genomic subcategories are ranked hierarchically based on therapeutic potential (their “luckiness”). Emergent forms of biosociality in the Duchenne community occur then, not only

in the context of the recent uptake of genetic testing, but also in light of the present commercialization of personalized genomic treatments for only two groups of patients (at the moment, those with nonsense mutations potentially treatable by ataluren, and those whose mutation is amenable to exon-51 skipping with the compounds eteplirsen and drisapersen).

In other words, it is important to note that a child's specific mutation—whether it be lucky, or unlucky—is but one aspect of biosocial identity, and one factor of many that influences how parents congregate and interact within the Duchenne community. My research suggests therefore that the concepts of biosociality and genetic citizenship have been surprisingly determinative and narrow in scope.⁸⁵ These frameworks have tended to posit connections between patient-citizens as emerging only or primarily from biological substance, whether it be genes, blood, or skin.

In the present case, I have shown how parents' perceptions of biosocial connection with other parents are mediated not only by their child's particular mutation, but also by the current state-of-play in the marketplace of therapeutic development, by their perception of their own "luckiness," their decisions about trial enrolment, their allegiances with particular disease advocacy groups, and their cultural affinities with other parents. Still other factors, including those described above (age, ambulatory status, attitude toward coping, etc.), as well as the usual

⁸⁵ Nguyen (2010) has made a similar argument in the context of HIV/AIDS in Africa, arguing that an over-emphasis on biosociality reduces a vast array of differences and commonalities to their biological substance, leading us to overlook the important role that access to treatment, politics, and technology play in configuring patient communities. Comparing divergent forms of what he labels "therapeutic citizenship" that have emerged among HIV-patients in the Global North and West Africa, Nguyen notes that in the North, the roles and responsibilities of good therapeutic citizenship "grew out of a sense of duty [to participate in clinical trials] so that others may benefit from treatments eventually found effective" (92)—that is, as a form of volunteerism in the name of advancing science. In Africa however, the duties of good therapeutic citizenship revolved not around altruistic "guinea pigging," but around "taking one's pills properly"—that is, adherence to one's antiretroviral regimen and dutifully returning to the clinic to obtain care. In Africa (like in the North) good therapeutic citizens were the ones who received "good drugs," but for different reasons, as an emerging logic of triage was used to ration drugs in limited supply.

demographic characteristics (including class, education, geography), also operate to structure and organize social relations within the patient community. Parents are in essence constructing kinship with each other from multiple domains, drawing on both new biosocial affinities and existing cultural ones (Rapp and Ginsburg 2001).

The picture presented here then, shows that in fact parents' experiences, identities and relationships are much more complex than the concepts of biosociality and genetic citizenship imply. These dimensions of community-building in rare disease communities represent pressing areas for further ethnographic research. They are also of immediate practical concern to leaders within the rare disease advocacy movement seeking to overcome the emerging scaffolds of mutational and therapeutic difference and to foster unity and cohesion within patient communities.

Chapter 4: Parents' Paths to the Clinical Trial

Families take different paths to the clinical trial, given their different backgrounds, illness experiences, cultural understandings and knowledge of their child's disease. In this chapter, I address the following question: What "kinds" of parents choose to (or are able to) pursue an experimental intervention? I approach this question by examining the stories of three parent-families. I argue that the paths they traveled to the clinical trial represent archetypical cases or categories, and I label these cases respectively: 1.) The Connected Parent; 2.) The Semi-Connected Parent, and; 3.) The Actively Unconnected Parent. I then shift to a discussion of what we can learn from these parents' narratives about their paths to the investigational trial.

4.1 "The Connected Parent"

Sandy and Jennifer Williams are parents of 14 year-old Michael, one of 38 boys enrolled in the original Phase 2a trial of ataluren.⁸⁶ He is a bright and inspiring young man: a talented musician who dreams of "curing muscular dystrophy," going to university, and travelling the world. Though Michael will never play hockey, when he reaches adulthood he wants to manage a professional hockey team. He came off his feet at age 12, "rolls" in a power wheelchair, but has already lost a great deal of independence. In just two short years, Michael's muscle weakness has progressed such that he can no longer move from his wheelchair without being carried, and he relies on his parents when toileting and dressing. In the past several months, his parents have started spoon-feeding him at mealtimes, and they are concerned he will soon start

⁸⁶ The Williams family are composites. Their characteristics and experiences are real, but they are combined from several families in order to maintain anonymity.

choking on his food, given his weakened esophagus. Michael is experiencing frequent bouts of constipation due to the disease's effect on his digestive system, and is dealing with constant muscle spasms, aches and pains; the disease has removed his capacity to move his muscles, but left his nerves intact. Michael's father Sandy tells me that lately Michael has become upset and self-conscious about the cherubic body shape that is partly a side-effect of his cortico-steroid regimen, and that he is experiencing anxiety about his self-image that is both typical of teenagers his age and something else entirely. Still, his parents are pleased that Michael has a good network of friends at school and enjoys going there, in contrast with a great many teenagers with DMD who are socially isolated (Gibson et al. 2013; Gibson et al. 2007).

Sandy and Jennifer are deeply connected to the patient-advocacy community; their involvement with ataluren (and experimental medicine more generally) dates back much further than Michael's initial enrolment in the trial. They describe being connected with the drug not only as experimental subjects, but also as fundraisers and advocates in the drug's development. Sandy is a businessman who lives on the Eastern seaboard of the US, and Jennifer works in the home and volunteers in her community. When Michael was first diagnosed at age 4, his parents were devastated. Jennifer decided to quit her job as a freelance journalist to be at home with Michael and his infant sister, and they both poured themselves into Duchenne. As we sit in the waiting room at Valleyview Children's hospital, Sandy grows wistful when recounting the past. "We were young and enthusiastic, and pretty naive back then. We were broken after the diagnosis, but determined to make things change. We thought all this needed was some more money, more attention, maybe a celebrity, to get us to a cure."

Immediately after the diagnosis, Sandy devoted himself to learning everything he could about Duchenne. He stayed up long hours into the night, reading online posts, assembling

journal articles, and contacting research laboratories. “I came home from work and went straight to the computer, sometimes for 6 or 8 hours a night. I think I spent over a thousand dollars on journal articles just in the first year alone,” he says. “I read everything I could get my hands on.” His undergraduate education included a minor in biology, and Sandy believes this helped him to become comfortable with the languages of muscle biology and genetics. Sandy’s experience in business had him looking for opportunities to invest in promising research. In their spare time (usually after the kids were in bed), Sandy and Jennifer discussed potential experimental strategies they felt were promising. “Back then, gene therapy was the hot idea,” he says, “but we were also interested in gentamicin.”⁸⁷

When it appeared that some experimental strategies were going to be mutation-specific, the first thing Jennifer and Sandy did was to find out Michael’s specific mutation. They paid out-of-pocket for gene sequencing by sending Michael’s blood to a specialized lab in Utah—a process that took over six months to complete. When they learned that Michael had a nonsense mutation in exon 52—in other words, a lucky mutation—they were hopeful.⁸⁸ “Even though we knew that he still had this disease, it was something concrete. It gave us something to go on, a place to focus our efforts, so that was really positive” noted Jennifer.

In the meantime, Sandy and Jennifer became involved with Parent Project and with their local MDA chapter. They started networking and fundraising by first holding small charity dinners, and later corporate golf tournaments, in an effort to enlist support from Sandy’s business connections. Funds raised were donated to PPMD’s research development efforts. Michael

⁸⁷ The antibiotic gentamicin has been shown to promote readthrough of premature stop codons in various diseases and has been examined as a treatment for DMD, however long-term use raises concerns about toxicity (Malik et al. 2010). See also Chapter 6.

⁸⁸ I discuss lucky mutations in Chapter 3.

became an ambassador for the MDA and appeared on the Jerry Lewis telethon. His parents attended PPMD conferences and meetings, where they spoke with neuromuscular researchers, geneticists and clinicians in an effort to learn as much as they could about current research strategies for Duchenne. Sandy and Jennifer placed Michael on steroids early and started him on an extensive supplement regimen. When published research appeared to show that losartan (a treatment for hypertension) might also have beneficial effects in DMD patients, Sandy and Jennifer sought out their pediatric cardiologist and asked her to prescribe the drug off-label.⁸⁹ When a compound manufactured only in Asia appeared to have promising results in early animal studies, Sandy used his business acumen to source and import a consistent supply, administering it to Michael daily. Later, Sandy and Jennifer enrolled Michael in an n-of-1 study of gentamicin, giving the drug by infusion at home twice-per-week, after convincing their neurologist to oversee the study and apply to the FDA for its approval. However, they discontinued this treatment after only a few months when it appeared that the PTC124 clinical trials were imminent.

It was through their involvement with PPMD and their own self-initiated research that Sandy and Jennifer learned about PTC124. Having developed contacts with various prominent research scientists, they sought the advice of several neuromuscular experts, including one of the academic research scientists involved in the early animal studies of the drug. It was at the suggestion of this research scientist that the parent organization undertook to collaborate with PTC Therapeutics (then an upstart biotech company), and to raise a million dollars to fund a Phase I trial and toxicology studies. This startup money—delivered at a risky point in drug development when venture capitalists are typically reluctant to invest, and scholarly grant

⁸⁹ It is speculated that losartan may also have a beneficial effect in Duchenne by downregulating the production of Transformative Growth Factor-Beta [TGF- β], a protein involved in muscle repair (Bish et al. 2011).

funding is often insufficient—was key to the drug’s advancement. Sandy and Jennifer devoted their energies to this fundraising initiative and advocated extensively for PPMD to develop close ties with PTC Therapeutics. “It was a promising, exciting time,” Sandy tells me. “We really felt that we were going to get somewhere with this drug, that it would be the treatment we’d been hoping for. We felt—we still feel—that we were partly responsible for bringing this drug to fruition.” When the Phase 2a study got underway, Sandy and Jennifer took Michael off the gentamicin and enrolled him in this 28-day trial. Later, Michael would participate in the Phase 2a extension trial. In total, he would undergo four surgical muscle biopsies, countless blood draws, and over 25 trips by plane from his home to the clinical trial site for study visits.

4.2 “The Semi-Connected Parent”

Maria Pauling is a single-mother who resides in a small mobile home in a rural town in Central Canada with her only son Larson, aged 9. Maria works odd jobs to make ends meet, and she supplements her income with social assistance. Larson has freckles and wavy dark hair, and he strikes me as a gentle child who loves toy cars. He’s a “handful,” Maria tells me; she and Larson have been through a lot together. Though he is still walking, Larson is beginning to fall more frequently, is losing the ability to climb stairs, and has a pronounced cognitive delay that has posed challenges at school. He has trouble sustaining his attention for more than a few moments, has difficulty with processing words, and requires extra support in class. On some days, she says, the behavioural issues are more significant than his progressive muscle weakness, but Larson has the same childish interests and innocence of his peers, and he and his mother share many happy moments.

Maria: Yeah, he's a happy little guy for the most part. He has a cognitive impairment that goes along with Duchenne which is probably, for me, it's almost kind of a good thing. I wouldn't call him seriously mentally handicapped or anything, you know, he can function quite well in life... I think a big part of his issues are the word processing, it's very slow. So it takes him time, and if he's in a group of people and there's a conversation going on, he gets lost. But he's very good at adapting. He'll watch other people and follow.

CJC: Can you give me an example of what that's like?

Maria: Like in a group situation, [such as at] swimming lessons at school, the whole group gets in there and they're divided up and a lifeguard has so many [students], seven I think. And she'll be out talking, "okay, I'm gonna get you to jump off the side and swim to me and then swim back," and after she said "I'm going to get you to jump off the side," I think Larson has lost the conversation. So when she says "okay, go," Larson sits there and he looks around, [thinking] "okay, what is everybody doing?" ... So and that's actually good for me to see that, because I forget too [that Larson often does not have an age-appropriate understanding of what is happening around him]. And also I notice, driving down the road in the car, if there's two or three people in there and you're talking and laughing and, you know, the conversation is really light hearted. After a while he'll say "what are you guys talking about?" because he wants to get in on it but he's lost it [the conversation].

When Larson was diagnosed, Maria was broken. She had been searching for an explanation for his delayed cognitive and physical development for over a year, but it didn't lessen the blow when she received confirmation that he had Duchenne.

As a matter of fact I remember when I got the diagnosis I was in a store in [the town where I live]... and just about to go pay for my stuff and Dr. Neurologist phoned me and gave me the results of the tests, that Larson did indeed have Duchenne. And I remember asking her about the premature stop codon and because they had, there was a potential treatment for it coming up and she said "well, no, that wasn't the case."⁹⁰ And I remember being devastated and I was like, I had to leave the store. I had to leave all my stuff right there and leave the store because I was crying so hard. It was just not very nice right? So I knew about it [the drug] way back then, you know, but it didn't make it any easier.

⁹⁰ A subsequent gene sequencing test would reverse this finding and confirm that Larson did indeed have a nonsense mutation.

By then, she had learned about premature stop codons, and about PTC124. Maria had learned about these facets of Duchenne because she had turned to the Internet on her home computer prior to receiving Larson's diagnosis. Having little or no formal education in biology did not stop her, and she began to consume whatever information she could find. A few months later, Maria joined a regional support group that met every few months, but found it difficult to connect with the other parents.

Well, I joined the chapter when I first, when I got over the initial, you know, [feeling that] I just wish the whole world would go away and let me die. I joined the chapter thinking it would be a thing that brought us together, support, interaction and it's not.

I only went to a couple of meetings because I thought they would have more social interaction and it's, it's not there. So for me the meeting just didn't do it, it was about fundraising and stuff like that, and that's all good, but I need some sort of a social support group, and I didn't really feel that it was there. I guess I was looking for something that actually wasn't really feasible anyway because when you think about it, I managed to find one person in [a neighbouring town], one person [further away], and one person in [a city much further away]. So how do you all get together, you know, so the kids can play. Even, camps, camps drive me insane.

My friends all disappeared and didn't want to talk about it [laughing]. It's sort of funny. Not funny but I mean I, I understand because I know how I don't know what to say to you, I know your child, what's happening, you know. ... I think a lot of people don't understand a lot of it. ... "oh yeah, you've got Duchenne's, okay." But they haven't got a clue as to what extent it affects the individual and even, even I don't. I live with him 24/7 and honestly I don't. I've bought him toys, I've gone out to the store and played with toys in the store and thought, "this works, I'm sure he can do it," and bought it for him at Christmas and he couldn't deal with them, you know, he's not strong enough, and had to take them back, Like, how sad was that, you know? So it's a struggle, even I forget. Lots of things I forget.

Interacting online, first in DMD-related chat forums and bulletin boards, and later in the PPMD community forum, Maria found understanding, support, and some information to help her cope

with the diagnosis. Despite living in a small rural community, she was able to develop a support network with other DMD parents.

Well it's moral support that you're not getting anywhere else. It's somebody else in the same boat, it's like I'm not the only person in the world whose living this life. So, yeah, as soon as you realize that you're not the only person in the world doing it even though they're millions of miles away and you don't know these people, you're still in the same boat and they're having the same issues and, you know, its, its support. We tried this and that didn't work and we tried this and that worked so, yeah...a lot of the issues can be different but the basics are the same, yeah. So, yeah, I think it was nice, like you have the support group even though not physically there. So thank god or whoever else for the Internet, it's been my savior. It's where I learned about everything.

It was here that Maria learned about the PTC124 trials, even before she had received her son's diagnosis. When her neurologist sought and received special funding from the provincial health-insurance plan to have Larson's DNA sequenced in closer detail, it was discovered that he did in fact have a nonsense mutation. Maria can't remember who brought it up first—herself or Larson's neurologist—but she kept asking about a trial spot, and eventually the research coordinator at the neuromuscular clinic phoned to offer Larson a screening evaluation. He would become one of only two boys at the regional pediatric hospital to enroll in the placebo-controlled Phase 2b trial.

When set against the case of Jennifer and Sandy Williams above, it can be seen that Maria has been comparatively less involved with the Duchenne community. She has, for example, not engaged in fundraising, advocacy or lobbying, and she has not pursued other experimental therapies or supplements for Larson. Maria's network with professionals is restricted primarily to those involved in treating her son. When she was interviewed for this study, she had developed only a few online relationships for mutual support, though she did read

extensively within the patient-community and lay-discourse about Duchenne. Though Maria did not complete high school, she has done her best to acquire an understanding of the biology and genetics of Duchenne, and she has successfully advocated with her neurologist for a spot in the clinical trial despite living some distance from the trial site.

4.3 “The Actively Unconnected Parent”

In contrast with the two previous cases, some parents were entirely unconnected to the patient advocacy and support communities, did not follow scientific research, and were unaware of the ataluren trials outside of their interaction with their child’s physician. Presumably, some of these parents are not able to access information online, are overwhelmed with their diagnosis, and/or have other demands on their time (including making ends meet). However, several interviewees in this study described how they deliberately and actively avoided getting “caught up” in the torrent of information and community discourse online. These parents preferred instead to go it alone, primarily because they felt that peer-support does not fit with their own attitudes toward their son’s condition. Accordingly, they followed a more traditional, non-digital path to the clinical trial. That is to say, they were typically made aware of the clinical trial via their neurologist at one of their regular clinic appointments. Parents who have taken this path to the clinical trial tend to be fewer in number, given the inherent gatekeeping effect of the high educational, informational and social hurdles parents face in pursuing a specialized investigational treatment like ataluren.

Scott and Julia Shilling offer a typical case for the actively unconnected parent. Their son Geoffrey is older at 17, and it is remarkable that he is still walking. Scott is a factory worker and Julia operates a small business part-time. As I sit with them in the kitchen of their home in

Eastern Canada, they explain their path to the ataluren Phase 2b trial. Geoffrey was diagnosed at age 6, with no family history of the disease. As our interview gets underway, it is quickly apparent that for Scott and Julia, normalcy, consistency and independence are deeply valued; they have striven to treat Geoffrey as they would any “normal” son. Scott and Julia have always been diligent about attending clinic and following the advice of Geoffrey’s neurologist (including placing him on corticosteroids), but they have not pursued supplements or “alternative” treatments.

I ask them why they feel Geoffrey is doing so well, given that he is still walking at 17, and Julia answers, “I think it’s just because we’ve never coddled him.”⁹¹ They are careful not to use his diagnosis as an “excuse” for special treatment. She continues,

You know, [we’ve treated him] just like your average child. And so we’ve never done that [coddled him or made a big deal of his diagnosis]. I mean he’s just been the same as, every other child and, when we go for a walk, if we figured Geoffrey could do, you know, a block, then he did a block. And, we never ever mentioned to him, “are you tired? Would you like to go in the wagon? Or the stroller.” I mean, he thrives to keep up with his siblings. He always has. Sometimes he’s had to manipulate things, like when they would race down the driveway all the kids would be at the end. They’d start coming back. Geoffrey would only go half way, and as soon as they went back this way he’d turn around and go back. So, he’s always been very good at altering things to his own needs. So, you know I think that’s what’s taken him so far, is that we’ve just, never, ever, um, I don’t want to say, “given in to him.” But we haven’t fed him with the notion that you have a disease so therefore you can’t [do this or that].

Geoffrey has two other siblings. His parents have always made it a point to make little fuss about his condition. Scott and Julia try to do things “their own way,” and they haven’t spent

⁹¹ Julia’s answer to the question of why her son is still walking at 17 is intriguing. A neuromuscular physician or geneticist would likely hypothesize that his longevity in walking is at least partially attributable to a milder genetic variant, to a “leaky mutation” (sometimes called endogenous exon skipping) that results in his muscle cells producing a partially-functioning dystrophin protein, or to as yet unexplained epigenetic phenomena.

much time reading up on their son's disease. Their independence is an obvious source of pride, because they have actively resisted being "caught up in the disease."

Julia: When Geoffrey was first diagnosed, you know you get a ton of websites. A ton of information, you know. I mean, if we had delved into all of that? We never did. We never did! We always figured Geoffrey is not like this little boy that we're reading about. So if he's not like this little boy, how can we perceive that these things [i.e. milestones] are going to happen when they say they're going to happen? Now here he is, 17 years old. Still walking. And we know another Duchenne boy who is two years younger than Geoffrey and he hasn't been walking for several years. So we never let ourselves fall into this and this, and this [i.e. getting hung up on prognostic information about disease course].

Scott: We've never looked for it.

Julia: You know, it's the same as parenting books. You don't sit there and say, okay by this age you should be cooing. And by this age they should be babbling. And by this age they should say their first word. They're going to do it at their own pace. ...

Yeah, so I mean, it's like we say, we never put too much into [support groups and meeting other people with the disease], we figure Geoffrey is his own person. And we are our own family and, I think it just depends on how you raise the child.

In a similar way, Scott and Julia haven't actively sought contact with other families. They view the support groups as "needy," and likewise do not keep apprised of developments in scientific research. Instead, their focus is on Geoffrey's quality of life and on maintaining a positive attitude. Scott and Julia feel that Geoffrey is unique and that his disease course will not fit "all the predictions." Even though they are faced with a considerable burden of care, they are trying to eke out a semblance of normalcy.

CJC: Do you follow, I mean, do you follow the research closely? Or do you read about it online?

Scott: Not really.

CJC: Scientific stuff?

Scott: No. no, not really. [chuckle]

Julia: Not at all.

Scott: [chuckle] Somewhat vaguely, you know, we've never really, just, like we were saying before, you know we just, whatever, we leave it to his abilities and disabilities, and we work with those. And, you know, sometimes now...I think it might have been, maybe a drawback, because we talked to other people [over the years they have met a few parents in passing at clinic, and others whose children have other disorders], you know, [who are saying] "oh, have you been in touch with this agency and this agency?" And like, no [we haven't] [chuckle]

...

Yeah, [we are starting to need] lifts for the bathtub. Before, he was small enough, you know, I just heaved him in and out. But now he's getting a little bigger. We're gonna need that type of stuff, right, to give him a hand and other people have had this for years. [chuckle]

In constructing a positive and independent attitude toward Duchenne, Scott and Julia have preferred to focus on what they can control. They have not been hung up on seeking additional services, diagnostic testing, or pursuing experimental therapies. For example, Scott and Julia did not actively pursue learning Geoffrey's specific genetic mutation, and when their neurologist ordered and delivered the results of their son's mutation analysis, the information appears to have had little significance to them:

CJC: And do you know now what mutation he has? Have you had genetic testing?

Scott: They've done [testing], but I can't remember what, you know, they've said. But I don't know what the heck they were talking about, so. But I know, Dr. Neurologist did something before this test. They had to have a certain, or before this study. Have a certain uh, whatever. [*ed.: mutation type*]

Julia: Yeah, so it's a certain thing in their blood, I believe it was they had to have this certain criteria in their genetic strain. So if they had the criteria, again, they

would be able to go on this study. And, so, of course we had a lot of hopes and prayers for that, [chuckle] you know.

CJC: Do you remember what the criteria was? Or what they told you or?

Julia: I can't remember.

Scott: They told us but I don't remember. [chuckle]

Julia: I should have wrote it down. [chuckle]

Julia explains their approach to managing Geoffrey's condition.

Julia: Yeah and he's so mobile though, too. So that's the other thing. You know we, I don't want to say denial, because we know he has this [condition]. We're aware of, of um, you know the outcome of Duchenne's. We're aware of the longevity and the life span of Duchenne's. It's not like we're totally oblivious to it. But when we read something that says, when he turns 15, he will be needing his heel cords cut.⁹² And for us that's very traumatic. It doesn't mean that we're not in tune. If there's something going on with Geoffrey, definitely we call Dr. Neurologist. We call clinic. We find out, you know, this is what's going on. So we don't [neglect things, but we also] don't sit there and go, "well this is not happening."

... And that's the trouble, sometimes when you go reading stuff like that, you look into it too far, and you actually can see things that aren't even really happening.

... [Some parents] they have binders on their child. And, you know we go down to clinic. We get our printout, or we go to [the local Child Development Centre for occupational therapy] and we have our yearly review. And they do a printout of our review with them. And, you know we were there, we talked to them, and that goes into the filing cabinet [i.e. we don't look at it again]. ...

Scott: We keep him movin' and do what he needs day to day.

⁹² Heel cord release (tenotomy) is a surgical procedure performed on some Duchenne patients to release contractures in the leg as a last-ditch effort to prolong walking. The procedure has fallen in and out of favour and there is little consensus on its efficacy (Bushby et al. 2010b).

Scott and Julia, in other words, did not go looking for ataluren, or for any experimental medicine for that matter. They take things as they come, focus on the present, and have tried not to “mope.” The opportunity to enroll in the trial came unexpectedly one day when their regular neuromuscular specialist called to gauge their interest in the trial.

CJC: How did you learn about the drug? Where did you find out about it?

Scott: Dr. Neurologist called me at work one day and said, “you know what? There’s this study going on, this test drug.” And he explained it to me, and he gave me the website. We looked on the Internet. He says, “you know, read up about it. I’ll send you more info.” So we did that, and it sounded good. So then we went down [to the hospital] for an information [session] thing and whoa, they gave us a big pack of papers to read. So we went home with it.

In summary, Scott and Julia have actively sought to remain “unconnected” from online discourse about their son’s disorder, and from experimental science more generally. However, they have been diligent in following the advice of their pediatric neuromuscular specialist, while simultaneously avoiding “getting caught up” in their son’s diagnosis.⁹³

4.4 Discussion

The above cases contrast the differing levels of community engagement and knowledge that parents bring to the clinical trial, as well as the different pathways they take to arrive at it. In the first case (that of Sandy and Jennifer Williams), there was a high level of connection, involvement and advocacy that led the parents not only to advocate for a trial spot for their child, but also to involve themselves heavily in the development and funding of the experimental

⁹³ Callon and Rhabeharisoa (2004) discuss a similar case in the setting of spinal muscular atrophy (SMA), in which a patient named “Gino” refuses to interact with other families in the patient community in a manner described by the authors as an active refusal to be a “deliberative subject.”

therapy itself. For others, such as Maria Pauling, the connection to online support networks and information proved important (it was there that she learned how to cope with the disease, and this is also how she became aware of nonsense mutations, and of PTC124), but this interaction was comparatively more passive and sporadic rather than all-consuming. Still other parents arrived at the clinical trial via the more-conventional means of it being suggested by their care provider (usually a neurologist, or acting as a proxy, the research-coordinator). In the case of Scott and Julia Shilling, there is a conscious rejection of the moral imperative to actively seek information about experimental science and therapies in an effort to live a “normal life” and avoid getting “caught up” in the disease.

Taken together, the above cases reveal how for some (but not all) parents, key steps along the path to the clinical trial take place not in the physical environs of the hospital, but rather in the virtual spaces of the web. This phenomenon is rather recent, as described to me by a neurologist and site-investigator.

Neurologist: Yeah. Well, I think definitely there are a sub-group of people who are very active on the internet. And in fact, you know, I have actually gene sequenced most of my patients already anyways. I mean that was part of my standard practice. And so, we had patients who knew they had nonsense mutations ... and in fact I remember distinctly one of the patients ... who came to clinic and was sitting there when I entered the room and, you know, [held out a piece of paper describing the ataluren study], and said, “I’ll go anywhere. You have to send me.”

You know, and this was before I had started to share that we had actually been selected as a site. And, so it was very interesting to see. So I think people are largely getting it from the internet. I mean in fact I would say, almost exclusively.

For these parents, engaging with online discourse about PTC124 was a key element of their success in obtaining a trial spot for their child, since their awareness and self-initiated

research prompted them to pursue inquiries with staff at clinical trial sites or with the trial sponsor itself.

But perhaps more importantly, the archetypal cases discussed above also highlight emerging inequities in access to investigational trials within some rare disease populations, as drug development for orphan disorders picks up steam. The activities of online investigation serve as entry points to the world of experimental science, but they also function simultaneously as gates of restricted-entry, by permitting easier passage to parents with the linguistic and educational aptitude required to “understand” the disease. These parents often speak the languages of genetics and neuromuscular biology, and they have the initiative, strength and resources (in other words, the social and cultural capital) to pursue a limited number of coveted clinical trial spots. Parents whose children have lucky mutations and who are “connected” and “semi-connected” are much more likely to obtain investigational treatments for their children, while those who are “actively unconnected” from—or simply unable to access—information from online and patient advocacy sources are likely to be offered a trial spot only if they are “on the radar” of a neuromuscular physician or clinic. And yet, as evidenced by the case of Maria Pauling (a semi-employed mother of limited means who nevertheless developed a detailed understanding of DMD and self-advocated for a trial spot), parents’ paths to the trial do not necessarily map neatly to socioeconomic categories.⁹⁴ Several factors operating together mean that certain parents are more likely than others to both pursue and to get their child into a clinical study.

⁹⁴ Socioeconomic status and background information of clinical trial participants are not routinely published in the scientific literature.

First of course, rare disease patients are much harder to find and recruit than those with more common conditions, and recruitment delays—which can be extremely costly for trial sponsors—are common. There are unique challenges finding enough patients to fill a trial, as an already-rare population is segmented into smaller groups based on genotype (as discussed in Chapter 3) (e.g. Griggs et al. 2009). Though patient-initiated registries operated by non-profit advocacy groups (which curate patient information in databases that can then be searched and accessed by trial sponsors seeking participants)⁹⁵ have begun to circumvent the need to reach potential subjects through medical clinics (e.g. Rangel, Martin, and Peay 2012; Scully et al. 2013; Forrest et al. 2011; Rubinstein et al. 2010), patient rosters at specialized medical centres are still the most common method of identifying potential trial subjects.

Such clinics are in turn often attached to academic university hospitals in urban centres. Trial sponsors (or increasingly, the contract research organizations they hire to carry out trials)⁹⁶ develop or draw from existing lists of approved clinics when choosing sites; in other words, from networks they have screened for the requisite expertise, institutional capacity, and willingness to carry out a trial. The result is that clinics selected as trial sites, and physicians selected as site investigators, tend to be those with an established reputation in clinical research and/or who are sub-specialized in the applicable disease (a trend reinforced by the fact that such physicians with academic affiliations are usually the ones with the available research time and interest in carrying

⁹⁵ Several patient registries are operated by patient-advocacy groups. These resources aim to collect clinical data on patients in order to facilitate further study and recruitment for trials by biopharmaceutical companies and academic researchers. In some cases, their presence can be a crucial means of attracting capital investment in research on a particular disease, since small-cap companies with a therapy, theory, technology or molecule are attracted to disease areas with organized patient populations that can aid trial design and help to reduce recruitment and trial costs.

⁹⁶ On the topic of the emergence of contract research organizations (CROs)—an industry that grew from \$7 billion in 2001 to \$17.8 billion in 2007 (Shuchman 2007), see Petryna (2009); Shuchman (2007); Centerwatch (2014); Fisher (2008).

out medical research). One result is that trials tend to be carried out at “premier” centres of care located in urban centres.⁹⁷ Patients who attend such centres for their usual clinical monitoring are thus likely to be the first recruited for trials, while those unable to access these clinics (whether due to a lack of health insurance, geographical distance, or even awareness of their existence) are simply not on the radar. Notably, this picture differs from ethnographic work conducted by anthropologists such as Petryna (2009) and Rajan (2010b; 2010a) in the emerging offshore trials industry of the global South. There, clinical trial participants are more likely to be recruited from among the poor and disadvantaged, and to participate in trials as a way to obtain otherwise inaccessible primary health care (see also Farmer 2005).

However, even when a child who (on the surface) meets the eligibility criteria for a trial and *is* on the clinic roster at a trial-site, there is no assurance of being offered a trial spot. For example, according to site-investigators—who operate independently but whose recruitment decisions are subject to review by trial sponsors or their proxies—they may be disinclined or discouraged from enrolling patients for whom there is concern about their ability to complete the outcome measures successfully. Children whose parents are judged to be insufficiently attentive to their broader health needs (such as nutrition and physical therapy) or who might be predicted to decline significantly (such as by becoming non-ambulatory during a trial that measures walk distance) may be informally “screened out” and not offered an evaluation at the outset of a trial. Similarly, those with behavioural or cognitive difficulties who are unable to follow instructions consistently may potentially confound a trial’s results by not completing the outcome measures and trial procedures properly. Families coping with other social issues, or whose children have

⁹⁷ Clinical trial sites used in the ataluren (and other) trials can be accessed on www.clinicaltrials.gov.

additional diagnoses may also be less likely to be offered a trial spot. Neurologists I spoke with described anxiety at having to assess and make decisions about eligibility, and bearing the brunt of disappointment for families who are hopeful or expecting to participate in a trial despite having little input into formalized eligibility criteria for studies. Several remarked that occasionally such decisions are made in the absence of explicit guidance from trial sponsors, and stories of *ineligibility* do not form part of the written history of the clinical study.

For patients and caregivers, the matter is much more than an issue of possible selection bias in experimental design, and most pressingly so for young men with DMD who have already “come off their feet” and lost the ability to walk. Given the current lack of outcome measures for this group, those unable to perform the 6MWT are immediately ineligible and thus excluded from the opportunity to participate in most trials.⁹⁸ For young men whose disease has progressed to threaten their survival, if an investigational drug performs as intended and given that the trial or extension trial affords the only realistic chance for accessing it, such ineligibility may mean the difference between living and dying. This reality contributes to a generalized sense of exclusion from the research process felt by many non-ambulatory patients with Duchenne, and their parents. Young men with DMD whose disease has progressed have little chance of benefitting from investigational therapies despite arguably being the most in need of rescue, since their disease symptoms are much more severe.⁹⁹ Moreover, in the event treatments *are*

⁹⁸ PTC Therapeutics did initiate a trial for non-ambulatory patients with Duchenne, and to my knowledge remains the only company investigating a novel therapy to have designed a trial specifically targeting this population. (<http://clinicaltrials.gov/ct2/show/NCT01009294>). This trial was terminated in 2010 (see Chapter 7).

⁹⁹ Recently, new endpoints for this population have been proposed and are in the process of being validated, however this process is cumbersome and slow. There has also been recent discussion about the use of biomarkers in this population, but there is no assurance that an adequately reliable biomarker will be found and/or approved for use by regulators. See TREAT-NMD (2014); Lowes et al. (2013); Govoni et al. (2013).

commercially approved, it remains to be seen whether labelling rules will exclude their being prescribed to this group, and/or whether payors will reimburse for treatment costs expected to range in the hundreds of thousands per patient per year (since their efficacy will not have been demonstrated in the non-ambulatory population) (Iskrov and Stefanov 2014).¹⁰⁰ Parents have responded by appealing for the development of new outcome measures for non-ambulatory participants, for greater use of biomarkers and patient-reported outcome measures in clinical trials, and in some cases by withdrawing from active participation in research and patient-advocacy (PPMD 2014b; Condin 2005).

Within the patient community, the timing of advances in curative research for the disease has therefore provoked discussion of a “lost generation” of Duchenne boys who are on the cusp of a new era of treatability but were born just a little too early, when the medicine is “not quite there.”

Over the next 15 years, these same individuals [boys without access to a viable treatment] will lose the ability to walk, to lift their arms, to breathe, to live. Clinical trials in Duchenne are limited to a very small subset of individuals who are considered sensitive to change in the primary outcome measure, the 6MWT. All other individuals, the very young and those who have lost the ability to walk wait on the sidelines. Within the process of developing, conducting, and analyzing a clinical trial, some of these individuals will lose function and others may lose their lives. If indeed new drug development takes 10 years for any given compound and no flexibility or urgency is applied to the process, the

current generation of boys will not have benefit from the potentially amazing opportunities we feel should be in their future.

--Pat Furlong, Mother and Patient Advocate (2013)

¹⁰⁰ It also remains to be seen whether new treatments for DMD which aim to restore dystrophin expression will be efficacious in older patients, whose disease may have progressed to the point where insufficient muscle tissue remains to be treated.

Companies are also reluctant to invest in such trials (at least initially), given the paucity of validated endpoints available for measuring muscle function in men with near total-body paralysis, and a much lower likelihood that they will experience improvement due to the progression of their disease.

The net result is a drug development regime that currently excludes a large portion of the patient population. Instead, there is an entrenched market-based and scientific logic of triage when selecting both sub-populations for experimental research (in the present case, ambulatory boys), and individual candidates for clinical trials. Since companies must invest millions in a clinical trial programme and may have only one shot at demonstrating whether their drug is effective, and since the scientific conventions used in clinical research are ill-adapted to rare diseases, participants are chosen based on the probability they will show improvement on the chosen outcome measure, rather than on the basis of medical need or the urgency of their condition. Outcome measures too, are usually chosen based on whether they are deemed credible by regulators, rather than on whether the domains they measure represent patients' treatment priorities for improved quality-of-life. These practices are often critiqued by parents but rationalized in drug development by referring to the conflicting goals of research (which is designed to prove or disprove a hypothesis) and individualized treatment.¹⁰¹ Parents often find this position perplexing because it ignores the market, scientific, and regulatory conditions that shape which kinds of trials are performed, and on whom.

¹⁰¹ I do not take up the extensive bioethical debate between research and treatment—which broadly falls under the rubric of *therapeutic misconception*, here. On this point see, among others (Appelbaum, Lidz, and Grisso 2004; Henderson et al. 2007; Appelbaum et al. 1987; Miller and Brody 2003).

In raising this argument parents are pointing to a more fundamental gap between the current experimental research regime and a moral imperative to align research with the social good of improving patients' lives—in this case by targeting investigational treatments to populations with greater medical need, and providing equitable access to research participation and potentially life-saving treatments in the most efficient way possible. Their arguments also raise questions about representativeness and external validity in clinical trials performed in rare disease populations (e.g. Rothwell 2005; Britton et al. 1999).

Here though, I have focused on showing how a trial spot for a potentially curative therapy is a rarified and lucky position indeed, and how only a certain subset of children are likely to gain access to these experimental treatments. In the case of placebo-controlled trials, recall further that the number of children actually receiving “the real medication” is smaller still, since (depending on the phase and design of the trial) typically only a proportion of trial participants are assigned to an active-treatment arm.

4.5 Conclusion

The claim that patients take different paths to the clinical trial is of course a rather basic point, but it is important to note how it is frequently overlooked. Exploring the various paths parents take to a clinical trial serves as a useful starting point for restoring a focus on the idiosyncrasies of the experimental trial, as well as the social, cultural, and politico-economic context in which the trial takes place. These aspects of research subjects' illness experiences are erased from the process and narratives of drug development, which are oriented toward group-level and statistical analyses of patients' experiences with investigational medicines that often take equivalency and comparability for granted.

Parents' idiosyncratic paths to the clinical trial suggest that they are also likely to approach the trial with different expectations, given their different hopes and their various personal, emotional (and occasionally financial¹⁰²) stakes in its outcome. It follows that parents will have different needs within the trial for information and different vulnerabilities. Parents are likely to hold different ideas about the meaning of "reasonable risk"; "reasonable benefit"; "efficacy"; and "Quality of Life" in the context of a progressive fatal disease in a child. Research (including this study) shows that DMD patients and their parents are often willing to shoulder a higher degree of risk in light of their prognosis of early premature death in the absence of treatment, and the question of whether regulatory policy is overly paternalistic in restricting some parents' access to investigational treatments remains controversial (Franson and Peay 2013).

Perhaps even more significantly, the clinical trial as a research methodology provides relatively little insight into patient and family experiences prior to and during a trial, and/or their bearing on perceptions of a drug's efficacy. Despite a vast literature in both anthropology and other related disciplines (such as sociology, psychology and social work) that suggests that one's expectations, perceptions, and interpretations of efficacy are deeply influenced by cultural and social factors (e.g. Moerman and Jonas 2002; Brody and Miller 2011; Lakoff 2002; Kleinman 1986; Etkin 1992; Van der Geest, Whyte, and Hardon 1996; Guess et al. 2002), the trial

¹⁰² Notably, trial participants may also have made financial investments in the outcome of a trial, either by donating to or fundraising for charities that have funded a drug's development, by holding stock in publicly traded companies, or (rarely but increasingly) by starting their own biotech companies to source and commercialize new treatments (Anand 2006; Tirrell 2014; Marcus 2011). The connection between such stakes and a trial subject's perception of an investigational drug (if any) is an issue that has received little attention, and to my knowledge there is no published regulatory guidance on how trial co-ordinators should handle such situations (if at all). In the case of the ataluren trials, the trial sponsor PTC Therapeutics was privately-held, but like many comparably-sized biotech companies working in the rare disease space has recently issued public shares.

experience of research subjects, including their complex efforts to navigate the question of efficacy, to make sense of their perceptions, and to interpret their interactions with clinical staff, remain largely a black box.¹⁰³ Such experiences, as narrated by parents, form the substance of the roller coaster that is the curative experimental trial. Nevertheless they remain curiously bracketed from the “real” data of the clinical study, namely the quantitative outcome measures that (ideally) represent changes in function. In the process of rendering qualitative experiences into quantitative measures, however, the meaning and significance of a drug may be removed from its personal context in everyday lived experience. This chapter has sought to demonstrate the diversity of experiences that parents bring to their first screening evaluations and study visits when enrolling in a clinical trial. My task in this dissertation is to unpack some of the ways in which this complexity is elided or overlooked in the ethical, regulatory, clinical, and statistical discourses of drug development.

¹⁰³ I take up this point in the following two chapters.

Chapter 5: The Clinical Trial Experience I:

The Clinical Trial as Extended Liminality

The clinical trial experience is marked foremost by profound uncertainty. Parents—whose decision to proceed is often the culmination of lengthy discussion and anxiety-filled decision-making—do not know at first whether their child will be accepted into the trial. They must await the results of initial screening tests (to check whether a patient meets the trial’s eligibility criteria) and confirmation that a spot is available, a process that can take weeks or months. When the trial begins, those in a blinded study are uncertain if the medication they are administering is in fact “the real thing,” or mere placebo. And if it is the real thing, will it work? Will it have any impact on their child’s condition, and if so, how extensive will that impact be? What will be the significance of these changes (if any) for the way a family copes with the biographical re-ordering that accompanies a serious chronic disease? Adding to this uncertainty, the clinical trial family lives under constant threat of being withdrawn from the trial if it is halted prematurely, or if their child exhibits adverse effects, abnormal test results, or an inability to comply with testing procedures. If one generalization is true in this entire process, it is that at the beginning of the trial most parents are not yet aware of just how deeply their engagement with experimental medicine will permeate and re-order their lives.

In this chapter, I examine this experience in closer detail. I argue that the clinical trial can be conceived as a form of extended liminality that inevitably shapes how parents experience and narrate their child’s illness. Deriving from the Latin *limen*, meaning “threshold” or “cross-piece” (in reference to the bottom of a doorway which is crossed when entering a building), the

concept of liminality was introduced to anthropology by Van Gennep in his seminal work *Les Rites de Passage* (1909), and later elaborated by Turner (1967; 1969). In its now widespread usage, the term refers to the process by which one acquires a new social identity or status through culturally patterned ritual.

Turner argued that such ritualized changes in social status entail the initiate (that is, the person undergoing the ritual) first being stripped of the status s/he possessed before the ritual, then being inducted into a liminal period of uncertainty and transition, before finally receiving his or her new status and being re-assimilated into the social group with a new identity. Though various aspects of Turner's work have been critiqued (e.g. Bell 1992; Anderson 1970), the process by which this occurs has been empirically documented in various cultures and is now regarded by anthropologists as a common feature of social life. Though Van Gennep and Turner elaborated the concept in regard to age- and marriage rituals in Africa, the more familiar examples of liminal rituals in "Western" cultures include marriage and childbirth, in which the initiate enters the ritual as a fiancé(e) or pregnant woman and emerges from it in a new social role—in the case of marriage as a wife, and in childbirth, as a mother.

While I avoid getting bogged down in the theoretical minutiae of Turner's work, I argue here that the concept of liminality offers a useful rubric for framing the experiential reality of the clinical trial. This is because the trial is also a period of extended uncertainty; one is "betwixt and between," as the normal social and medical anchors of everyday life are disrupted. A clinical trial participant is neither doomed nor cured, diseased nor "normal" during the clinical trial, a feature of the experience that provokes both anxiety and sense-making for parents and children alike. Murphy et al (1988) have argued that chronic conditions are themselves an extended period of liminality without a cure and re-integration into society. Here, I suggest that

clinical trials create an additional layer of liminality for children with DMD and their families. I examine how this extended period of liminal uncertainty is narrated by parents, and I discuss how it configures their experience in the trial.

5.1 The Beginning

Parents' experience of liminality begins early in their career as research subjects, as they endure an often-lengthy wait first to be accepted into the trial and then for dosing to get underway (in Chapter 3, I described how parents narrate this experience by telling "stories of waiting"). The usual routines of everyday life are disrupted as children undergo various screening procedures in order to verify that they meet the trial's eligibility criteria. In the present case, these included a functional assessment, review of medications, bloodwork, a baseline 6 Minute Walk Test (6MWT), and finally a surgical muscle biopsy. Results of these tests must be confirmed and validated by both the site investigator and the trial sponsor before a spot is offered,¹⁰⁴ a process that can take weeks. During this period, parents do not yet know if their child is "officially" accepted. For those referred by their regular care provider to a study site at another hospital, the screening process involved travelling with their child(ren) to a new and unfamiliar hospital in a different city. Once there, children must undergo a formal assessment and meet a new team of care providers, including the clinical investigator (usually a neurologist) running the trial. Initiating a new clinical relationship can entail its own challenges. For example, Martin Roberts described how he and his wife Mary needed time to work out the

¹⁰⁴ Increasingly, these tasks are delegated/outsourced by trial sponsors to Contract Research Organizations (CROs) (e.g. Petryna, Lakoff, and Kleinman 2006; Fisher 2006; CenterWatch 2001).

parameters of their relationship with their new neurologist, including how to approach and communicate with him.

As parents, you know that you gotta recognize that you're talking to a doctor here. And they sort of may have this impression of [how] all parents are, [that parents] want to be too involved and all this kind of stuff. So we as parents kind of play the game a little bit too. Like we don't, we get educated, but we don't, you know start coming in there too confident, over confident ... You have to be self-aware of yourself when you're meeting with a new doctor and getting their opinion. Because if you put too much, kind of, hope into them, and you show your vulnerability, they're gonna start to hold back a little more. They won't share as much. They won't give points of view you're looking for. But if you can kind of play the game with them a little bit, they will share more, I find.

After being accepted into the trial,¹⁰⁵ parents attend with the research co-ordinator and sign informed consent documents. Though this meeting formalizes their new social and legal status as guardians of a minor research subject on paper, the contours and implications of this role are anything but clear. The first task parents must shoulder in this process is to support their sons through the surgical muscle biopsy to obtain a baseline level of dystrophin present in his muscle tissue.¹⁰⁶ In most cases, the procedure involved a general anaesthetic and associated trauma and anxiety—especially for the child, for whom the biopsy was often the first surgical experience.¹⁰⁷

¹⁰⁵ This study recruited families via trial sites after their enrolment and thus did not include families who had been screened but were deemed ineligible for the trial. This experience no doubt entails profound disappointment for parents and is worthy of further research.

¹⁰⁶ In this (and many other) therapeutic trials for DMD that aim to rescue dystrophin production, a primary objective is to demonstrate an increase in the presence of dystrophin in skeletal muscle. Accordingly, all participants in the ataluren trials were required to undergo a biopsy procedure at both the beginning and end of the trial in which they participated. The inclusion of muscle biopsy in trial protocols is presently controversial among parents, trial sponsors, and regulators alike (Hoffman and Connor 2013).

¹⁰⁷ The fact that this was the first surgical procedure for many trial participants is itself a consequence of recent advancements in genomic knowledge. In the past, these children would have undergone surgical muscle biopsies in order to confirm the presence/absence of dystrophin at diagnosis, however genetic testing has made this procedure less common. For general findings on the experience of surgery in children, see Cameron, Bond, and Pointer (1996); LaMontagne, Hepworth, and Salisbury (2001).

The experiences above contribute to a general sense of destabilizing uncertainty as the trial gets underway. The social roles of both parent and physician must be renegotiated, often in an unfamiliar setting. As a mom or dad, taking care of a child through a painful surgical experience is difficult and emotionally draining. The biopsy in particular both symbolizes and makes real parents' entry into the liminal space of the trial. Performed to obtain the baseline percentage of dystrophin present in a child's muscle (a figure not known until the end of the trial¹⁰⁸ and not disclosed to parents), the excised and frozen tissue is also an artifact of hopeful suspense. It offers the concrete possibility of knowing if the drug is working, but *only later*, when the trial is over. The phosphorescent lines of dystrophin-positive fibres that appear in scientific journals and on screens at conferences—so familiar and often deeply powerful to parents who follow scientific research—may yet (if all goes well) appear in their own child's tissue sample.¹⁰⁹ For parents, the possibility is overwhelming and dramatic. In the meantime, however, they must resign themselves to a state of uncertainty that soon becomes familiar and all-encompassing; that is to say, a state of “not knowing.” Parents begin the clinical trial by proffering their children's bodies for surgical tissue extraction, a process that is both an indicator of the extent of their (and their child's) commitment to the curative scientific endeavour and the entrance fee for the experimental trial.

¹⁰⁸ If it is known at all. See Chapter 7.

¹⁰⁹ The methods for accurately quantifying dystrophin expression within biopsied tissue samples remain controversial. The protein occurs in trace amounts, and not all muscle fibres in a given tissue sample will express it. There is considerable subjectivity in choosing which cells to isolate, quantify and present for publication. There are also several methods for isolating and measuring dystrophin expression (for example using immunofluorescence and/or Western blot) and little agreement or standardization on how the protein should be measured and how such measurements should be expressed. This has been a topic of considerable discussion in light of the recent results presented by Sarepta Therapeutics pertaining its Phase 2 trial of its exon-skipping medication, eteplirsen (e.g. Beekman et al. 2013; Hoffman and Connor 2013).

After all of the waiting, travelling, medical procedures, suspense (and for some, fundraising and advocacy),¹¹⁰ parents find themselves suddenly—finally—in possession of a box containing small foil packets of white powder. Clinic staff refer to this powder rather austere as “study drug.”¹¹¹ For parents, this name elides the drama of what is—perhaps, maybe, potentially—the cure for their son’s fatal disease. Most of the parents I interviewed recalled this moment as one of mixed emotion; there is a sense of anticipation, suspense, anxiety, humility, relief, luck, and fear. Despite an informed consent protocol that emphasizes that therapeutic benefit cannot be expected, parents are still hopeful that the “study drug” is the real thing, and that it will stop the progression of the disease, as described by Gina Naicker, mother of 10 year-old Griffin.

When we got our first boxes of the drug, and we brought them home to start, it was, wow, such a weight off. I just had a rush of emotions, so many things at once. I realized how long we’d been so stressed about it. We totally understood, going into this program that you know ... they said that, no one was to know. The doctors weren’t gonna know. They weren’t gonna know. The only people who were gonna know were the drug company.¹¹² So we accepted that. But you know, for people like us, and I would assume the other families, this is hope. You know, there are very good signs that this drug works. The biggest fear—I don’t know if you’ve talked to the other families—but for us, the biggest fear here was, that he would not finish the testing. That a complication would come up and he’d have to be taken off. ’Cause the drug company told us, through the doctors, [if] that does happen he’s not eligible for the drug afterwards until it comes to market. So for all of us who got in, we were terrified that our child would have some

¹¹⁰ See Chapter 4.

¹¹¹ In the language of placebo-controlled clinical research, the term “study drug” is used to formally reference the investigational medication given to the patient-subject—a label that is designed to reduce the possibility of suggestive placebo effects by incorporating uncertainty as to whether the medication being consumed is the “actual” drug, or a placebo. Though I used this term when discussing the drug with parents in order not to bias their responses to my questions, it was rarely used in their everyday speech. Rather, most parents referred to the medication they had been assigned as “the PTC.” I use both terms in the following pages (henceforth without quotes).

¹¹² In reality, the trial sponsor is also blinded to individual patients’ treatment assignments. Trial subjects are identified only by number, and the unblinded data is seen only by members of an arms-length Data Monitoring Committee (DMC), who meet at pre-specified intervals to review the safety and efficacy parameters of the data as it is collected.

complication that would remove him from the final testing block [i.e. group] ... and then he would not be eligible. We're all working—I would assume we're all working—to the goal that once the testing's done, we get the drug and it works, and our sons are gonna live.

After being instructed on mixing the drug and having the first dose administered by a research coordinator in clinic, parents return home with a blue cloth bag filled with boxes of study drug dispensed by the hospital pharmacy. They must return to hospital every 6 weeks (12 weeks for those in the Phase 2a extension trial) for a study visit, where they engage, most for the first time, the rationality of the controlled clinical trial. Here, a knowledge system built on validated, replicable and quantifiable measures of function is emphasized—one specifically designed to eliminate the “noise” of parents’ subjective experience (and also that of their children) in order to discover an experimental drug’s “true” effects in the body. Study visits last two full days, during which children undergo blood draws, various functional assessments of their strength and stamina, and complete a 6MWT, the primary outcome measure of the trial (discussed earlier). In the interim, they must also attend at a local laboratory for bloodwork, complete various questionnaires and journals, and use a step-activity monitor (essentially a pedometer) worn on the child’s ankle for nine days after each study visit.

As parents began giving powder (mixed as a drink) to their child three times per day, they described transitioning to the rhythms of the clinical trial and adjusting to a new period of liminal uncertainty.

5.2 Time

Parents’ narratives of the opening days of the trial frequently invoked the theme of time. They described both the *time commitment* involved in completing the various activities mandated

by the trial, and learning to *mark time* in different ways. This occurred as the practical routines of dosing and visits to clinic and laboratory became incorporated into the often chaotic routines of everyday family life. The result is a period of adjustment to an altered routine. The administration of the study drug becomes the paramount activity of the day, around which (especially in the early days of the trial) all other aspects of life must be organized.

For example, mixing the study drug requires work. The medication must be consumed by dissolving it in water or milk, and ideally with a meal. But the powder does not dissolve easily and has a chalky taste that some children do not like. Parents must adapt to a routine of preparing the dose, and in many cases, convincing, cajoling and bribing a resistant child to drink it, three times per day. Concern with administering doses on time and developing strategies to cope with a child's resistance to doing so quickly become significant, as described by Mary and Martin Roberts in relation to their son Kyle.

Mary: It's a long study. And it's three times a day. It's in powder format, which doesn't dissolve a hundred percent. So it makes Kyle gag. He hates it. He can take pills like there's no tomorrow, so the fact that he can't get it in pill format is unfortunate. Because it would be so much easier for him. It's really time consuming. He never really liked it from the get-go.

Each six week period it's the same thing. Three A[-labeled] sachets [of powdered study drug], twice a day. And then two As and a B[-labeled sachet] at night. So you're given this little baggy of your morning's dose. ... But you gotta open them up, you have to get all the powder out. See how fine it is? So you have to get it all out. And you can't spill any of it. God forbid you spill any, because you have no idea how much you've spilled. Right?

...So if you mess this dose up, you've messed up. Right? So of course, so this is what we do three times a day. And it's a pain in the butt. Okay? My kid gags on it, and it can only be mixed with water. Or a little bit of milk.

Martin: And you have to stir it for like, three minutes. And Mary has all these books to fill out, like daily things.

Mary: Have you seen the log books? ... It's ridiculous. And if it's a placebo! And you're asking me to fill out how many times a day my son falls? For every single day. For 48 weeks... See how granular it is? He's gotta swallow that.

Martin: Yeah it doesn't dissolve. He takes like, three, four tries [to drink the whole dose]. We do it once and then we put water in and mix it, and do it again. And you need to keep [the empty packages] too.

Mary: You have to keep everything, right? For auditing purposes.¹¹³ And again, if it's a placebo who the heck cares whether he took it or not?

Parents' narratives reveal how the passage of time becomes marked by the clinical trial regimen. Schedules are re-arranged in order to see that doses are taken as scheduled, and parents expend considerable energy modulating their lives to the rhythms of the study protocol. This meant constantly planning in advance in order to have the medication on hand, properly stored, and appropriately mixed for consumption. One mother describes the effort involved.

When we're leaving the house, you know, you have to take everything with you. You have to pack enough of the drug, make sure you have enough supply. You have to be somewhere where you can mix it up properly at the right time, have a cup, spoon, and water to mix it. And it's supposed to be stored properly too—you can't let it get too cold or too hot. So you really have to think ahead when you're going out, even for the day, you know, "do I have what I need to give him the next dose? And the one after that." And that's just for one day. Don't even talk to me about going on vacation, or away for the weekend... It sort of just becomes your life, thinking about it all the time.

Sending children to sleepovers, playdates, and meals at other homes, for example (which can already be challenging for children with additional needs), required extra planning to account for how the drug would be transported, mixed, and given on time. Several families also remarked that their plans to go away on vacation were disrupted or cancelled altogether, mainly because

¹¹³ Patients are asked to return the empty sachets to the study site in an effort to verify that doses are being taken as directed.

they had to be available for blood draws and clinic appointments, but also because they needed to transport and carefully store doses in order to administer them properly. Going camping for example, or—as in the case of one family—planning a trip to Disneyland, presented additional challenges (on top of the existing hurdles families already face when travelling with a child of limited mobility). The trial protocol also required that a dose be administered at lunchtime, which usually meant involving the school in the dosing regimen. Some parents sought the assistance of their child’s teacher, but many encountered a school bureaucracy reluctant to administer an investigational drug due to liability concerns.¹¹⁴ This meant that some parents had to travel to the school each day to administer the lunchtime dose in person.

In addition to orienting family life to the dosing schedule of the clinical trial, parents described re-ordering their lives to accommodate other requirements of the study, including the use of a step-activity-monitor, filling out questionnaires and keeping a daily diary, monitoring the number of falls, and managing the drug supply. All of these requirements of the trial necessitated a great deal of labour and time, as well as increased surveillance of the child. Mary Roberts described all of this when she recounted using the step activity monitor (SAM) fitted to her son’s ankle at each study visit, and worn continuously for nine days thereafter.

So you’re familiar with that step watch? ... He hates it. He wears it all his waking hours, for the first nine days of that six week period. And if he’s gonna go swimming, he takes it off and then I have to mark down that he took it off for this many hours. I have to jot down what time he woke up, what time he went to bed, [and] if there were any changes to his activities. [Also] if he used any [mobility] aids that day. So for example, one day he used a manual wheelchair. And then I’ve got to do that every single day for nine days. And like, I got two other kids! You know? Do I know what time he woke up? I don’t usually know what time

¹¹⁴ Policies with respect to the administration of medication by school personnel vary. However, it has been noted in the setting of other pediatric illnesses that parents often experience barriers to medication administration and accordingly must make arrangements to either attend the school themselves, or to send a proxy (Committee on School Health 2003; Yewchuk, Morrison, and Yewchuk 2012).

he goes to bed, like honestly, right? He's my oldest. So I'm usually more, you know, um, tuned in to the others. I mean this deflazacort log? So every day, did he take it? It's like, can't I just log when he doesn't take it? And assume that all the other days he did take it? [chuckle] Like do I have to do this? And then there's the actual drug, the PTC. So every single day I have to say [i.e. log] whether he took three sachet As and no Bs, and then the day dose and the mid-day dose and the evening dose. So I have to be paying attention to everything that he's doing from day-to-day, all of these things I'm supposed to be doing, but man, it's a lot.

Finally, parents must adapt to the rhythms of study visits. As I have discussed elsewhere, trial subjects were required to attend the study site every 12 weeks in the 2a trial, and six weeks in the 2b trial. (These visits are also interspersed with trips to a local lab or hospital to have interim blood and testing performed.) At the study visits, children underwent a more extensive battery of tests, including blood draws, urinalysis, cardiac monitoring, timed-function, and muscle strength testing. The study visits also involved the completing the 6MWT and various questionnaires. Since most families did not live in the same city as the hospital trial site, these visits often included significant travel, and each required an overnight stay, as described by Scott and Julia Shilling.

Scott: The hardest part has been the travel. The running back and forth. Oh my God! The going back and forth to [the trial site].

Sometimes like you know you got, your scheduled appointments, but then you know the next day, you get the phone call [from the research co-ordinator, saying], "Well you know there was something wrong with the blood, you need to have him back down here," you know.

Julia: Within 24 hours! [chuckle]

Scott: Yeah, before, four o'clock 'cause the lab calls. Well we're both at work and he's in school. Oh man, now we gotta... be off of school the rest of the day, you know. Pack him up and zoom back down there.

Julia: Good thing we both have [i.e. work for] businesses that have been very, very bending towards [the trial]. You know, I think it, for me like why I've been away, more often than Scott, and I work part time to begin with.

The above narrative descriptions clearly illustrate just how much time and energy families devoted to the ataluren trials. As discussed throughout this dissertation, the trial imposed significant burdens on the patterns of everyday family life. Not least, for example, some parents stopped work or re-arranged their occupational lives in order to be able to adhere to the study protocol. Parents often described trying to manage their child's absence from school, taking time off from work, and co-ordinating child-care for siblings.

And yet surprisingly, though some parents complained in interviews about “all the hassle of the trial”—travelling, staying on top of dosing and carrying around pouches and/or boxes of study drug, for example—many were circumspect about the challenges this posed. When I commented to one mother who was leaving work each day to drive to her son's school to administer his lunchtime dose (a 20 minute trip each way, every school day for a year or longer), that this sounded like a lot, she replied: “it's just what we do. I don't really think about it. It's just the cost of being in the trial, of getting the drug.” In general, parents also expressed a strong desire to follow the study protocol in order to ensure their child had “the best chance” of benefitting,¹¹⁵ and many (though not all) narrated these activities in ways suggestive of reciprocal exchange. “It's just part of the bargain to be part of the trial,” one mother told me in a

¹¹⁵ In general, parents described going to considerable lengths to administer doses on time. In the Phase 2b clinical trial, patients reported taking 97% of assigned doses as prescribed (a figure provided by the trial sponsor based on self-report and the collection of empty dosing packets from study participants). This level of adherence is remarkable and is perhaps a unique feature of clinical trials for curative therapies, as opposed to medications of comparatively lesser consequence. A lack of alternative treatments, the fact that this is a pediatric population, and a general lack of discomforting side effects from the study drug were also likely factors. Of course, though I believe parents' descriptions of their adherence to the study protocol with regard to dosage were given in good faith, it is possible that some parents did not want to disclose missed-doses or non-adherence to the trial protocol.

hallway conversation at a patient conference, after sharing that she and her son were travelling six hours each way to reach her trial site every six weeks. “I wish it wasn’t the case. I wish that there was a site closer to us, but there isn’t, and if I want to have him in this trial, to get him on this drug then that’s how far I have to go. That’s what I have to do. We try to make the best of it, but yeah, it’s hard.”¹¹⁶

Such statements illustrate how as parents went through the trial, their narratives reflect a process of routinization and adaptation to the study routine in the face of considerable disruption. But they also show a re-orientation of timekeeping itself, as parents begin to emplot time itself according to the rhythms of the study. The trial becomes such a predominant part of everyday life that the passage of time becomes a matter of “getting to the next dose” or the next study visit, as the routines and practices of the trial come to usurp other ways of tracking chronicity. A key feature of the trial experience is thus deeper than simply “re-arranging one’s schedule,” but rather a re-ordering of how time itself is perceived and narrated (Frankenberg 1988). I suggest that this is but one piece of the unsettling sense of liminality that constitutes the trial experience, as parents give up control of their lives and set their watches to the schedule of the trial protocol.

5.3 Living on the Edge

Enrolling in a clinical trial involves a set of exchanges. One way to frame these theoretically is by turning to Mauss’ notion of the gift. In his now-classic work on the subject, Mauss (1990) argued that the act of gift-giving is never a value-neutral transfer of goods and/or labour, but rather creates a set of enduring social obligations on both parties in the exchange.¹¹⁷

¹¹⁶ Paraphrased from fieldnotes.

¹¹⁷ Mauss’ theory is not without its critics. See, for example, (Testart 1998; Laidlaw 2000).

In examining clinical trial participation, it is useful to keep Mauss' theory in mind, since at root clinical experimentation involves a set of gift exchanges. The trial subject offers his or her body—its tissues, in this case muscle—as an *in vivo* site for metabolizing a drug and evaluating its effects. These are obtained through functional measurements, analysis of excreta and fluids, and secondarily by compiling answers to questionnaires and the like. In return, a trial sponsor (usually a pharmaceutical or biotechnology company) agrees to provide a medication that may (if not immediately then later on, once it is approved) deliver a therapeutic benefit for the disease in question.¹¹⁸

However, this exchange is contingent and fragile. For example, research subjects are increasingly difficult to recruit (especially in economically developed countries) and have been noted to drop out of clinical research trials in surprising numbers (e.g. Probstfield and Frye 2011; Yancey, Ortega, and Kumanyika 2006; Northouse et al. 2006). From the perspective of drug developers, problems with recruitment and retention threaten the success of a trial by increasing costs and biasing outcome data.¹¹⁹ On the other hand, trial sponsors have been criticized for limiting access to trials by employing overly restrictive eligibility criteria and by removing “deviant subjects” or “outliers” who threaten the standardization of a trial without an adequate rationale (e.g. George 1996; Fuks et al. 1998).¹²⁰ Moreover, it should be noted that a trial subject

¹¹⁸ In the process, the gifts exchanged are commoditized (Sharp 2000).

¹¹⁹ Recruiting and retaining trial subjects from diverse cultural, ethnic and economic (i.e. underprivileged) backgrounds is a particular challenge due to linguistic, cultural and class barriers (e.g. Epstein 2009; Lovato et al. 1997; Ejiogu et al. 2011). Difficulty recruiting and retaining research participants in developed health systems is one factor driving the offshoring of much clinical trial research to countries in the global South (Petryna 2005; Rajan 2010b).

¹²⁰ Though a pre-specified list of laboratory values of concern and actions to take in the event of their occurrence in a patient is provided to site-investigators, the ultimate decision as to whether a trial participant is able to continue in the trial usually rests with the trial sponsor's medical monitor and/or its proxy representative.

has no guarantee that a sponsor will continue the trial and/or provide the drug as agreed at its outset, and there is little recourse available for trial subjects should a sponsor fail to do so.¹²¹

The continued existence of this gift exchange depends on the fulfillment of certain social obligations inherent in the roles of research subject and trial sponsor, some of which are readily apparent, and others less so.¹²² The sponsor's obligation, for example, is to provide a reasonable degree of protection to the trial subject by making available a drug whose safety has been characterized to the extent possible and which offers at least the possibility for benefit (whether direct or indirect). This benefit must also be sufficiently tempting to the research subject so that it outweighs the burdens of trial participation, and (in the case of placebo controlled trials) the possibility of taking placebo during the blinded portion of the trial. In return, the sponsor seeks standardization and a controlled setting in which to test hypotheses, with the objective of demonstrating safety and efficacy. Accordingly, the trial participant takes on an implicit obligation within the exchange, whether (s)he realizes it or not; namely, to remain within reference ranges that ensure the integrity of the trial—its standardization, the safety of its participants, and thus its likelihood of producing a statistically significant change in outcomes measured. Of course, this is the rationale cited by biopharmaceutical companies for employing

¹²¹ As I discuss in Chapter 7, this has been controversial—several pharmaceutical companies have been sued and excoriated for halting clinical trials that, in the eyes of the trial subjects, afforded access to a lifesaving therapy. The obligations of the trial sponsor to continue a trial and/or provide access to a medication on a compassionate basis are unclear (e.g. Carroll 2014; Houyez et al. 2012; Cuccia 2012; Siren Interactive Inc. 2014).

¹²² These obligations are formally encoded in both regulatory law and institutional policies pertaining to research oversight. Examples include the Canadian Tri-Council Policy Statement on the Ethical Conduct of Research Involving Humans (Interagency Advisory Panel on Research Ethics 2010), and in the United States, the Federal Policy for the Protection of Human Subjects, also referred to as “the Common Rule” (United States Office for Human Research Protections (OHRP) 1991).

eligibility criteria and screening procedures to identify a homogenous study population most likely to show improvement on the study drug.¹²³

Given the emphasis on standardization and safety in the clinical trial model, laboratory values that fall outside the normal ranges pre-specified in the trial protocol are the subject of intense scrutiny. Such measurements are firstly a safety risk for the patient, and they also potentially jeopardize the development path of the experimental treatment, along with the capital invested in it. If abnormal lab values are not explained and persist, the study protocol and the principals of good clinical practice (as mandated by regulatory agencies such as Health Canada, the European Medicines Agency and the FDA) require that the administration of the study drug be stopped and potentially that the subject be removed from the trial.¹²⁴ This is particularly true in cases where the laboratory value in question (such as those testing hepatic, adrenal or renal function) indicates a possible safety issue related to the drug.

A common theme raised by parents when they are discussing the uncertainty and liminality of the clinical trial experience revolves around the precariousness of their status as trial subjects. Parents' narratives reveal how participating in a trial is a tenuous existence that involves the constant threat of their child being excluded from the study because of a deviant laboratory value or safety concern. As one mother put it to me while sitting in the neurology clinic waiting room, there are "no guarantees in this process," and this reality looms large. The

¹²³ There is controversy around enrolment criteria in drug development for both rare and common diseases. Pharmaceutical companies often employ restrictive criteria and screening procedures in order to screen out likely non-responders, or to select a sub-group of patients more likely to show improvement. Many have argued that this practice "rigs" the clinical experiment in favour of success, and undermines the degree to which a study population is representative of the broader patient population likely to use a drug if it is approved (e.g. Rothwell 2005; Angell 2005).

¹²⁴ The Guideline of Good Clinical Practice is an international standard mandated by the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. See ICH Harmonised Tripartite Committee (1996). For a discussion of the implications and political economy of the ICH, see Petryna (2005).

following quotation from Gina Naicker, mother of 10 year-old Griffin, captures the suspense parents experience when an abnormal lab result (in this case an EKG) potentially imperils their child's enrolment in the trial (not to mention his health).

Gina: We got a phone call, and they asked us to get to [the hospital trial site] immediately. Um, [sigh] so of course you know, you're thinking the worst at this point.

CJC: Did they tell you why?

Gina: They said that there was something wrong with the heart, the pictures of the heart, or the EKG or something.

Worried, Gina excused herself from work, collected her son from school and started the two hour drive to her clinical trial site. She relates that her concern was not only for her son's health, but also for his status in the study.

Gina: So I'm driving down there and I'm thinking, "oh great, you know. We're gonna get kicked off this study, you know, something's going on." It was really scary. But [while driving to the hospital] I talked to one of my friends and she said, "look at it as a positive, you know what it is, you can deal with it." ... And you know, when she said that, it totally flipped my perspective. You know, [I thought] "yeah, you're right."

And so we got there and they did another EKG and an echo [echocardiogram]. And, what it ended up being is that he has a prolonged QT. But it's borderline. It's not something that's catastrophic at this point. He [the neurologist/site-investigator] gave us a list of medicine that we have to avoid. If he gets sick then we have to call Dr. Neurologist and... tell him what he's been diagnosed with, what the medication is, you know and we have to take the list with us whenever we go to the doctor and, and that kind of thing. So, it's a big deal. It's a big deal, when he's sick.

So Dr. Neurologist [Site-Investigator] sat me down. My sister came up with me, 'cause I couldn't tell her. I mean, I didn't know what that meant or anything and I was really scared. And she had a million questions 'cause she works in [a medical profession]. And, my dad, my uncle, my cousin, my grandmother and my grandfather, so both sides, had heart issues. And so my sister's like, really

worried. Everybody in the family has died of heart or stroke, and so she wanted to find out. And so we got there and Dr. Neurologist explained it to her and she was very satisfied that it was an electrical, it's not um, like the actual heart muscle. But we were worried. I was worried that he was gonna have something wrong, and I was worried we were gonna get booted out of the trial. That this would be it.¹²⁵

Obtaining test results that are of concern to the neurologist/site-investigator is treated as an urgent condition. Such results are referred to as safety signals, and must be investigated to determine whether they constitute an Adverse Event (AE) related to the study drug. If the event is serious (a Serious Adverse Event, or SAE), there is the potential that dosing would have to be interrupted or discontinued, and/or that the patient will be required to withdraw from the study. The laboratory value must first be confirmed by a repeat test, a procedure that can involve taking time off work to return to the hospital or laboratory. Loren and Kim Redford—parents to 8 year-old David—narrated a typical experience.

Loren: Kim took David one time to do blood and it's a Friday evening, and I get home from work and the phone message is blinking. So I'm getting dinner ready and I hit that. And it's Dr. Neurologist on there and he basically says "David's blood's unstable." So I call him back and [ask] "what are you talking about, his blood's unstable? [chuckle] You know, if he's a bad boy, is he gonna explode on me?" [laughter]. So he said the blood sample was really weird and we had to get him in for another blood test, you know, right away. So they schedule it for the following Monday since you know, hospitals don't work on Saturdays and Sundays for some reason. And I said I'll bring him down right now...

So we take him for a blood test and something had happened to the sample they had sent in, and it just wasn't right, you know? They have to repeat the blood test and make sure ... that David is alright, that there's nothing strange going on and that, you know, for the trial you need to have that blood sample delivered.

Kim: But they make you wait, and well, I mean, you're already being a mother, I mean you're a worry wart anyways. So you're just [worried that], "oh my god,

¹²⁵ According to Gina, a retrospective review of Griffin's medical records would reveal a previous EKG from several years prior, in which his borderline prolonged QT rhythm was present. This suggested that the abnormal EKG was not related to the study-drug, and he was able to stay in the trial.

they're going to take us off the trial oh, no.” You know there is always that in the background.

In this case, the abnormal result was caused by a degraded blood sample, and was later verified to be of no concern. In a multi-sited, geographically distributed trial of this size, the flow of tissue and fluid samples means that specimens are occasionally degraded and need to be re-obtained. In the process however, parents bear a great deal of concern and worry that their child's abnormal result will lead to his being withdrawn from the trial. Their status as research subjects is tenuous and depends on the child's body metabolizing the drug within a pre-specified range of safety values.

An even greater concern for parents was the possibility that a child would be unable to fulfill his part of the exchange by completing the outcome measures specified in the trial. For boys with Duchenne, the worst-case scenario would be for a research subject to come off his feet during or just prior to the trial, thus leaving him unable to complete the 6MWT. Before they lose the ability to walk completely, children with DMD fall frequently. Most Duchenne patients in Northern countries also take corticosteroids, which cause side effects of decreased bone density and osteoporosis.¹²⁶ This means that many children with Duchenne fall and break their bones.

For an unaffected child, breaking a limb is a painful but temporary and usually uncomplicated experience. But for a Duchenne patient, a broken leg is often an injury from which one never fully recovers, leading to catastrophic muscle loss and the permanent loss of walking ability. Carol Williamson's son Avery, for example, suffered two separate leg fractures around the time of the trial. In the first instance, Avery slipped on the garage floor and broke his

¹²⁶ Many patients with Duchenne already suffer from reduced bone density (osteopenia) and/or osteoporosis—a symptom of the disease that is exacerbated by the side effects of corticosteroids. A growing number of Duchenne patients are now being treated with drugs aimed at preventing bone loss, such as biphosphonates.

femur just prior to the 2a extension trial getting underway. His parents engaged in a grueling three months of rehabilitation to get him walking again and thus to keep him eligible for the extension-trial. Then, only a few weeks into the trial, Avery slipped off a step at a local community centre and broke his other leg. Carol describes her and her husband's reaction after this second fracture. In addition to being concerned for her son's wellbeing, she was also worried that Avery would be disqualified from the trial if he was unable to fulfill his part of the exchange.

You know, I feel like I already hover over him, and you can't be a cushion that falls on the ground before they do I guess, I don't know. And then I called my husband, and I said that "Avery just fell and said he broke his other leg." And [my husband] just sobbed. He sobbed like the night we found out what he had [i.e. when they learned of Avery's DMD diagnosis]. That's the only other time. Because we were both, we both thought, "now they won't let him take the PTC anymore. Now he'll never walk again." It was like the rug had been pulled out from under us. We thought, "why? Who is sabotaging this?" We both sat there just sobbing. And I'm sure these people [the paramedics and care providers at the hospital] are thinking "your child probably just broke his leg. What's the big deal?" Nobody knew, you know. It was horrible. It was the most horrible day I can even remember.

Such cases highlight the tenuous nature of the gift exchange of standardized bodies for experimental drugs within the rare disease clinical trial. When they decide to enroll in the trial, parents are advised during the informed consent process that administration of the drug may potentially be stopped, or that the trial may be interrupted due to safety concerns. However, many of the parents in this trial were still surprised at the precariousness of their status as research subjects, and of their implicit acceptance of their child's corporeal obligation to remain within the reference ranges specified in the trial protocol.

Clinicians, for their part, must mediate this gift exchange. In the process, they are faced with managing parents' desire to stay in the trial, while at the same time adhering to the study protocol. This position is ripe for ethical tension and can present challenges when communicating with patients, as described by one neurologist.

Yeah, we've had a lot of ... people [who] have reacted strongly to, what I view as fairly simple problems that have come up. In terms of an abnormal lab value, here or there. And how devastating that's been for people. Partly because, part of it is their fear, that they're gonna get axed from the trial.

... Yeah, and [the concern is that] then they wouldn't be on the extension trial. So, so I mean one mom whose boy's sodium came back a little bit high, so we had to bring him back in, and there's a sort of a 72 hour window [to get him re-tested, according to the study protocol], and, I mean she came in here bawling. Bawling, you know. She could barely keep it together, thinking that they were gonna be gone, you know, out of the trial. And that was the end of hope for her son.

And thankfully there haven't been many side effects or problems with the drug. We had a couple of abnormalities [i.e. test results], but again most people seem to be very, you know, very trusting. But they do, like as soon as they hear something's off, one of their first things [they ask] is, "will we have to stop the drug?"

And I must admit I fear a little bit, that people maybe aren't disclosing as much or as significant problems as they might otherwise, just to get through this randomized part of it.¹²⁷ 'Cause all of them of course know that there's an open label extension. ... And in effect that was obviously one of the—probably a big—motivator for them too. Cause there were some people who raised hesitations about placebo.

Here then, we see how parents' narratives of their experiences with abnormal test results during a clinical trial reveal the fragility of the gift exchange they enter into as trial subjects, and of their status as research participants. Parents described experiencing a considerable burden of stress

¹²⁷ In the Methods section (Chapter 2), I discuss the possibility—considered prior to the initiation of this study—that adverse events not reported to clinicians could be identified in interviews, and I developed a protocol to address this potential issue. No adverse events or side effects were identified in interviews that had not been discussed with the site-investigator.

and anxiety as they offered their child's bodies as sites for experimental investigation. Test results that were obtained frequently as part of the trial (in this case every three weeks) caused deep concern that an abnormal result could jeopardize not only a child's health, but also access to a potentially life-altering medication. This "nothing-for-certain" aspect of their experience as trial subjects contributes to a general sense of disruption, fragility, and uncertainty that characterize parents' experience in the clinical trial, a state I describe here as one of prolonged liminality.

5.4 A Blackout Period

Mother: Nothing, not a word.

Father: They won't tell you anything. They're not allowed to. We signed a contract. That no information would be [shared]. And that the doctors wouldn't even know. That Dr. Neurologist wouldn't know.

-Gina and Andrew Naicker, parents of 10 year-old Griffin

During the clinical trial, parents attend hospital much more frequently than they did previously for their child's regular clinical care. Paradoxically however, they receive almost no information about how their son is doing from research staff, whose primary concern when communicating with parents—in the words of one research co-ordinator—is to “avoid promoting placebo effects” among research participants.¹²⁸ Physicians and research personnel are quick to point out that they are not able to confirm or deny whether a particular change may be related to

¹²⁸ While routine test results are typically withheld, I discussed in the previous section how abnormal test results or those which indicate an unanticipated risk to a child's health are typically shared with parents, both to ensure informed consent and to obtain further samples for re-testing.

the study, because “reinforcing” a parent’s observation may induce or legitimize a placebo response. In a randomized trial, physicians and staff are typically also blinded as to which treatment a child has been assigned, and so may be genuinely uncertain whether any observations of functional improvement or decline are causally related to a child’s participation in the trial.

Test results and information about a child’s health status (for example, the results of timed-function tests, 6-minute walk distance, and blood tests) are also not disclosed to parents during study visits, but are instead recorded in the research subject’s study-chart, which is maintained and stored separately from his clinical record. Typically, parents are asked to wait in the clinic reception area and do not accompany their children when functional testing and assessments are performed. Thus for a period of nearly a year, parents are not given access to the measurements taken of their child’s strength during the study, nor to the results of his bloodwork and surgical muscle biopsies. Physicians and research staff typically do not comment on whether a child is improving or declining, and they are not supposed to speculate on whether a child is assigned to a placebo arm or “taking the real thing.” In essence then, parents enter an informational vacuum when they enroll their children as trial subjects, as described by Dawn McNeil, mother of 7 year-old Bradley.

Yeah, it’s hard, because even when we go for these tests, these studies, they don’t tell us much. Is it the drug? Well first of all we don’t even know if he’s taking the drug, he could be on a placebo so we don’t really know. ... So every time we go to the clinic, [we ask] “well how, you know, how’s he doing?” ... You know, and we don’t really get any answers... I don’t know like [we ask] “is it working or is it [that he seems stronger] just because he’s growing up and he’s learning these experiences on his own?” We don’t know. So it’s kind of hard because we don’t know... if it’s actually working, we don’t know, and we don’t really get any answers from Dr. Neurologist or anybody there.

Another mother, describing the demeanour of the research co-ordinator in the study, said,

Yeah, but she's more, like she's doing the 6 minute walk test and she's calibrating the step watch. And doing all those kind of things. Again, she's very, you know, poker faced. ... You know, she's happy to see him [the patient], but she doesn't she doesn't say too much. I guess 'cause she, was told she couldn't, so. But I'm sure that, you know afterwards, she'll have lots to say. You know, but she just can't do anything. Unless she doesn't want to violate the contract or whatever.

This practice deviates considerably from the routine (usually semi-annual) clinic visits that parents attend as part of regular clinical care.¹²⁹ At those visits, the neurologist usually performs various timed-function tests to determine whether a child's condition has worsened or improved. At organized neuromuscular clinics, such visits also involve a multidisciplinary assessment of the child's health, including visits to a physical therapist, who performs myometry and range-of-motion measurements; to a respirologist who may order lung-function tests; and to a cardiologist, who may order EKG or cardiac MRI testing in order to assess heart-function (and occasionally to other specialists, including orthopedists and geneticists). The results of these tests are routinely disclosed to parents, who are often keenly interested in them. A growing number of parents record their child's test results in a binder, journal or personal medical chart as part of their efforts to maintain continuity of care and organize services (Miller et al. 2009; Agarwal and Crooks 2008).¹³⁰ Parents are thus well-versed, even early on in the condition, in the practice of receiving test results and learning how their child "is doing" during their clinic visits.

¹²⁹ I accompanied several families to their regular clinical-care visits at two different multidisciplinary care clinics, one in Canada and one in the United States.

¹³⁰ Though this trial predated the current trend of biometric fitness and activity monitoring (by using smart phones, wearable devices and the like), it would be interesting to learn whether the recent revolution in smart phone data-tracking and wearable technology has led to an increase in the recording of health data by parents of children with chronic conditions. The use of this type of monitoring in clinical trial research is presently a topic of great interest and potential (e.g. Boulos et al. 2011).

This disruption in the flow of information to parents contributes to the extended sense of liminality that I argue characterizes the trial experience. Most parents found this position of “not knowing” to be disconcerting and anxiety-provoking. Like those carrying out the clinical trial, parents too are focused on the main empirical questions: they want to know whether the drug is “working” in their child’s body, and whether it is safe. The difference is that for parents, the stakes are arguably higher and more personal. They seek answers to these empirical questions not (or not only) as actors addressing a scientific problem, but in the hope of alleviating their son’s suffering and reclaiming his potential for a normal life. Many parents described an often overwhelming sense of anticipation, hope, and suspense as to whether this drug is, in fact, the cure they have been waiting for. They “want to know,” as described by Carol Williamson.

I think he is getting stronger every time they do it [i.e. every time we attend a study visit]. And I asked, “when will we find out about his biopsy?” And she [the neurologist] said, “a year and a half.”

And I said, “that’s not what I want to hear.” And she said, “Carol this is a study you know.” I said, “that’s not what I want to hear. [chuckle] I want to know.” I said, “you guys are gonna know, if he’s got dystrophin in his muscles now. You’re gonna know that. And how he’s doing, if he’s getting stronger. You’re gonna have that information. And, I’m *not* gonna know that. Unless I watch him and see that he’s doing better, which I think he is.” So, you know I’m gonna believe it if I see more and more improvement. But, to not know for sure, for another year and a half is, [pause] ... It hurts, you know. I, I wanna know. But that’s not gonna change what I do.

The structure of the clinical trial leaves parents on their own with such questions, without access to the results of functional assessments, to professional advice, or to counselling or psychological support. Most described being frustrated at the lack of information they received about their child’s health status during the trial. However, others were more accepting of the limited information provided by research staff, and it appears that feelings of frustration were not

universally experienced. These parents expressed an understanding of clinicians' reluctance or inability to provide information, and in some cases even an understanding of the different goals of research and treatment, as described by Loren and Kim Redford, parents of 8 year-old David.

CJC: How do you deal with not knowing? Is that difficult?

Loren: No.

Kim: No, because we went into this thinking, even if he has a placebo it doesn't matter, because he is given this opportunity. And if anything, even if he's getting the placebo, he's getting extra medical care, he's getting an extra set of eyes looking at him, he's getting some extra therapy. And he's going to help hopefully further this research, so later he might be able to get this [drug, when it is approved]. ... To us, either way it was a win-win. ...

Kim: Well the other thing there is, you know, we understand that the trial is not the same as going to clinic, and that we have to follow the protocol of the trial, you know, to participate in the trial we agreed that we'll follow these protocols.

In describing their relative comfort with the lack of information during the trial, the Redfords drew on their previous experience and trust in their child's neurologist, with whom they had a previous relationship.

Kim: So, you know, having dealt with Dr. Neurologist for years before this, you know, there's some faith there, there's trust that if there's something wrong, he's gonna know. If he sees something wrong in the trial, he's gonna let us know, you know, "this is showing up on David, we have a problem here." He going to let us know if there's something wrong on that end.

Loren: Yeah, I've met some doctors before and I wouldn't trust them to start a lawn mower [laughter] you know, and so there's that whole doctor-patient confidentiality but you build a trust up there, and talking with the doctor, if you interact with them. And you get to know them more on that professional level, you get some trust. [So] it might be different if we had never met Dr. Neurologist before; we might be asking questions that you know, we're not asking now because we have trust there.

As illustrated by the above quotation, trust in one's clinician appeared to play a role in

the extent to which parents described frustration with the lack of information provided during the trial. However, this finding is not generalizable to all parents, since many who described anxiety and discomfort with this aspect of the trial experience also went on to discuss their trust in their child's neurologist/site-investigator, with whom they often had a previous care relationship. Nevertheless, for all parents the trial appears to have disrupted the boundaries and informational continuity of their relationship with their child's physician (and with research staff), a process that posed greater or lesser degrees of anxiety and/or difficulty.

And yet, neurologists too, are in their own liminal space. They described struggling with navigating the constraints of their altered roles and relationships with their patients, now as investigators and trial-subjects respectively. It must be remembered that clinicians are also constructing the meaning and significance of an experimental drug in their own work, while simultaneously navigating a doctor-patient relationship that is contorted by the clinical trial, all in the course of a clinical encounter "on the fly." With most having already-established care relationships with their patient-subjects, and as physicians who witness the lethality and trauma of Duchenne on a daily basis, neurologists also discussed caring deeply about their patients' outcomes and survival. In practice, the lines between research and care are blurry since clinicians too, want the drug to work, even as they seek to approach the trial dispassionately. This leads to tension in their work between the competing ethical dimensions and affective relationships of clinical care, and their obligations to adhere to the trial protocol by managing patients' expectations and "staying objective."

For their part, clinicians were wary of inducing placebo or meaning response effects, recognizing that their guidance could have tremendous power in influencing or confirming parent's perceptions of efficacy (or the lack thereof). For example, in discussing the guarded

nature of their approach to parents during the trial, several neurologists expressed concern that their comments could affect how parents complete secondary questionnaires, the extent to which they monitor their child in a particular activity, how they communicate with their children about the study-drug, or their commitment to administering medication according to the protocol. All of the trial investigators and study coordinators who participated in this study had developed strategies to avoid sharing their personal impressions, study data, or information about other research subjects. In both casual conversation and formal interviews, some physicians also described it as emotionally taxing and time-consuming to enter the quagmire of parents' hopes and expectations for the drug during their clinical interactions. For instance, one neurologist commented that she did not believe it was her role to offer guidance to parents grappling with uncertainties of not knowing their child's treatment assignment or whether the drug "was working."

Sure. I don't ask [whether parents think their child is on placebo or ataluren]. In fact, so I purposely don't. [Instead] I ask, "how are you doing?" and you know, whether there's been changes either negative, or positive. But I have made it clear to people, like our job is not to try and guess. ... I kind of draw the line with them and say, "oh, it's exciting," to see him doing the things that they might have noticed [i.e. showing improvements in strength, function or ability], you know. Of course I make [reference to it and say] "certainly that would be exciting if you know what we're seeing is a result of the therapy." But then I try and bring them back to say, "you know, at this point we don't know." And that it might not be. Again I think we just need to be documenting what he's doing that's different and new. But you know not necessarily, trying to make that reference back to what he's on. My job is to document it. Make sure that it's clear that, you know he's noticing these changes. Make sure he's safe. And, we'll, you know, see what happens, with the results.

In her influential work with occupational rehabilitation therapists, Mattingly (1994) has argued that patients and clinicians engage in a process of "therapeutic emplotment," by co-

constructing a shared narrative of the patient's illness, what it means, and how it should be managed. The parameters of the clinical trial in essence truncate this process for both patient and physician alike, leaving both to construct the significance of the drug in isolation from each other even as they are in the same room, as described by this neurologist,

It's extremely hard. You're really trying to stay poker-faced, but in the back of your mind, sometimes you're going, "whoa, what if this is the real thing?" I had a patient recently [in a different clinical trial for another personalised treatment called exon skipping], and his mom brought him in, and as we were sitting in the exam room, she said, "I want to show you how he can dance." And I'm just standing there, I can't say "no," but I have no time to prepare my reaction. So she turns on the music and he does his breakdancing routine, and I'm standing there thinking, you know, "this is completely outside of the expected natural history of the disease, that he can do this," and I'm trying to keep my composure, to stay straight-faced. So it's hard sometimes, to balance your excitement for these patients and your obligation to manage their hopes, and your own personal investment in their success. (Paraphrased from fieldnotes).

Reporting on the same Phase 2b trial, Peay and colleagues (2014b) note that several investigators described developing an emotional investment in the outcome of the trial, developing their own hopes and allowing themselves to "get too optimistic." Though I have focused mainly on the experiences of families, deeper ethnographic exploration of clinicians' subjective experiences as clinical investigators is warranted.

Importantly, for parents the net result of this truncated clinical relationship with both clinicians and research personnel is that they are offered little or no support in reconciling the tremendous uncertainty of the trial and making sense of their observations of their child while on the study drug, a topic I elaborate in the next chapter. For families, the clinical trial can be likened to a "blackout period" in which the normal flow of clinical information essentially stops as the clinical relationship is constrained by the trial, a process that occurs ironically as families

attend clinic much more frequently than in the past. For the majority of parents, this provokes considerable anxiety and concern.

5.5 Conclusion

In this chapter I argued that the trial experience can be viewed as a form of extended liminality, drawing on Van Gennep's notion of social transition and the disruptive space we sometimes inhabit "betwixt and between" different social roles. The trial essentially upheaves day-to-day life, forcing parents to re-establish the normal social and cultural schemas through which they make sense of and narrate their child's illness. Parents are in a protracted period of transition from being "regular patients" to being both research subjects and newly minted parents of a "potentially cured (or curable) boy." The implications of either role are difficult to anticipate.

As the screening process gets underway, I discussed how parents are at first uncertain about their status: Are they patients, or are they trial subjects? Over a period of weeks or months, the children of these parents are accepted into the trial, and they approach it with both anticipation and trepidation. Though a transition to their new social role as research subjects is formally demarcated during informed consent sessions and their first study visit, parents are largely left on their own to sort out the contours and implications of this new status, including the emotional challenges, parenting burdens, uncertainty and social (i.e., gift exchange) obligations that come along with it. As the trial gets underway and wears on, parents must adjust to the disruption caused by its imposed practical routines, re-arranging their lives and learning to mark time according to the schedule of doses and study visits. Finally, I have discussed how the trial

experience creates considerable anxiety for parents as they learn just how tenuous and fragile their child's status as a trial subject truly is. Parents must also come to terms with blockages in the usual flow of clinical information, re-negotiate their relationship(s) with clinician(s) and hospital staff, and learn how to manage their hopes for the drug.

A parallel process occurs for the neurologists in the trial, who must balance and reconcile their now-hybrid professional role as clinicians who are personally invested in their patients' care and investigators with a professional obligation to maintain objectivity and protect the integrity of the trial.

For parents, these factors cause tremendous uncertainty and anxiety in everyday life. In their parental roles as guardians of their child's wellbeing, parents also want to know if they "made the right decision" by enrolling in the trial. A state of not knowing—both whether they will be able to continue in the trial and whether the drug will benefit their child—essentially prevents them from fulfilling their self-perceived roles as parental protectors of their child's happiness and security. "Did I do the right thing?" "Will he get better?" and "Will I be able to protect him?" are questions constantly in the back of parents' minds. Such uncertainty further reinforces the pervasive sense of liminality and disruption in everyday life that I have argued characterizes the clinical trial experience.

Most significantly, parents in this study confronted these upheavals in their lives with virtually no professional support and with very little acknowledgement by their care providers of their impact on family life, let alone guidance for how to deal with them.¹³¹ There is an inherent

¹³¹ I do not wish to imply that physicians and research staff were unaware or unresponsive to the impact of trial participation upon the lives of their patients, since as I discussed above the professionals I encountered were deeply appreciative of the burdens of trial participation and went out of their way to accommodate parents where possible. Still, the conditions of the trial appeared to prevent nuanced and deeper discussion and the offering of professional advice about how parents should navigate these aspects of their experience.

tension between the ostensibly controlled experimental conditions of the trial—that is the obligation of research staff to “maintain objectivity” when carrying out the study—and the messy, subjective, and personal ways in which the trial alters the lives of its participants. This tension appears to foreclose opportunities for meaningful dialogue with clinicians and research staff about how parents should negotiate the impacts, anxieties and disruptions the trial imposes on everyday life, as well as how they should interpret their observations of the drug’s potential efficacy (a topic I turn to in the next chapter). My research suggests a need for closer engagement with parents’ everyday experiences within the trial, and for greater discussion of how professional guidance and support offered to parents might be improved. A more nuanced understanding of parents’ experiences could advance the objective of enhancing the trial experience and alleviating its burden for families. Such work might also yield insight into aspects of research participants’ experience in the trial that may have a bearing on the data gathered and thus the ultimate conclusions of a clinical study. Often however, these issues are bracketed and removed from the clinical trial as “scientific experiment,” and are not subjected to empirical research.

Chapter 6: The Clinical Trial Experience II: Narratives of Efficacy

In the previous chapter, I discussed the beginning of the trial and the ways that parents adjust to its rhythms, routines, and liminality. As a child starts to take the study-drug and engage in the study-related procedures, parents are keenly interested in the same key question as the trial's investigators and sponsor: they want to know whether the medication their son is taking is having any effect on his condition. As her son began his course of blinded study drug, one mother asked me rhetorically: "What's going to happen? Will it work? You never stop thinking about it, watching, waiting for an answer." For parents, these questions are much more than scientific ones, as the dispassionate approach of the clinical experiment collides with the inescapable reality that the answers to them are likely to determine their sons' futures.

In this chapter, I examine the *processes* and *experiences* through which parents addressed the question of the study drug's efficacy during the trial. Many (but not all) of the parents I interviewed felt the drug had led to improvements in their son's physical and/or cognitive capabilities, despite in most cases not knowing whether their son was taking a placebo or active drug.¹³²

I argue here that parents tell "Narratives of Efficacy" that weave their experience in the trial, their anguish and hopes for a new treatment, and their observations of their son's functioning in the course of day-to-day life. In constructing and relaying these narratives, parents use the information they have available to them: their own perceptions, their tacit

¹³² Recall that this study included parents from both the open-label Phase 2a extension trial, and the randomized, blinded, placebo-controlled Phase 2b trial of ataluren. The latter trial had three arms: placebo, "low-dose," and "high-dose."

knowledge of their child's body and personality, and the observations communicated to them by significant others, to assess the impact of a drug (if any) on their child and on their own lives. As I discussed in the preceding chapter, the experimental conditions of the trial mean that parents often assemble their impressions and narratives of efficacy with limited access to clinical information or support from care providers and research personnel. However, their narratives also show them bringing their longitudinal and tacit knowledge of their own child's personality, strengths, behaviours, and abilities to the task, as they invoke their own understanding of their child honed as caregivers, mothers, and fathers. This knowledge has both tremendous value that is often not fully capitalized in drug development—especially in the setting of rare diseases, where parents often act as full-time caregivers to children with functional challenges—and its own limitations.

As I described above, parents' observations are often deemed by investigators, regulatory authorities, and other experts to be of limited significance and value. Indeed, these personnel often dismiss parents' observations as the unreliable, biased, and "subjective" perceptions of overly hopeful moms and dads "desperate" for a new treatment. The stories parents offer are usually assessed in terms of whether they are "correct," true or false, believable or not, and they are inevitably compared to the "more reliable" and ostensibly objective outcome measures and clinical data of the controlled trial. Here, I wish instead to examine parents' descriptions on their own terms, to ask what they can tell us about the clinical trial experience and "experiential outcomes" of a drug in everyday life. In examining parents' narratives, I emphasize some of the ways that qualitative exploration of parents' stories of efficacy can provide insight into the possible therapeutic effects of an experimental medicine. Some of these effects may not be captured by the outcome measures of the clinical trial, may not be anticipatable and/or may occur

“downstream” or even extra-corporeally (in the lives of caregivers and family members other than the research subject taking the drug). I suggest that closer attention to parents’ stories of efficacy can supplement (but not replace) quantitative outcome measures, thereby leading to a more robust understanding of the impact of an investigational drug on the patients for whom it is intended, and by extension a fuller assessment of the potential benefits and risks. And yet parents’ narratives of efficacy raise their own questions, as they are entwined with hopes and expectations for a treatment benefit, with parents’ efforts to cope with the burden of their situation, and with the social milieux in which they travel.

I address these themes in parents’ narratives of efficacy by examining three case studies before turning to a comparative discussion of their content and implications.

6.1 The Case of Carol Williamson

In Chapter 3, I drew on the case of Carol Williamson to illustrate the background illness experience of families who have a child with Duchenne. Carol’s son Avery, age 12, was one of the first patients to take ataluren in the initial Phase 2 28-day study. Later, Carol enrolled Avery in the open-label Phase 2a extension trial after enduring a lengthy wait for the drug, during which he broke his leg. I interviewed Carol just as Avery was recovering from his fourth surgical muscle biopsy in his career as a clinical trial subject. He had been taking ataluren (open-label) for nearly 6 months, during which time Carol and her husband Peter had observed improvements in his strength and ability. She described their efforts to make sense of what they were observing.

I remember that one day we were at my mom’s condo, and I saw him run across the little driveway. And like, man! It was *fast*. And I didn’t say anything to my

husband. I was afraid, 'cause you think, “did I really see that? Did I? Or am I just hoping that something, you know, is helping him?” And then a couple of days later my husband said, something about Avery, [he said] “I just saw Avery moving in the pool much better than he did before.” And I said, “oh! I’ve been wantin’ to tell you what I saw!” But you know, we both felt like we saw something. But we were afraid to tell each other ‘cause we thought, “is it just hoping?”

When Avery walks, his gait is tenuous, wobbly, and barely-balanced, as he swings his arms wildly and thrusts out his stomach to counterbalance his scoliosis. His unsteadiness and posture are potent and constant reminders that it will not be long before he is unable to walk on his own at all. He can no longer climb stairs or keep up with his friends, and must be dismissed early from class so that he is not trampled in the school hallway. Avery has recently started descending the stairs on his posterior, and his independence is rapidly declining. He already uses a wheelchair part-time, “when he’s tired,” and though he is back walking now, in the past two years he has relied on his wheelchair for extended periods as he recovered from his leg fractures.¹³³ In the absence of treatment, soon he will come off his feet full-time.

Carol’s assessment is therefore tentative—she realizes she has a strong desire to notice changes, and her son’s neurologist warned her about placebo effects when the trial began. She discusses her hope that Avery will not turn out “that way,” using this phrase repeatedly to avoid verbalizing his impending loss of ambulation and his presently fated premature death. Carol speaks slowly, and her voice belies a hopeful despair.

I can never, not, and I don’t know, I don’t, [sigh]. I know this sounds like a typical mother talking, but I don’t ... want to see him that way. I honestly believe in my heart, that he’s not gonna be that way. That he’s gonna beat the odds, that he’s gonna last a long time. And, I, I, [pause], I don’t know, I’ve,

¹³³ This in itself is remarkable, since many children with DMD who experience leg fractures never regain the ability to walk.

always felt that way. And I am an optimist, and my husband's a pessimist [chuckle]. But, I honestly believe [the changes I've seen], it was something, [that it's] not just a mother not wanting her child to be that way. But there, I really believe that he's not gonna be. That way. I can't ever see him that way. So, you know, I don't know.

Carol's words highlight the central tension for parents in the trial. She is struggling to make sense of what she is seeing, but she's not sure if she can trust her own eyes. Her hopeful optimism is inspiring, adaptive, and likely a significant factor in her rather successful adjustment to her role as a parent of a child with a fatal disease. However, in the setting of the clinical trial, this approach to life takes on a different dimension. For Carol, the trial has surfaced the difficult question of "how much is too much" hope, and whether her hopes and desires for the treatment are influencing how she perceives her own son.

You don't want to get your hopes up too high, too much ... You know, um, 'cause everybody asks "did you see something? Did you, did you notice anything?" And we'd say, "well, we did but, we don't know. *We don't know what that means.*" [emphasis added]

Carol and her husband Peter wrestled with how to interpret subtle signs of change in Avery. Could they believe their own eyes, or was this just "wishful thinking" influencing their perceptions? Were these changes, if real, actually caused by the drug, or were they attributable to something else? Still, Carol insists she has noticed concrete changes in Avery's strength and function. A key point is that in describing these changes, she invokes her everyday practical knowledge as his mother.

At first, the signs were subtle. Avery began to wrestle "more strongly" with his father.

My husband wrestles with him all the time. Tickles him and they flick each other all the time, you know...guy play. And, I'll say you know, I even wrestle with him too, and with just, his hand strength. He's stronger! I truly know that he's

stronger. Now whether God just gave him that strength, or the PTC? I don't know, but I believe PTC is giving him strength ...I, I honestly do.

Their observations of Avery's strength in everyday play were supplemented by "little things that we noticed." Carol points to the small waterslide at the edge of their modest pool in the backyard (a pool they spent thousands to build for Avery's physical therapy).

You see our slide out there? Now at the end of last year he [was able to climb up the steps of the slide], and now this year, he couldn't go up [because he had lost strength] ... Which made me cry, of course. But now [that he is taking ataluren], he could put his hands up there [on the bottom of the slide]. He swims like a fish. He'll put his hands up there. And he can pull himself up..., not out of the pool, but he puts them [his hands] on the [bottom of the] slide, and like, pulls himself up a little bit. And we're like, "he could never do that." ...

He could never, even the least bit pull himself up. ... So, honestly we really think that it is [due to] improving his muscle strength. At least in his arms and, I do think he's also walking better.

I ask Carol whether she has noticed any other changes in Avery, and she answers,

Yes, he can carry things that he wouldn't normally try to pick up and carry. Like today he came from his room, and he's spoiled. In the summer time I let him sit in his bed and eat breakfast. And watch TV. And he carried a couple of plates and a couple of cups, with no other hand to grab, if he had to grab a wall or anything [i.e. to catch himself if he were to fall]. And he walked them into the kitchen. And he said, "Mom here's my dishes," he said. ... He would have never done that before [i.e. walked without having a hand to support himself if he fell].

I ask for more examples, and she responds,

Um, now he says, "no, no let me try. Without you." Where he wouldn't have done that before. Like Peter [father] will say, "here hold my hand and we'll do this." [And Avery responds] "No, no, I wanna do it myself." And in the house, he has started to walk around without his walker, and we would say, "okay, you know hold on to the wall," and he'd say "no, I want to do without the wall." [Or I'll say] "Well let me stand right next to you in case you want to grab me," [and he'll reply] "Okay, but I'm not gonna need you. I'm gonna do it myself." He's

become more determined. I think he feels more confident. And I don't know if it's because he knows he's takin' the drug, or because he feels stronger. I don't know.

I ask Carol whether Avery's quality of life has changed as a result of the changes in his function that she has observed, and she replies,

Yeah, I think, partly because, he feels like he can do more. Yeah. I mean, he feels better about himself. A little more independent. I mean I think that anything that he can do on his own has to make him feel better. More empowered. He's always had a little anger issue. ... He would just get so frustrated, he'd just bang something, or scream. Or cry. And he doesn't do that as much anymore, and I think having control over your body that you didn't have before, has got to make you feel better. Has got to. You know, the more independent you are, the less frustration. [He says] "I can do it myself now instead of waiting for somebody to help me," you know. That's gotta improve his quality of life.

When I ask Carol whether *her family's* quality of life (as opposed to Avery's) has changed at all as a result of the improvements she describes, she responds,

You mean since he's been on the PTC? Well I think so. Oh yeah, I mean, we all ... [as a family], you know we're able to do even more things, I think, [now] that he can do things by himself more. I don't have to constantly pick him up and put him in his wheelchair as often. Now he can stay up for longer. Now in the morning just, in this last week, he started to get up, and get himself dressed. Without my help. That's big, *huge*. Because we were helping him get dressed even in the mornings. ... Um, you know it takes, some of the, I'm not gonna say, I don't mean burden, but some of the rest of us. So I don't have to say [to my daughter], "go get this for Avery," while I'm in the middle of doing something. "Go get his walker and take it to him." Or, "go get his dishes from his room and, bring 'em, and wash 'em out, and, you know." I try not to do that to her too much.

And getting ready, him getting himself out of bed in the morning. Because he feels like he can stand better now, more um, stable. He can move better and get his socks on and he can [put on] his shorts and his shirt. And get into his shoes. And, you know he'll walk right out and I'll say, "I didn't even know you were awake! Why didn't you tell me?" And he'll go, you know he's real proud of himself. I'll say, "you did it all yourself." He goes, "I even brushed my teeth and went to the bathroom too." You know. Yeah, so I think his attitude has really

improved. And I think it has helped us to not have to do so much for him. Yeah.

Later, Carol tells me,

Like he'll come in now, and try to make his own lunch. Stand at the counter and make his own lunch, where, you know, if he was in his wheelchair, he couldn't reach everything that he needed. Well now he can reach everything he needs and he'll make what he wants. Which is great. You know he's not always asking somebody to fix something.

Finally, Carol describes how Avery's increased mobility has made it easier for her physically, because she has to carry him less often.

In the pool, or at a curb, or you know if we go to someone's house and he has to go up a step. Now, if there is a lot of steps we don't even try it. I put him on my back. I might not look like it, but I can carry 88 pounds on my back. [chuckle] and I can pick him up and, put him in the car, you know and ... [I do that] much less. He's doing so much more on his own now. ... And I think, hearing Dr. Neurologist say that [he's doing really well], just reinforced it for me. And makes me think that the PTC has something to do with it. I really do. I think he's stronger. I honestly do. And I think that it's [the PTC] helped his attitude, and attitude is a big thing. You know, if you think you can do it, you're more apt to try and, try it over and over again. So I think that's helped him a lot.

I ask Carol about her expectations for the future, and for the drug. "Everybody wants a cure. I'm not expecting a cure," she had said earlier, "but I hope that he can have a more normal experience at school."

Maybe he can just go [to school] with his walker, to walk from class to class. He is allowed to go to lunch a few minutes earlier so that he's not in a big rush. And he, you know, he gets to school and my husband walks him to his room and gets his stuff out, helps him get his things out of his locker. I don't want him in that wheelchair. So [when I suggested that to him], I saw him smile. You know, I said, "you don't want to have your wheelchair at school?" And he said "no!" ... [Maybe] he won't feel so, so different. Kids won't notice him as much, 'cause he won't be sitting in the wheelchair all the time. He'll be sitting on a regular chair

and being more like them.

Like many of the parents I spoke with, Carol's narrative of efficacy is told in the context of her desire, not necessarily for "a cure," but rather for a modicum of normalcy—for an opportunity for her son to be "like the other kids." It is this wish that animates her hopes for a therapeutic intervention and her motives for participating in clinical research.

6.2 The Case of Maria Pauling

Parents' narratives of efficacy are dynamic and changing; they develop in relation to expectations for treatment and cure, and to parents' current circumstances coping with the anguish, trauma, and physical care burden imposed by a disease. Narratives of efficacy also take surprising and unanticipated directions, unsettling easy assumptions about the trial experience.

These points are illustrated by the case of Maria Pauling. Maria lives in rural Central Canada and is the single-mother to Larson, age 9. In Chapter 4, I used her case to illustrate the archetypal "Semi-Connected Parent." Maria has a grade-school education, but she demonstrated a relatively sophisticated self-taught understanding of DMD, and had successfully advocated for both a genetic diagnosis and a spot in the Phase 2b placebo-controlled trial.

At the time of our interview, Maria had been pulling Larson out of school for three to four days every six weeks to drive him a distance of 1,000 kilometres round-trip, in order to attend study visits at Mountainside Children's Hospital, the regional tertiary-care centre. In between these visits, she removed him from class for blood draws every three weeks at a laboratory in a nearby city, a two-hour round trip involving a needle and usually tears. She also completed various other activities for the study, including tracking Larson's activity and falls,

administering doses, and completing Quality-of-Life questionnaires. All-told, she had devoted “hundreds of hours” to her new role as the mother of a research subject. Larson had already undergone one surgical muscle biopsy prior to starting the drug, and was scheduled for another in three months.¹³⁴

All of this was worth it, she said, because at the outset of the trial she had high expectations for the drug. I asked her what the drug meant to her and she responded, like Carol Williamson above, with a plea for a sense of normalcy.

Yes, I have lot of hope attached to it. ...That he won't have to spend his life in a wheelchair. That he will be able to continue to swim. He loves swimming so much maybe he'll go to the special Olympics if this drug works for him, I don't know but its, that's hope for us. Maybe one day he'll be able to ride a bike, um, maybe one day he'll be able go out and play soccer with the other boys, you know. That he will, that he'll never have to be on oxygen. That he'll never have to be hand fed. That he'll never have to be put up with the indignities of having someone else, you know, wipe his bum for him, you know, to me people shouldn't have to live that way.

That's sad. If he died at twenty-five years of age then that's what's supposed to be. If I die tomorrow that's what's supposed to be right? But at least I haven't had to have somebody hand feed me or wipe my backside or push me around in a wheelchair. You know, I can come and go as I please in my life, you know. And that's hope for me, that he'll have all those things.

When the trial began, Maria was initially very excited.

I bet you I spent four years [and] I probably had enough tears to build my own ocean, my own ocean sitting at night reading the internet and stuff. What people have gone through in the past and, you know, what the research says. ...But, you know, I'm also realistic, I know what the end result could very well be, I know. I just feel like this is like this is a lifesaver stick, you know, handed to you. You know its potential, but it's not guaranteed to save your life. ...

So, I'm excited, yes. Plus, you know, you go on the web, and parents are saying things like well, we took “Johnny” to the park [with] all these kids and he was

¹³⁴ I discuss the study-related procedures further in Chapters 1 and 5.

managing to keep up with them, and all of a sudden he disappeared and somebody said, “well, he’s up there sitting on a log at the top of the hill.” Well how did [he] get up there? So the medicine is working for these people right? And another lady whose child couldn’t get himself into the car, from what I read ... he was this close to being in a wheelchair permanently. [He] went in the twenty-eight day study and went from that to being able to get in the car himself. So, yeah, significant improvements in one to three weeks.

As Maria and Larson attended their first study visits, they began making the drives to Mountainside Children’s Hospital, stopping along the way and trying to make “little vacations” out of their time together. Larson underwent his first muscle biopsy—a procedure that induced anxiety and panic in him, and she tells me about accompanying him into the operating room so that he did not have a panic attack. They received their packages of study drug, a period she describes with excitement. In the initial weeks of the trial, she describes her optimism.

When he first started on it, you know, it’s a double blind placebo-controlled [study]. ... We were excited, because in the first month we’d seen some changes. Over the summer, Larson’s birthday is in March so I had bought him a little quad from Wal-Mart, a little battery operated quad. He just was in seventh heaven, and I was too because it entertained him, he loved it. So he rode it and rode it all summer, like he just rode it so much.

September rolls around and it’s time to go back to school. I have the same vehicle and he was having trouble getting in it, and we’re like “I think that riding that quad too much made him go, helped him go downhill.” That and a poor diet because we camped the whole entire summer and we just ate garbage food really. So, that was my thing, and then he started on the PTC at the end of October. He was struggling to stand up, he was having difficulties getting in my car. He was using both hands and pulling really hard struggling to stand up once he crawled into the car.

But he started on the PTC and probably within six weeks I noticed he was getting up, and he’s still struggling but only using one arm to pull up, and struggling not quite as hard. He actually dropped a couple of toy cars. ... and twice he bent over, he just bent over and picked them up without using his hands to push himself up. And he hadn’t done that in a loooong time.

So I'm thinking "oh well, yeah, we got the right stuff, we got the right stuff, it's working." He walked up to the school and he's never done this before. He walked up to the school with his right arm—he's got right side weakness—grabbed the door, opened it wide with one arm and walked inside. He's never done that before. The big heavy school door. He struggled to push it open from the inside with both hands. So I went "yeah, we got the real stuff, it's working, it's working," right? I was all excited.

Maria describes her experience as "an emotional rollercoaster."

So when it first, when I first thought it was working, yeah, I was excited. Even at Larson's school, they said "well, yeah, we're seeing some changes and, yeah, we're excited too." [*In other conversations with me, Maria related that Larson's school teacher had observed that his cognitive delays and attentional issues had improved, that he was "less frustrated" at school, and that Larson seemed to have more energy.*]

For around two months, Maria tells me that things were going swimmingly. She felt invigorated to be part of the trial, that she had found hope and began pondering potential horizons for Larson. She let herself think about the possibilities, to "even wonder about the future a little," instead of actively repressing it. However, Larson's improvement—and Maria's excitement—were not to last. He "seemed to taper off," she says.

And, then nothing. Those improvements or those things that seemed to be improvements were not consistent, [they] didn't last.

So at that point I said to Dr. Neurologist, I said "well, we're right at that six month mark and we don't see consistent improvement. Those improvements that I've seen, like he's pushing himself up more with his hands [now] [*an indicator of reduced muscle strength*]. He does still open the door at the school. He was able to open a bottle of water twice, and he's never done that before in his life. But he can't do it anymore. Those are about the only changes. He's still good with the car like he was.

So I don't know if it's possible for him maybe to go down a little bit, and then if you catch it before he goes too far maybe you could level it off, I don't know. ...

We go in August and then in September he'll get the real medicine. ... So we're kind of at this point just living for that day.

Maria is describing a shift in her expectations for the trial and for the drug, and she struggles to maintain her composure. Her hopes for a "breakthrough" have not materialized and part of her, she admits, was expecting to see dramatic improvement for Larson. At the time of our interview, her perspective on the trial is in flux. And yet she is confident that she observed changes in Larson near the beginning of the trial. "I don't think we were seeing what we wanted to see," she says, echoing her uncertainty about her own perceptions described by Carol Williamson, above. "You know, sometimes you think you see things because you want to see them."

"How do you explain your observations then?" I ask Maria. She responds,

What do I think the explanation is? I honestly think it was just a little bit of a developmental improvement for him because he's young, you know, he's nine. And you know, he's just a little tiny guy. Like when you look at him you think he's like six, maybe seven. Most people think he's only six or seven.

I think, you know, it was a coincidence. Like I think he just had a really good day or two or and, you know, and [some] improvements, developmental improvements. Because I've seen it prior, you know, when he was younger. ...

So I don't know what happened there, but now I don't think he's on the real stuff because he's actually gone downhill. ...

Everything I've read on all this stuff, nothing has ever come up that it didn't work in some of the boys. [I've] never ever heard that, other than it took a little longer for some of them to work, I guess. So that's kind of where we're at. Well the last I heard was one to three weeks, you should see significant improvement, significant. And it might take the odd child as much as six months.

Maria has started to consider the possibility that the improvements she observed in Larson were fleeting and perhaps unrelated to the study drug. This has been a devastating blow for her

emotionally, she tells me. As she speaks, I am reminded of how difficult it is to steer large ships. She is trying, in essence, to pull back on her hopes and expectations—to place them in reverse-throttle, regain steerage, and to re-orient her perspective. “I try not to think about it,” she says.

It was disappointing for me. And for six weeks, you know it was really hard to take anything seriously ... then it’s like, I pulled up my socks and said “you know, you agreed to do this medicine or not.” It doesn’t last forever, it’s going to end in September, and he’ll get the real medicine then, so you know, follow it through. And that helped me, but it’s been so hard.

But what she says next surprises me. “Now I’m really hoping, I’m praying actually, that it’s the *placebo* he’s taking,” she says, “and *not* the real stuff.” Somewhat paradoxically then, Maria’s wish is that her son is *not* taking the active drug, since this leaves open the possibility that, given later in the extension trial, the “real thing” might still be effective. Things go “up and down” she says, but she has not given up hope for the possibility that the drug will work in her son. She’s had a taste of what could be.

Some days are really easy, some days are really hard. And there might be no real reason, or no apparent reason for it, you know. ... But you know it’s something, it’s more than we had before. And I think that all of us, every single one of the families just would like to see that faint glimmer at the end of the tunnel, right? And when *you do*, you know, it just makes life a little, maybe a little easier. because there’s some hope. It comes back to the hope. If you don’t have any hope,

she says, as her voice trails off with a quiet reluctance to speak about what that would be like.

Later, I left her home wondering about the relationship between perception, hope, and expectation.

6.3 The Case of Aaron Murphy

The scientific aim of any drug development project is to characterize the molecular effects of a drug; that is to say, to learn more about how a certain biochemistry alters cellular processes, organic systems, and thus the bodily experience and lives of the patients for whom the drug is intended. At the molecular level, drugs are modelled, tested, and hypothesized to work in a particular way. But many of the ways that a new treatment affects patients' lives are impossible to anticipate and/or are not captured by the outcome measures in a clinical trial. These "downstream impacts" of a therapeutic intervention on the lifeway of an individual *person* can be highly idiosyncratic, as they are often unique to the particular life and body in which they occur.

This point is illustrated by the case of Aaron Murphy. When I interviewed him, Aaron was a 17 year-old grade 12 student living with his parents in a typical suburban home in the Southwestern United States. I had the opportunity to meet with Aaron when his parents Jonathan and Sarah invited me for an extended visit in their home. I met with Aaron and his family at the suggestion of a neurologist at one of my study sites. Aaron's parents had tried to enroll him in the ataluren Phase 2b trial, but he was deemed ineligible because he was no longer ambulatory. Subsequently, Aaron's parents pursued a different but related treatment on their own called gentamicin. I include his case here because, though the treatment and the manner in which they accessed it is different, the Murphys' experience with gentamicin is relevant to our present discussion. Colloquially called "gent," the drug is an aminoglycoside antibiotic discovered in 1963 and commonly used today to treat various bacterial infections. More recently however, gentamicin has been observed to have a curious molecular property in addition to its antimicrobial one: when present in the cell, it induces readthrough of premature termination

codons in a manner similar to ataluren. This treatment effect generated intense interest in gentamicin as a potential therapy not only for DMD patients, but also for those with other diseases caused by nonsense/premature-stop mutations, including cystic fibrosis and hemophilia (e.g. Zingman et al. 2007). In the case of DMD, studies in the early 2000s indicated that for some patients, administering gentamicin caused increases in dystrophin expression and decreases in creatine kinase (CK) levels (a marker of muscle deterioration), leading to optimism that the drug would be the first approved therapy for the disease (Malik et al. 2010). More recently, these hopes have been tempered by the drug's side effects: it causes hearing loss and kidney damage when administered for long periods or in high doses (Wagner et al. 2001). However, a small number of patients have taken or are currently taking the treatment, either as participants in organized clinical trials or as part of individual patient protocols (called an "n of 1" studies). Gentamicin's readthrough mechanism—a characteristic noted in other aminoglycosides and drugs—inspired the biochemical search for a molecule with similar properties but less toxicity, which led to ataluren's discovery.

For Aaron's parents Jonathan and Sarah, gentamicin was worth trying as their son's condition deteriorated in his late teens. I quote from my fieldnotes recorded after our first meeting:

Aaron is tall—almost "normal" height for a boy his age, even as he sits in a large power chair. [*This is remarkable because most boys/men with DMD are of shorter stature.*] His brown hair is cut short and his face and body are slimmer than many boys his age with DMD. He must be in control of his diet, which is a constant struggle for Duchenne patients and their parents. Aaron sits in a large power wheelchair with a clear plastic tray across his lap, for carrying items or holding books. When Aaron came off his feet, his parents extensively (and expensively) renovated their home, installing an elevator and lift system and widening all of the doorways. Now, he can get around through the house except for one door, which he has to take the tray off for (the door between the

kitchen/eating area and the formal dining room). Aaron sleeps each night with assisted ventilation (an oxygen mask) to help his breathing. He needs assistance with pretty much everything. He is “not quite full-time care,” his mother remarks to me, “but he’s getting close.” It takes an hour to get ready in the morning, she says, and an hour to get him into bed each night. His parents are finding it harder to lift him. In addition to Aaron’s physical limitations, Duchenne has also presented some psychological challenges for him too. He has problems controlling his emotions, he told me later, when we were speaking alone. His father remarked that he experiences “roid rage” from the steroids he is on, and is prone to frustration and anger. He is often depressed and socially isolated. All of these things are bound up together.

As we talk it is apparent that Aaron is an incredibly articulate, smart, and passionate person. At 17, he is starting to think about university and has just applied to attend college in another city, where he would be able to live independently from his parents for the first time with the help of a personal care aide and the college’s disability services office. He just returned from a youth leadership conference where he participated in several panels and was nominated as a leader—all accomplishments of which he is proud, and which he attributes to his regained physical strength. In the interview, he talks about how he was able to participate in a skit during the evening, which he feels he otherwise wouldn’t have been able to do, were it not for the gentamicin. As we talk, it is clear to me that Aaron has incredible ambition. He speaks of his desire to become a political activist to “ensure that minorities are treated with respect in this world.” He feels strongly about issues around disability and accessibility. His parents are encouraging him to think about a career in politics or law, but Aaron’s ambitions lay elsewhere. He wants to train first in business, and also pre-med.

His real ambition is to become the first neuro-psychiatrist with Duchenne muscular dystrophy—a plan that he expects will take him until age 31 to complete. He wants to be able to provide guidance on the psychological aspects of neuromuscular disease to parents and kids with the disease, and he aspires to work in pediatrics. Neuropsychiatry is a highly specialised field, he tells me. There are only 150 neuropsychiatrists who are board certified—triple board certified—in the US. “And none of them,” he says, “has Duchenne.”

Lately, Aaron has been thinking a lot about his future, but these dreams and ambitions are unusual for him. He struggles with his condition, he tells me, and has coped with long periods of depression and social isolation. Aaron has had difficulty making friends at school, and has been teased by some of his peers.

I've never really experienced real friends, because most of my so-called friends, weren't my friends. They would talk behind my back and they would make fun of me. And they would pretend to be my friends, but they weren't really.

He laments a lack of support for these peer-group and emotional issues in his school environment. "Many times in my life," he says quietly, "I have not been in a good place." The depressions he has experienced were "more, related to the fact that I'm gonna get worse, I was always [thinking] 'I'm gonna just gonna get worse.' I was always gonna have to rely on others, and I wouldn't be able to, live my life, as myself."

However, things have changed recently for both Aaron and his family, as a result of using gentamicin. Indeed, our interview occurred at a "particular moment" in his life. Aaron and his parents feel strongly that he has improved considerably since starting the gentamicin nine months earlier. Aaron described feeling "stronger" and having more energy and stamina. His parents are both experienced in managing their son's condition and have noticed his arm strength has improved, his contractures in his hands, fingers and ankles have lessened, and he is better able to adjust and reposition himself in his chair without assistance, meaning he calls less often on his parents to move and reposition his legs (to alleviate pressure sores). Aaron can also stay in his chair longer, now for up to 16 hours without having to move to bed. His mother tells me that his bladder and bowel function improved almost immediately after taking the drug. This is a big issue, she says, because children with DMD often experience bladder and bowel-control issues at school due to muscle weakness, resulting in embarrassing "accidents" (these incidents can have far-reaching social consequences in a high school environment, where peers may be less than understanding). Aaron's parents are especially excited because they have just returned from a six-month checkup with their neurologist, physiotherapist, and respirologist, all of whom

agreed that Aaron's muscle strength and function, flexibility, and lung function have improved and are surprisingly "above where he should be for someone his age."

For Aaron, these improvements have significantly improved his wellbeing—in ways that are difficult to measure or predict. He has started to muse openly about his future. For the first time in his life, these visions and plans for himself are not burdened by the prospect of dying prematurely from his disease. Regarding his application to university, Aaron envisions moving away from his parents and living independently for the full four years of a college education program. This possibility has become "real," his mother says, "whereas before it was more theoretical, because we didn't know if his disease would progress to the point that it would be impossible." Aaron adds,

Before, I didn't even see myself starting one year of university, and if I couldn't finish university, what was the point of graduating from high school?... Now I have the ability. I'm gonna live longer. I'll be able to finish university, and you know with medical school and a residency, I'll be able to do that. I'll be 31 years old but I think that I'll live through that. ... I'll be able to do it, I'll have the physical and emotional ability ... I can see the future now. There's more things I'll be able to do.

He has also started to dream that he may one day have his own family.

I do feel that I will be able to have a family. Just maybe not a nuclear family. ... Because I didn't think I'd have an opportunity to, have a family, but, [pause] now I do have the opportunity. Because, I probably wouldn't have lived long enough without the treatment, I probably wouldn't have lived long enough. But now it looks promising that I'll live long enough, and I'm happy, about [that]. ... I want the ability to have a family, like to have children and stuff that I love.

Aaron's functional improvements also enabled him to reduce his dose of steroids, which as mentioned have caused considerable side effects for him. Lowering his steroid dose has in turn helped Aaron to better manage his anger. He describes being more assertive, "knowing who

my real friends are,” and being more patient and confident when handling difficult social situations. “I’m more able to stand up for myself, and to stand up to people [i.e. peers at school who are teasing him], without getting in trouble.” When people say “stupid stuff to me,” he says, “I can say ‘you’re entitled to your opinion,’ and then I can ignore them” instead of getting upset and angry. Aaron’s mother Sarah confirms that his difficulties managing his frustrations are greatly reduced, especially at school. She has not been called regarding behavioural issues at school in six months, and relates that her son has not been removed from class (for being unable to control his frustration), “which is a real change for him.” As for Aaron, he talks about one day being able to wean off the steroids completely.

Getting off the steroids would help. [The dose has been] cut in half though. I mean I don’t have as many problems as before ... They make me angry. ... That’s a side effect. ... I don’t want it in my system. It [also] makes me angry to have something in my system that I don’t want or don’t like. But if I’m already on the gentamicin and [if I can get on] the PTC, I might not need the steroids. I don’t want to be on the steroids at all. ... That would be huge.

Though the above-described benefits have been significant for Aaron, he tells me the gentamicin treatment has affected a much larger issue in his life; namely, his ongoing efforts to reconcile a mismatch between his body and gender identity, and his desire to live life as a woman. Aaron identifies as transgendered and has felt for some time that he would be happier living his life “out” as a woman. However, he has been constrained in exploring this side of his identity by his disability, which causes him to be reliant on his parents for nearly everything from getting dressed to transportation.

Interviewee: I self-define as um, female and without the treatment I’d never be able to live that. And now with the treatment I am able to live that. I’ll eventually have the opportunity for that. And I’m going to college, where I’m protected [in expressing] that aspect of my gender identity. And most places in

the country, I would not be offered that protection. ... I think it's only about like 13 states and about a hundred jurisdictions in the United States. So that's pretty good that I'll be able to express that. And I probably wouldn't have been able to, if I was just gonna die in like a year after I finished high school.

CJC: So you see now an opportunity to be able to live your true gender identity? Is that what you're saying?

Interviewee: Yeah. I didn't have the opportunity before and that makes me much more, [pause] *happy* because everything would have been suppressed, and I wouldn't have been able to do that. And now I might have the opportunity to be off the steroids. And, [pause] potentially to start ... hormones and stuff. I'll have the ability, the potential, the possible eventual ability to do that. But I'll also, since I'm stronger and I'll probably live longer, I'll have a longer time to explore and express that [side of my identity].

CJC: Does that make a difference to you in terms of your emotional wellbeing right now? That you'll have a chance to explore those kinds of things?

Interviewee: Yeah. And, probably, if I would have continued to get weaker. Like right now, I can like, I do this occasionally, I put makeup on and stuff. I can do that, because, now I have the physical strength and, um, most people probably wouldn't be able to, or be willing to help me do that [put makeup on].

In addition to his gender identity, Aaron describes changes in his sexual identity since taking the gentamicin.

CJC: Does having the treatment, has that changed how you explore some aspects of your sexuality? Not your gender identity? But your sexuality? I don't know if you feel comfortable sharing some of that with me. And if you don't, that's okay.

Interviewee: Well it's changed it, because I've been able to, actually, [pause] I've actually felt like, with my disability I was depressed, but now I've actually been able to feel romantic attraction to people. Not just sexual attraction to people.

CJC: Hm, so what kind of a difference does that make for you?

Interviewee: I don't know, it makes me feel that I have more of the opportunity to, um, to find a relationship, to have a relationship with someone. [pause] And like I said, to either father children, or to adopt children. ... And this, this is important to me. ... It's just, [pause] complicated I guess.

Aaron feels uncomfortable discussing these issues with his parents—“they have enough to deal with already,” he says—and has struggled to find support in dealing with them. His limited social network and his reliance on his parents when pursuing friendships have made it difficult to connect with others his age with similar identities and experiences. Aaron has raised the topic of his gender identity with his psychiatrist, whom he felt was dismissive. The lack of support leaves him very angry and frustrated. “But,” he says “I’m happy now that I’ll have the potential to live, who I can consider myself to be.”

A lot of people don’t know, or don’t ask about the sexuality or identity of people with disabilities. And I think it’s important to discuss that we do have these aspects of our life. People may not understand them, but we do have them. And they need to try to understand them, and, ask ... questions about sexuality and gender identity. But not in front of our family or our parents. So we can be more open.

Later in the interview, Aaron tells me that a key part of his hopefulness and newfound confidence in managing his identity as a transgendered person stems from his regaining the ability to write. Since beginning the gentamicin treatment, the contractures in his hands and fingers have lessened and he has re-acquired some of his lost arm strength and fine motor control. This has enabled Aaron to hold a pen and to write in his journal for extended periods of time—something he could not do before taking gentamicin.

I can do more things myself, I don’t have to rely on a computer. If something’s on my mind, I can just jot it down. I write poetry and a lot of stuff. It cheers me up. A lot of my poetry is depressing, but it’s better to get it out than to keep it bottled up inside. Before I started writing, people would always be complete jerks to me, and when something happened, I would get really angry and I would overreact. I would get really pissed off. But then when I started writing, it was better to get things out and then I wouldn’t explode. Like someone was telling me “you’re crippled, you can’t do a damn thing, you’re stupid.” And I would explode. The more I can write, the happier I can be. Because if I write more of

myself, I can express myself better in writing than I can in speaking. I can write cheerful things, and I can write the depressing things to get them out of me. ...

[Before taking the gentamicin] I couldn't write at all by myself. It took me forever to write things, and I got really tired writing things, and I almost always needed a scribe, before the gentamicin. But [since taking the gentamicin], I'm able to write more because I have stronger hands. I was happier that I had more strength in my hands, I had a bit more movement. ...

[Being able to write] also benefits my social skills because I can share my writing with other people, like with my friends. ... I can express myself in writing. And that's made me, happier too. ... Because I can write about, it [my gender identity]. I can write about, everything. ... I write a lot of dark depressing things. But I also write a lot of happy things.

I can also write much more, and I don't get as tired. I wrote all of my final exams, and I did all of my writing on [a recent college entrance exam].

Duchenne, he says, is a part of his identity and if it was cured tomorrow, he's not sure if he would be interested.

A lot of people want a cure from the disability. I don't want a cure for DMD, I want a treatment, [so] that I can get stronger. But not a cure, not something where I can stand up and walk the next day. I want it to be gradual, where I get stronger, not like, instant. Because I feel that DMD is a part of me, of who I am, and I think it would be hard to transition from having DMD to not having DMD. I would like to gradually regain my strength, so I can adjust better. It would be hard to adjust if it was just one day. Right now, I can't imagine having a life without DMD, it's a part of who I am. It's influenced my life in almost every aspect, sometimes positively, sometimes negatively. ... It's made me a political activist for people with disabilities, and for all kinds of marginalized people in this world. The time I've spent in my chair, I've had time to read and research things, and that's why I have become an intelligent person.

I'm getting stronger. Until the one-year trial is done, I won't know the impact, but I'm pretty positive about it. We had a dance [recently] and I wasn't able to dance, but I was able to "dance" [i.e. in my own way]. I worked out a way to dance, and everything worked fine, all these girls wanted to dance with me. I was able to do the electric slide in the wheelchair. That was so awesome!

Aaron describes some of the other ways he feels gentamicin has changed his life.

I'm stronger. Before, I was getting weaker. ... After I was done urinating I couldn't lift my urinal and put it up on my desk, but now I'm able to do that. It's just really these little things that make me more happy and motivated to do more. Not big things, but little things. Like to be able to pick up a china plate. [When I was eating] soup, I couldn't hold the spoon without spilling everything, so [now I am] able to pick up the bowl and drink [the soup] out of it. I've become more and more independent. I'm able to do some of my own care. I can feed myself more, and I can do more things for myself. I can open the door myself when I go to church. It's like 50 lbs or something, but I can put some leverage on it. ...

I can adjust myself in my chair better, you know like slide over, or slide back or to the side if I'm in an uncomfortable position, and it's good that I'm able to do that.

Aaron's father described some of the changes he has observed in Aaron: When stretching, he says, Aaron can now lift his legs against gravity and twitch his feet. At his recent physical therapy appointment, Aaron was able to elevate both legs above six inches and hold them for a count of 10-15 seconds. "That's a significant improvement in his strength that he couldn't do before," says Jonathan. It means that Aaron can help with some of his own stretches. He can move himself a little bit more in his chair and is not as uncomfortable. Aaron adds: "Before I could only use my hip muscles to move in my chair, but now I can use my hip muscles, my hamstring muscles and my leg muscles, and it's much easier for me to move if I'm in a position I don't like." This gives Aaron some greater individual control over his life, says Jonathan. He can make himself more comfortable, or communicate on his computer, or write, because he doesn't get as tired.

If you are irritated by something you will straighten your pants out, or shift your position, or get rid of a wrinkle in your shirt. He can't do that because of his disease, he simply is physically incapable. But now he is more able to do a little wiggle here, or a little twitch there to alleviate some of his discomforts that, as an individual without a disease, we would take for granted. ... a twitch a millimetre

this way, or a centimetre this way For him, that's *significant*, since it's a pressure point irritating his body, it is significant. As a caregiver trying to alleviate his discomfort, that can get frustrating, and now he's able to do a little bit of the wriggling that he needs to make himself comfortable. It sounds like nothing, but it's *major*, because it takes time.

Aaron adds,

It gives us another 15 minutes to a half-hour [in the morning]. Before I wouldn't have time to even eat breakfast before the van came to take me to school. But now I have time to eat some breakfast before I went to school, and that's also benefitted me because I get more [food] in me, I'm less angry and irritated. ...

Before, if I was in a bad position I had to ask my parents to move me or shift me, ... and do you know how irritating that gets? ... But [now] I'm able to do that myself in my chair. It's a bit easier for my parents in the mental and emotional sense, they get less irritated.

Lastly, Aaron describes how he can sit now in his chair longer, too:

Before, I wasn't even able to be in my chair for 16 hours, when I got home I had to instantly get in bed, around 6:00-7:00. I would poop out. But now I can stay in my chair until 8:00 or 9:00 or 10:00. ... I normally try to get to bed at a good hour so [my parents] have time to sleep. I normally get into bed around 9:00, but by the time everything's done it's at 10:00. ... Now if I stay up, I can write [during the evening].

Aaron has also written a skit during his evening writing sessions, directed and presented it in a recent talent show, and plans to further refine it. He traces his initiative and creativity to his re-acquired strength on the gentamicin.

Before, I wouldn't have been able to do something like that, because it requires a lot of effort, and physical involvement, like I would have to lift the microphone up and hand it off to people. So now, I can be more physically involved [in the production] and less just "behind the scenes."

I can hold the microphone too. It's one of those old-school, heavy microphones, so I can actually hold it that way. ...It made me happy, it made me smile [to do the skit].

Toward the end of our interview, Jonathan summarizes some of the changes we have been discussing.

All of these things seem so minor and insignificant. But when you don't have the skill or capacity to do it, it becomes a *major* achievement. ... these are things that you cannot necessarily measure quantitatively in a prospective study. But in terms of quality of life issues, you can say, just from that alone, gentamicin has made a dramatic change in his affect. His productivity in school went way up. As he indicated, he was depressed and saw no purpose in school because he had no reason to live. But now he realizes that he has a life, he is going to go to college, he is going to get a job, and he has a future. That makes all the difference in the world.

6.4 Discussion: Paying Closer Attention to Parents' Narratives of Efficacy

Considering the above cases together draws our attention to several points. The first, overarching point is that a closer examination of parents' narratives can unsettle easy assumptions about hopeful parents and the clinical trial, by illuminating the idiosyncrasy, nuance, and complexity of their experiences. When we take the time to listen to them, parents' narratives of efficacy contain knowledge about their experience with a study drug that may be surprising and unexpected—as in the case of Maria Pauling hoping her son was assigned to the *placebo* arm of the trial, and Aaron Murphy's contemplating both an aspirational future and a new gender identity as a result of re-acquiring the strength to write. The narratives also contain a great deal of information about the impact of a therapy on caregivers and families, as well as parents' assessments of the risks and benefits of a treatment. In illuminating the social and personal contexts in which drug effects are observed (or fail to materialize), parents' narratives

highlight the need for individualized approaches to understanding how both the clinical trial experience, and the therapeutic intervention itself, affect everyday life.

To be sure, even with all of the powerful technology and knowledge medicine has at its disposal, assessing efficacy is a challenging task for all involved. In the setting of pediatric neuromuscular disease, for example, the simple waxing and waning of an illness in a growing child confounds researchers' efforts to determine whether a functional improvement is attributable to an investigational drug. Simple changes in height (and thus stride length), for example, have recently been shown to positively affect 6-minute walk distance (6MWD) in growing boys between the ages of four and seven, thus potentially diluting a treatment effect over the course of a trial (Henricson et al. 2012; McDonald et al. 2013). For Duchenne in particular, a great deal of clinical, genetic, and phenotypic heterogeneity in the disease—mediated by factors such as age, mutation, genetic modifiers, differences in care standards, variations in use of corticosteroids, and differences in physiotherapy and supplement regimes—further compound the challenges of demonstrating whether a drug is having an effect in a sub-population of patients. These challenges are apparent in the clinical trials testing ataluren, and more recently in trials testing other therapies for the disease (Hoffman and Connor 2013; Mendell et al. 2013).

Parents' narratives of efficacy show how they are confronting this same problem; they are in essence performing their own analyses alongside the formalized routines of the clinical trial. Some parents even went so far as to measure their child's progress more systematically, for example, by timing his performance at tasks such as climbing stairs. Changes observed in a child who has started an experimental medication must be made sense of and incorporated into an explanatory illness narrative. Conversely, a lack of hoped-for or expected improvement must

be reconciled. In a vacuum of meaningful clinical information, parents construct their narratives as assemblages using their everyday experience, the remarks and observations of others, and their own tacit knowledge of their child as parents, in order to create an explanatory model that makes sense of what they are observing.¹³⁵ Their narratives weave their identities, obligations and expertise as mothers and fathers with the significance of a new treatment in their lives and their conceptions of what constitutes meaningful improvement.

Given the stakes, it is perhaps unsurprising that parents began conducting their own lay-assessments of efficacy in this way. After all, chronic illness is at root a *moral* experience that calls out for interpretation and explanation (e.g. Kleinman 1988, 2013; Kleinman and Kleinman 1991; Mattingly 1998; Garro and Mattingly 2000; Frank 1995; Becker 1997; Sontag 1978; Hyden 1997). Parents and illness-sufferers are constantly engaged in attributing significance and meaning to the events in their lives,¹³⁶ and recall that for parents, the clinical trial is but one phase of a much broader (and longer) biographical experience (Bury 1982; Becker 1997). Though the experimental conditions of the clinical trial strive for a suspension of belief—a “blackout period” of equipoise described in the previous chapter—parents (and children) are constantly engaged in the activity of interpreting their observations and determining their meaning. In each of the above cases, parents’ narratives of efficacy reveal their efforts to bracket their hopes and to assess their child’s functional status dispassionately—an agonizingly challenging feat which they attempted and accomplished to various degrees.

¹³⁵ Though I do not pursue the connection here, parents’ conceptions can be described theoretically as symbolic *bricolages*, using the concept introduced by Levi-Strauss (1966) to describe how cultural representations (such as myths, or artistic creations) are created by cobbling together symbols from different cultural domains.

¹³⁶ Of course, interpreting the world around us is a basic part of human nature and is not unique to parents. Though here I focus on parents, it behooves us to remember that clinicians, research co-ordinators, pharmaceutical professionals and academic scientists are also engaged in attributing significance and meaning to events around them while carrying out clinical research, but working with different information and cultural schemas.

Research participants' narratives of efficacy highlight a central tension in rare disease clinical research. Paradoxically, these stories simultaneously illustrate the need for, and the shortcomings of, the controlled trial as a "gold-standard" method of assessing a drug's efficacy. On the one hand, parents' assessments of efficacy are deeply subjective, variable, idiosyncratic, and dynamic. They are unique to each child and family, to the life circumstances and personal biographies from which they emerge, and they are imbricated with a parent's deeply-felt hopes for relief of their child's disease—if not for a cure, then at least for a semblance of normalcy. It is for this reason that controlled clinical trials and cohort-derived outcome measures are required in the first place, in order to screen out the "noise" of patient perception and the possibility of placebo response; to identify the "true" signal of a drug's clinical effect(s) in a group of individuals, here recorded as a change in a functional outcome measured over time and (usually) in comparison to placebo (e.g. Temple 1982).

And yet parents' narratives simultaneously highlight the shortcomings of the controlled methods used to address the very problems they pose, since the controlled outcome measures used in trials often elide the very substance of families' experiences with an investigational drug, by capturing only part of the picture. In rigidly designed trials, changes in a child's functional capacity in domains that are outside of a trial's pre-specified outcome measures may go unaccounted for, suggesting a need for increased flexibility in how trials are designed and interpreted in rare disease populations. We might also ask what a slower rate of decline in one's 6MWT scores compared to a placebo group; a change in the time it takes to climb four steps; or even a statistically significant increase in the Quality-of-Life scores obtained via questionnaire, actually *tells* us about the substantial impact of a treatment effect on the life of a patient. Arguably, these measures offer relatively little insight into how being able to dress oneself, to

carry dishes independently and fix one's own meal, to walk oneself to class (as in the case of Avery Williamson), or how having a vision for one's future in college, living a life with reduced rage, and attaining a sense of comfort with one's own body and personal identity (as in the case of Aaron Murphy) might influence the lives of a patient and his family. Though the controlled trial invokes a paradigm of objectivity and detachment, it is in this very act of scrubbing patients' experiences and sifting them in relation to a cohort of individuals and a limited menu of pre-specified outcome measures, that the subtle and idiosyncratic effects a drug may have on an individual life (and on a patient's family and caregivers) are overlooked.

This can be especially problematic in the setting of rare disease, where little is known about an illness and the effects a drug may have upon it, and where limited numbers of patients may preclude the use of controlled clinical trials to capture treatment effects in the first place. The meaning and significance of a treatment effect may not be immediately obvious or predictable at the outset of the trial, as in the case of Aaron Murphy. For Aaron, the impact of treatment with gentamicin was eminently specific to his own circumstances, and would have been difficult to anticipate, capture, and quantify using outcome measures that are developed at the group level, and which must be pre-specified at the outset of a clinical trial. It is this very significance, arguably, that forms the substance of "benefit"—that is, of improvements in one's "quality of life"—that drug developers, regulators, patients and physicians alike seek; and yet the qualitative nuance of changes like those experienced by Aaron often fall through the cracks of a drug development regime enamored with statistics, quanta, and p-values. The cases above illustrate how parents' narratives of efficacy contain data that are often overlooked, but which offer potential for expanding, explaining, and in some cases contradicting those gathered by the statistical paradigm of the clinical experiment.

This is not to claim that parents' narratives of efficacy are objectively true or that they are a panacea for drug development. Like all types of research data, narratives come with their own limitations. It is well-established in qualitative research, for instance, that determining the relationship between a respondent's narrative recollections and "objective reality" can be difficult, if not impossible. Patients' narratives have been shown to be emplotted with and told to others in specific settings and circumstances (a process labelled therapeutic emplotment, described in the previous chapter) (Mattingly 1998; Mattingly and Garro 2000). Narratives may also take specific forms depending on their intended audience (Hunt 2000), the moment in which they are communicated (Kirmayer 2000), and the cultural conventions of storytelling (e.g. Frank 1995; Price 1987; Sontag 1978; Mishler 1995), and they are subject to the vagaries of memory and recall (Garro 2000). As such, they must be viewed as inherently partial and subjective accounts.

Indeed, it is possible that all of the changes observed by the parents in these cases (and others of which they are typical) were attributable to placebo response, selective observation (observer bias), or other factors. To be sure, the cases above show how the clinical trial experience heightens parents' awareness and scrutiny of a child as they adjust to their new social role as research subjects. Parents may "search for" changes that can both sustain their hopes and justify their exertion as trial participants—commuting long distances and subjecting their children to various medical procedures and impositions. Children too, have been shown to respond to changes in routines in the home, clinic and hospital, and as any parent knows, children often seek to emulate and please their elders (Weimer et al. 2013; Moerman and Jonas 2002; Brody and Miller 2011). Though there is surprisingly little published data on placebo response rates in children and adolescents, they appear to be higher than in adults (Weimer et al.

2013), and the concept of placebo-by-proxy has been proposed (Grelotti and Kaptchuk 2011).

And yet it is equally true that we do not have an evidentiary basis for so casually dismissing parents' observations of treatment effects in their children. As the above cases show, when assessing their observations of their children, parents invoked a longitudinal and tacit understanding of their child's abilities that can only be gleaned from a lifetime of raising and caring for a son or daughter. The present reality is that there is a paucity of longitudinal qualitative research on how parents of children with rare disease experience the clinical trial, make observations, and interpret their experiences within it. This gap in our understanding of parents' experiences limits our ability to make empirical and evidence-based assessments of their claims of efficacy or non-efficacy.

A better understanding of parents' narratives of efficacy—and the experiential context in which they are assembled and relayed—would enable a clearer picture of their validity in the unique setting of rare disease, the information that might be reliably gleaned from them, and their potential pitfalls and sources of bias. We might also ask whether educational, training or support initiatives could be effective for promoting the reliability of parents' narratives as data to supplement the quantitative measures of the trial itself (e.g. Curry, Nembhard, and Bradley 2009; Rapport et al. 2013). As I discuss later, this claim is at the centre of arguments made by patient-advocates for a more patient-centred and collaborative approach to clinical research. It also anchors a shift toward alternative methods of data collection in clinical research, including the use of Patient Reported Outcome Measures (PROMs) (e.g. Gershon et al. 2010). Though narratives cannot always be taken at face value, I suggest that the cases above demonstrate how narratives do have probative value for learning more about the significance of a therapeutic intervention, and that this value warrants their collection alongside other types of data gathered

during the trial.

Lastly, the cases above show how parents' narratives of efficacy can yield insight into how parents' hopes and expectations for treatment connect with their perceptions of a study-drug's activity. Narratives of efficacy make clear that despite efforts to control the experimental conditions of the trial, parents do not operate or develop their perceptions of efficacy in a vacuum, but rather in a social arena in which claims about—and other parents' narratives of—a drug's efficacy circulate. This social arena tends to be overlooked in the execution and reporting of clinical trials, and remains bracketed from the “real data” collected in clinical research. And yet parents' narratives reveal the central role that their social context plays in how they experience a new treatment and interpret its risks and benefits.

This can be seen clearly in the case of Maria Pauling, who initially believed her son Larson was taking active treatment, but later developed the impression he had been assigned to the trial's placebo group. Maria described how she approached the trial with high expectations for a treatment effect, given anecdotal reports she had read about the drug online. Her information came mainly from other parents' testimony about a range of positive changes in their children, including one account of a child on open-label medication who climbed a large hill at the park. She had also heard about another local family who had experienced significant changes in their son's stamina for walking longer distances. These testimonials had led her to expect “significant improvements within one to three weeks.” When these changes did not materialize as hoped, her experience in the trial and her perception of the study drug she was administering to her son changed, and she began to both hope and expect that he was taking placebo. Similarly, in all of the cases above (and in other cases not detailed here), parents incorporated the perceptions and comments of others about perceived changes in their sons into their own

interpretations of whether the medication was making a difference, including those of family members, teachers, school staff, health care practitioners, and others. In the cases of both Carol Williamson and Aaron Murphy, the perception that a drug was working had the beneficial effect of sustaining caregivers' hopes for a better life for their child, and were thereby intertwined with their ongoing efforts to adapt and cope with their sons' progressive disease.

These social dimensions of research subjects' experiences in clinical trials are worthy of closer scrutiny and discussion. Of course, the circulation of anecdotal reports of efficacy within the trial is a well-recognized and vexing problem in clinical research, given the potential for introducing expectancy and ascertainment bias into trial results (Jadad and Enkin 2008).¹³⁷ Trial sponsors are obligated by regulatory agencies to refrain from making inaccurate, unsupported and/or exaggerated claims about potential efficacy—a stipulation, it should be noted, that is often flouted within the broader pharmaceutical industry (Silverman 2013)—and to take steps to reduce the circulation of such claims. In the United States, the FDA has recently released long-awaited guidance for how trial sponsors should respond to such claims on websites, blogs, and social media, articulating an onus on the drug manufacturer to correct inaccurate claims (FDA Center for Drug Evaluation and Research 2014a). “Solutions” to this problem employed by trial sponsors include efforts to suppress interaction between research subjects by having them agree in writing not to discuss the trial with each other and/or post about it online, and by scheduling patient-subjects' clinical appointments so that they do not overlap.

And yet in an era of social media and global communication, photographic, video, and

¹³⁷ This issue first came to prominence in clinical trials in the 1980s testing early antiretroviral therapies for HIV. In that case, trial subjects shared not only their impressions of efficacy with each other, but also commingled and redistributed their allocation of study drug amongst each other to ensure an equitable distribution of active medication (Epstein 1996).

written accounts are circulated online with unprecedented ease and anonymity, thereby raising doubts about how successful such measures are likely to be. More recent experience with other investigational drugs both for DMD (eteplirsen and drisapersen) and other rare diseases has shown that anecdotal claims circulate with considerable resonance within the patient community, and are also instrumental in advocacy and political debates about regulatory reform (see Chapter 7). In light of these developments, it may therefore be worth asking whether instead of suppressing the social dimensions of the trial experience, a more effective approach might instead be to enhance our empirical understanding of how such claims circulate, their role in patients' accounts and perceptions, and their connection with the overall illness experience.

It is likely, for instance, that parents' construction and communication of narratives of efficacy help them to cope with the stresses of the clinical trial experience itself, and their child's prognosis more generally (Peay et al. 2014b)—a point that is generally recognized by clinicians working with rare disease patients who know that maintaining hopefulness is important for coping and adjustment to a serious diagnosis (Good et al. 1990). Claims about research subjects' elevated expectations for benefit in the trial have also been discussed in the scholarly literature under the rubric of “therapeutic misconception” (Appelbaum et al. 1987), which (as described earlier) postulates that parents' hopefulness and expectations for research can amount to a form of confusion regarding the purposes and parameters of research (as opposed to treatment) that impedes informed consent. And yet there is remarkably little empirical data with which to understand the relationship between hope, expectation, and perceptions of efficacy within the clinical trial, and the social context of the trial remains a curious black box that is omitted from the collection, analysis, and reporting of clinical trial data. Closer examination of parents' narratives of efficacy may yield insight into the individualized ways that hopefulness—and

specifically hope for treatment—may affect how a new therapy is perceived, and whether such hopes promote resilience in the face of devastating, progressive and terminal disease. Rather than dismissing parents’ stories as overly hopeful and subjective accounts that are of little value, we might instead resolve to better understand how such hopes and expectations vary over time, whether sustaining hopes for treatment might mediate the impact of a disease by improving psychological and social functioning, and/or whether such changes have ethical weight or value when evaluating the impact of a treatment on everyday life (see also Peay et al. 2014b).

Perhaps more importantly, a more robust effort to capture and understand parents’ narratives is likely to show the unexpected, individualized, and dynamic nature of their expectations for treatment. In each of the cases detailed above, parents (and in Aaron Murphy’s case, sons) were ambivalent about the prospect of cure and expressed hope that the investigational treatment would bring about a stabilization, if not an improvement, in their sons’ functional abilities. Maintaining a child’s functional status and arresting the progressive loss of further milestones was seen as a desirable and sufficient benefit from treatment, *even in the absence of cure or improvement*. This point was made by many parents in the present study and was detailed by both Carol Williamson (mother to Avery in the open-label ataluren trial) and Jonathan Murphy (father to Aaron, taking gentamicin) above. It has also surfaced in parents’ comments posted publically online in response to recent deliberations about US regulatory policy in relation to Duchenne.

My criteria of what trials my son would or would not participate in are changing as he gets older. Duchenne has taken so much from him that I would consider treatments that would allow him to just keep the function he has now even if there were some risks. This may not have been true 10 years ago. The concept of risk vs. reward has changed for me. So I think it is important for the FDA to realize that in the Duchenne community there could be many views but the older boys

who need treatments as fast as possible are probably willing to accept more risk for what may seem a little reward.

I think it is important for people to understand that the ability to do simple things becomes very important in daily life and contribute[s] greatly to the boys' quality of life. Being able to brush their own teeth may not seem like much of a success but it means so much. I think the 6 minute walk test for measuring outcomes of a treatment ignores all of the possible treatments for the boys who just want to preserve some dignity. Or they may want to contribute to society so being able to type on a keyboard at work would be a tremendously successful outcome.

There has to be a way of getting some treatments to these boys. I used to think a wheelchair would be horrible, well it's not so great but definitely not the end of the world. What would be the end of the world is having my beautiful son lose his battle when treatments are just so close. (Anonymous Parent 2013)

As this quotation and the cases described earlier show, parents' narratives of efficacy offer considerable insight into the qualitative nuance and personalised nature of patients' expectations for benefit, and how these relate to their perceptions of what constitutes an acceptable improvement in the quality-of-life of both patient and family. Attending more closely to their narratives can help us to learn more about the ways such expectations emerge from their biographies and illness experiences, as well as how they vary and change over the disease course. This approach might also be fruitfully combined with other innovative methods for capturing patients' perspectives of risk/benefit and quality-of-life to create a comprehensive, valid and individualized approach to identifying patients' priorities for therapeutic improvement. These approaches might include the use of best-worst scaling (BWS) (Peay et al. 2014a), measures from the Patient Reported Outcomes Measurement Information System (PROMIS) developed by the National Institutes of Health (NIH) (e.g. Gershon et al. 2010), and/or other Personalised Evaluation Models (PEMs) such as the Personal Outcomes of Specific Interest (POSI) (Collet et al. 2014).

Crucially, the issue of understanding patient perspectives on therapeutic improvement and designing new methods to account for them is much more than an academic question for parents, whose children's outcomes hinge on the time it takes to develop and provide access to useful new interventions. The following public comments made by a mother in a patient-advocacy forum reinforce the stakes parents have in the design and execution of clinical research.

Max is our oldest son, he is 8. Max's muscle strength is in a decline. There are things he could do three or four months ago that are becoming increasingly more difficult for him. He is falling more often. Two weeks ago he fell and hurt the tendons around his knee. He limps and uses his medical stroller more now than ever before. We hope that as his tendons heal, his mobility will come back. However, because of Duchenne Muscular Dystrophy there is no guarantee that he will bounce back. Just yesterday he fell trying to play soccer, hit his head and has a concussion. He was falling like this three months ago. The hardest for me to swallow is that Max does not always finish putting a lego set together. That was unheard of a couple of months ago; Max would sit for hours to complete a set, but now he doesn't seem to have the stamina.

As a parent this is very hard to watch. No one should watch their children regress. Parents dream of watching their sons grow into men, watching their dreams come true. Duchenne and the lack of treatment threatens to steal this dream from us. It threatens not just the loss of one son, but three sons. It threatens to take half of my children from me. My husband and I feel we are proactive, we are doing everything within our power to save our children. We make financial sacrifice to take our children to the best doctor available (14 hours from our home), we follow a strict diet, we home stretch, we fund-raise to help finance research. In fact, Max participates in the Imaging DMD study and ataluren trial in hopes that not only we help, but that he can have access to a drug that may save him and eventually his brothers.

Our experience with the ataluren trial has been heart wrenching and I would like to share with you why. We screened Max for the study 6 months ago, before his decline, and he did not make it into the study because he walked too far during the 6 minute walk test. We re-screened this February and he made it in, and although we are happy he did, it was because his muscle strength had declined and he was no longer able to walk too far. If there had been no 6 minute walk test, Max could have had access to ataluren before his decline and his strength could have been saved. We do not know if Max is receiving a placebo or the actual drug.

However, based on the changes we have seen in his strength the last couple of months, I think it is very likely he is on the placebo. If there was no placebo, his change in muscle strength, his decline could be stopped. This is why I believe with all my heart, that every day that it takes to approve a drug, is a day my sons do not have. It is why I believe so strongly is a faster approach to approve the drugs that could help.

I want my sons to be saved. I want to watch all 5 of my children blossom into amazing adults and see all the things they accomplish. The possibility that I might see only two children live, should not be a possibility I have to consider as I think of the future. I have attached a picture of our family so that you can see those cute boys and know what we are fighting for and that you would join our fight to save them. Max, Rowen, and Charlie are the three we are holding.

-Betty Vertin, mother of 3 children with DMD (2014)

6.5 Conclusion

In the previous Chapter, I discussed how the clinical trial experience unsettles taken-for-granted social roles, constraining clinical relationships and leaving parents to construct the significance of an experimental treatment in the context of limited information. This chapter has elaborated on this *process* by discussing how parents make sense of efficacy while in the clinical trial. By describing the cases of Carol Williamson, Maria Pauling, and Aaron Murphy in close detail, I have suggested that while in the trial, parents assemble and tell “narratives of efficacy” while administering study drug to their children, drawing on their own observations and those made by others. Though parents’ narratives are often dismissed as mere anecdote, I have tried to show that they also offer insight for developing more individualized approaches to clinical research and outcome measurement for rare diseases, by restoring focus upon the nuance, idiosyncrasy, and context of families’ experiences with investigational treatments. I also discussed how an improved understanding of how such narratives circulate within communities, and their significance in parents’ efforts to cope and hope with their child’s disease, might aid

trial sponsors and patient advocates, who are increasingly placed in the position of responding to the circulation of stories of efficacy through online social networks and to elevated or unrealistic expectations for investigational treatments. In addition, I elaborated some of the limitations of parents' narratives and suggested that a better understanding of them is mandated. To be clear, I am not suggesting that parents' and patients' accounts of efficacy are "objective," or that they can replace the need for controlled approaches to the evaluation of investigational treatments, but rather that they can provide useful information for filling in the gaps of traditionally designed clinical trials. In the following two chapters, I conclude the dissertation by turning to the outcome of the Phase 2a extension and Phase 2b ataluren trials, and explaining their impact on parents and the patient community.

Chapter 7: The Results and Impact of the Ataluren Trials

In this chapter, I describe the outcome of the Phase 2a extension and Phase 2b trials of ataluren for DMD, and the impact of these developments on both patients within the trials and the broader illness community. In the following chapter, I turn to a summary of the main findings and implications of the dissertation.

7.1 Outcomes

When taken together, the previous chapters give readers a sense of the hope, tension, and anticipation surrounding the ataluren trials (and other similar trials for rare diseases), and of parents' stakes in their outcome. These sentiments buttress a familiar narrative for DMD, other rare diseases, and cancers, where a lack of cure, a high burden of care, and the emotional paroxysm of a dismal long term prognosis for one's child collide. In a biotechnical era, the result is clenched-fist expectancy for science as a means for salvation—a faith and yearning for therapeutic redemption with almost-religious undertones. A father once remarked to me that he disagreed with some of the images commonly evoked by drug development and cutting-edge medicine—the pictures of laboratories, mice, hospitals, and sick children that usually come to mind, and which populate the PowerPoint slides shown at conferences. “For me,” he related, “when I think of medicine and science, all I see is a giant pressure cooker with all of our lives, hopes, and dreams jammed inside it, running at a boil.” The flames heating the pressure cooker were fuelled, in this father's metaphor, not by gas, but rather by burning piles of dollar bills. “Drug company timelines are literally our boys' lives,” a different mother tweeted recently.

One can therefore imagine the anticipation in the room on a Monday in February 2010, as the clinical development team from PTC Therapeutics gathered at a hotel in New Jersey, along with their statisticians and representatives from then-partner Genzyme (which administered the trial sites outside Canada and the US). Having just received the unblinded database from the Phase 2b pivotal trial, the team planned to run initial analyses to see if the trial had met its pre-specified endpoint. Ataluren, then the first disease-specific treatment for DMD and the first compound advanced by PTC Therapeutics into clinical trials, had a lot riding on it for company personnel too—the culmination of a decade’s work, hundreds of millions in investment, and the company’s lead candidate for commercialization (and thus survival, and perhaps profitability). By all accounts, staff had also come to care deeply about the patients whose diseases they were working to treat, and had been lauded for their close relationship with the DMD patient community (Winkler and Finegold 2008).

All, however, were soon slated for disappointment. As the first analyses of the trial data were run, it was discovered that the trial had not reached its pre-specified primary endpoint—an outcome that would soon lead to chaos and confusion. Recall that the trial had three arms: a placebo group, a low-dose group (40 mg/kg/day) and a high-dose group (80 mg/kg/day). Owing to the progressive nature of the disease, boys in each of the groups were expected to decline over the course of the 48-week trial. In order for the drug to be considered effective, the data would have to show that the distance walked in six minutes (6MWD) by boys on active treatment declined 30 metres *less* than their peers on placebo.¹³⁸ And yet as the 6MWD scores were

¹³⁸ Several factors went into this calculation, including the number of subjects in the trial, the statistical power of the sample, the sensitivity of the 6MWT measure, and the fact that a 30 metre improvement in 6MWD had been correlated with improvements in quality of life in trials with other diseases using the outcome measure (McDonald et al. 2013).

plotted on graphs and analyzed in regression models, the actively treated groups did not show a statistically significant improvement over the placebo group, marking the drug as an ineffective treatment or cure for DMD. When the data were re-examined with the two groups separately (that is, low dose vs. placebo and high dose vs. placebo), the *high*-dose group and the placebo-group tracked near parallel declines in 6-minute walk distance over the course of the study. However, in a surprising twist, the *low*-dose group came close to showing a significant treatment effect. Boys in that group declined by a score of 13 metres in comparison to their counterparts on placebo, who declined by 42 metres. This left a difference of 29 metres between the two groups, just one metre short of the required difference of 30 metres for success.¹³⁹ Paradoxically, it appeared that taking a *lower* dose of the drug showed a trend toward efficacy, while taking a *higher* dose appeared—at least statistically at the cohort-level—to have no benefit over placebo. Though a surprise to the trial sponsor and to many in the patient community, this phenomenon has been described as a property of other medications as well, and is known in pharmacology as a bell-shaped dose response curve (Davis and Svendsgaard 1990).

More crucially however, though the trial had missed its primary objective of a 30 metre increase in walk distance by only one metre, the trial results did not meet the test of statistical significance (initially, a confidence level of 85%, $p = 0.0628$, were reported). This meant that the possibility that the improvement observed in the low dose group over placebo was solely attributable to random chance could not be sufficiently ruled out. Missing statistical significance meant that regulatory authorities were likely to approach any claims of efficacy in the trial results with scepticism.

¹³⁹ These figures were presented by the company at the American Academy of Neurology Meetings, and to the patient community in April 2010 (PTC Therapeutics Inc. 2010).

Families in the trial would soon become painfully aware of the implications of the bell-shaped dose-response curve and the concept of statistical significance. The problem was that the extension trial—that is, the protocol under which all of the trial participants were by then receiving ataluren open-label (after completing the 48 weeks in the placebo-controlled study)—was designed using the *high*-dose, since pre study it was expected to have the greatest chance of proving effective. From the standpoint of research ethics, the fact that the trial data showed no appreciable difference between this high-dose and placebo was inescapably problematic, because it disturbed the state of equipoise required to make the trial ethically justifiable (Freedman 1987). If the high-dose regimen was *known* to have no treatment benefit, the reasoning went, then there could be no benefit to outweigh the corresponding burdens of risk and inconvenience borne by subjects in the study. One of the most well-established principles of research ethics—the beneficent notion that the burdens and potential risks of participating in research must be balanced with a corresponding potential for benefit—seemed here to plainly indicate that proceeding with the extension study in its current form would be unethical.¹⁴⁰ In what was rather a straightforward decision within the established frameworks for research ethics (e.g. Pocock 1992; Grant 2004), the independent Data Monitoring Committee¹⁴¹ reviewed the results

¹⁴⁰ This point emerges from the Declaration of Helsinki (World Medical Association 2013) and is established in various guidelines for the conduct of clinical research, including the Good Clinical Practice Guidelines (ICH Harmonised Tripartite Committee 1996) as well as the policies of institutional review boards which oversee clinical research. The World Health Organization’s international guidelines for ethical biomedical research involving humans state that “scientifically unsound research [i.e. research lacking a clear justification] involving humans as subjects is *ipso facto* unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of subjects’ and researchers’ time in unproductive activities represents loss of a valuable resource.” (WHO Council for international Organizations of Medical Sciences 2002:25)

¹⁴¹ Data Monitoring Committees (sometimes called Data and Safety Monitoring Boards) are groups of independent experts appointed to review patient safety and efficacy data while the trial is ongoing. These committees have access to the unblinded dataset but are independent from those operating the trial. The committee issues recommendations to continue or stop the trial in the event of safety concerns, an overwhelming sign of benefit, or apparent futility (if the trial appears that it will not meet its endpoint).

of the trial and recommended that all ongoing studies be suspended—that is, that research subjects consuming ataluren be immediately taken off the drug.

7.2 Delivery of the News

When the results were announced at 9:00am EST on March 3, 2010, the news of the trial's results and stoppage hit the Duchenne community “like a hurricane” (Furlong 2010b). Most (including myself) had expected the trial to meet its endpoint, given the number of narratives of efficacy circulating within the community at the time. It would soon become apparent that many had begun to take this outcome for granted. Devastated and confused parents—some of whom had discerned functional changes in their children while on the study, and others who had only recently rolled over into the extension trial and begun administering the drug to their children—began inundating research sites with phone calls and questions. Co-ordinators and site-investigators, having only just learned of this development themselves, found they had little information to offer.

On Wednesday, PTC Therapeutics and Genzyme issued a joint press release at 9:00 am. In describing the preliminary results of the trial, the (notably brief) release stated that, “the primary endpoint of change in 6-minute walk distance did not reach statistical significance within the 48-week duration of the study.” In a perhaps futile attempt to render this result more positively, it continued, “these results further demonstrate the safety profile of ataluren and support continued development ... Importantly, this trial does provide a wealth of valuable data about ataluren and DBMD.¹⁴² Additional analyses will guide the overall clinical and regulatory path forward.”

That morning, the company had emailed the research co-ordinators and told them there would be two conference calls, one for those in the Eastern time zone, and one in the afternoon for those in the Pacific time zone. Research co-ordinators had to call in on the call, but the effect was that the release went out before the

¹⁴² Duchenne/Becker muscular dystrophy. See Chapter 1.

research co-ordinators in the West had even learned about the trial being cancelled. I spoke with [co-ordinators at two different sites]—both of them were in very difficult positions, having to phone parents and relay the news that the trial was suspended. It was “a difficult day,” one said, with considerable understatement. Patients have been asked to return any remaining drug to the clinical trial sites, and to cease taking it immediately. (Fieldnotes, March 7, 2010)

For its part, PTC Therapeutics had found itself in an untenable situation. Since its partner Genzyme was a publicly traded company subject to the disclosure rules of the US Securities and Exchange Corporation (SEC), the trial results represented material information that was required to be disclosed within 48 business hours of having been received and evaluated. This provision prevented both companies from communicating the results with trial sites and patients individually.

In times of crises, metaphors abound. Mother and patient-advocate Pat Furlong articulated the impact of the news on the community in a public blog post, as fraught parents sought to determine what this development meant for both their children’s health and their own personal biographies.

I cannot relate to [Hurricane] Katrina,¹⁴³ but on Saturday I felt like I was seeing the aftermath of our own “hurricane.” The wind died down and the reality hit. As a community, we were left in the aftermath, trying to make sense of the news, trying to find some meaning, some hope.

I have been following the discussions, the criticism, the sadness. These trial results are not what we expected or wanted. We all wanted a win for Duchenne. We depended on it as if it would feel like a neon sign that this one win would lead to more, would mean the stars were lining up just right. And sometimes when we hear bad news, everything else in the world looks bleak ... We are all reeling in the aftermath of our first (and hopefully only) hurricane. We have all fallen apart in our own ways. (Furlong 2010b)

¹⁴³ Hurricane Katrina devastated New Orleans in 2005.

Mothers and fathers too, began turning to online forums to articulate their grief and seek answers. Among the most potent public postings was this one, published by one mother and worth quoting at length:

Thursday, March 4, 2010

I watched as some joggers passed by my house today. My eyes following their young thin physiques. Watching as perfectly formed athletic calves carried these athletes. They appeared almost graceful like darting over puddles from the remains of winter. Standing there still holding the phone from the devastating call I had just received, tears began to run down my face.

Once again we were faced with another heart felt disappointment. The drug trial that had brought hope back into our lives the last few months closed. Recent medical data showed no signs of increase[d] muscle strength had been proven. I had just been told the drug PTC124 was in fact not working. The study was closed taking with it our renewed hope. Angry at myself I fought hard to hold back tears. I had known better than to get overly excited and build up hope. Letting my mind be controlled with my heart, I grabbed the chance to feel myself embrace the glimmer of light. Wanting desperately to believe that it was possible for science to finally have found a treatment to help stop the progression of Duchenne muscular dystrophy.

Turning away from my window still holding the phone, I knew I needed to make calls. I needed to have someone tell me I would find a way to put aside my sorrow and continue to be the strength that I had been for my boys. Being a single parent seemed to always have me searching for someone to help me walk through the hurts. Who could I burden today with my pain I wondered. I cried, as I let self-pity flood me. In a few hours my sons would be home. I knew I would have to pull myself together. I would have to stand alone in front of the beautiful brown eyes of my sons and tell them the study was over. Somehow I had to find a way to hide my tears and search for the delicate words that would not destroy all the hope for my sons.

I thought about hope for a moment. We as humans cling to it like the air we needed to breathe. Each day it kept us going facing our fear and heartache. Pulling us through despair. I wanted to stop the overwhelming disappointment I was feeling. I still had hope I thought. But, for the first time in many years I did not feel hope was something that would help Cody. Reality screamed at me, his door was closing. Cody was losing time. I knew this disease like the back of my hand. I had seen it take my brothers' lives. I saw how it ripped apart family members. I knew how it broke peoples' spirits. Most importantly I knew it

killed. It killed dreams and hope, before claiming its victims. ...

For now it appeared Duchenne was winning this battle. However, the fight was not over and for my sons I would be the warrior striving to find some weapon to slow my enemy. I would face this moment with courage. I would not let my beloved children feel we had been defeated. (Felling 2010)

As parents struggled to determine their next steps, company representatives stated that they needed time to analyse the results from the study so that they could decide on a path forward. Engaging in secondary statistical analyses of the data and informal discussions with the FDA might highlight a course of action. Perhaps the drug was more effective in certain sub-populations—those of a certain age, or with a particular type of stop-codon mutation, for example, might be more likely to benefit from the drug. On this basis, there might be a rationale for seeking approval of the drug, even if in a limited population. Completing these analyses would take time, however, and regrettably, parents and children who felt they had benefitted from the drug would have to wait. To compound matters, those parents whose children had *not* experienced significant improvement on the drug were hounded by an additional, agonizing possibility. Many families wondered whether the lack of effectiveness they had observed could simply have been a matter of incorrect dosage, rather than the drug's abject failure in their child's muscles.

7.3 Fallout

In the period that followed there was considerable debate within the patient community about what should happen next. As the company re-examined data from the trial, many families

considered litigation to seek access to the medication.¹⁴⁴ Many were angry at the sudden way in which the trial had ended, having expected to receive open-label access to the drug in the extension-trial in return for their participation in the placebo-controlled study.¹⁴⁵ Several parents contacted regulatory authorities in an attempt to secure access to the investigational drug outside of the clinical trial (colloquially referred to as “compassionate use” or “expanded access”), but were advised by authorities in various countries that though a policy framework existed, such a program would have to be designed and implemented by PTC Therapeutics.

For its part, decision-makers at the company were sensitive to the desire of parents seeking to keep their children on the drug, but found themselves constrained in their ability to develop an expanded access program. First, they argued that such a program would likely face regulatory hurdles given that data from the clinical trial did not show conclusive benefit within the treatment population. There were also concerns about having a sufficient supply of the drug available to meet demand, since medications for use in clinical trials are typically manufactured in small batches (usually by outsourced biochemistry labs) while in development. The company argued that an expanded access program would also place it in the ethically untenable position of providing the drug to patients who had participated in the clinical trials under a treatment protocol, while withholding it from others with equally compelling reasons for seeking access.

Who would decide which patients should be permitted access to the drug? As an organization,

¹⁴⁴ Some families retained an attorney but to my knowledge no court proceedings were launched in the United States or Canada. One case was brought before the courts in the Netherlands. In it, the Verhoek family sought access to the medication by arguing the company had breached its obligations under the Helsinki Declaration. The case was ultimately unsuccessful and before being heard on appeal patients were granted access to the drug through a new extension trial initiated in 2012 (Cinderella Therapeutics 2012).

¹⁴⁵ This point is itself an indictment of the facile notion that patients participating in trials give their informed consent as long as the language in the document is clear, since this potential scenario was clearly articulated in informed consent forms signed by parents at the beginning of the trial, and yet some parents were not aware of the possibility that the extension trial could be stopped in the event the placebo-controlled trial revealed safety issues or non-efficacy. See also Peay et al. (2014).

PTC Therapeutics had already experienced the moral, ethical and legal minefields inherent in such decisions, having defended itself in a 2008 suit brought by a mother seeking access to the drug for her son, and were likely to approach such a scenario cautiously (Malorye 2008; Peltz 2009). Further complicating matters was the fact that expanded access policies vary considerably in different countries, creating bureaucratic challenges and costs for implementing such a program.

Though the company did not emphasize the point publically, it has been argued in comparable situations that sponsors who offer investigational drugs through compassionate use invite challenges when conducting future clinical research on the drug in patients with the same condition (e.g. Usdin 2014; Siren Interactive Inc. 2014). It is speculated, for example, that patients receiving a drug on compassionate grounds would be unlikely to enrol in any future clinical trial if they were able to instead obtain access via expanded access and/or litigation. In the present case, the pool of treatment-naïve boys—already estimated at less than 1,690 in the United States¹⁴⁶—would also diminish considerably.¹⁴⁷ Undoubtedly, the company was also aware that should any adverse events occur in patients taking the drug through an expanded-access program (where a sponsor has diminished control over administration, safety, and monitoring but retains full liability for its investigational product), this could derail the development of the drug.¹⁴⁸ Regulatory policy also mandates that any safety information from such adverse events be added to the label of the drug on approval, thus potentially restricting the use and potential market for a new drug. From the perspective of a fledgling and not-yet-

¹⁴⁶ This figure is an estimate obtained from PTC's application to the FDA for Orphan Drug Status for PTC124, as quoted in documents filed in *Gunvalson v PTC*.

¹⁴⁷ On the politics and market-based logic of treatment naïveté in clinical trials, see Petryna (2009).

¹⁴⁸ Whether this fear is justified is questionable. There appear to be no cases in which a drug's approval has been jeopardized due to its being offered under expanded access (Usdin 2014).

profitable biopharmaceutical company, an expanded access program could be viewed as potentially jeopardizing its ability to obtain approval of the drug and thus to generate a return for its investors. Such a move could risk hundreds of millions of invested capital, and in the event of a significant adverse event, potentially result in no one receiving the treatment at all. The matter was no doubt complicated by Genzyme's announcement in 2011 that it was terminating its partnership with PTC Therapeutics and withdrawing from co-development of ataluren (McBride 2011), after having invested \$100 million dollars in the collaboration.¹⁴⁹ PTC Therapeutics' financial viability and its obligations to shareholders were also likely factors in how the company's officers assessed their options and their reluctance to offer expanded access before determining their next steps.

To parents who believed strongly that a drug may cure their son's fatal disease, such considerations seemed exasperatingly trivial in comparison. As a group, parents generally disagreed with the Data Monitoring Committee's recommendation that the extension trial be discontinued because the research posed an undue risk, given that the children were all receiving the high dose. In its reasoning, the Committee cited the fact that patients in the trial would have to forego other trial opportunities with no compensatory benefit, a calculus it deemed ethically problematic. However, many parents wondered what alternative opportunities there existed to forego, since there were no comparable trials in which to participate at the time. Others asked why the dose could not simply be lowered—a seemingly straightforward solution. The company responded that lowering the dose would require it to initiate a new clinical trial, including seeking regulatory authorization in 11 countries and IRB approval from 37 trial sites. Such a

¹⁴⁹ This decision was reported to be a made in conjunction with a wider review of Genzyme's business strategy conducted in the wake of its takeover by pharmaceutical giant Sanofi (McBride 2011).

trial would have to be designed from the ground-up, the company argued, consuming limited resources and likely increasing rather than lessening the time before it could determine its next steps. As to the cost involved, many parents suggested that they would be prepared to pay “whatever it took” to obtain the drug for their children, if only the company would provide it. Whether such claims were tenable was uncertain; the cost of manufacturing the drug and its anticipated market price have not been publicly disclosed, but like other rare disease drugs, its final cost is expected to be in the hundreds of thousands of dollars per patient per year (if approved).¹⁵⁰

Eventually, PTC Therapeutics *did* provide access to the drug to patients who had participated in its earlier clinical studies by initiating a separate clinical trial in Canada, the United States and eight other countries in 2012, a trial that is ongoing with around 96 patients currently enrolled.¹⁵¹ However, as the company completed its analysis of the Phase 2b trial data in the absence of an expanded access option that it felt could protect its interests and viability, parents were forced to endure a period of waiting without access to a medication whose efficacy had not yet been firmly established or refuted, and which many felt was beneficial to their children. For parents in the original Phase 2a and 2b trials, this wait would eventually stretch nearly two years (and for those unable to participate in clinical research, the wait is still ongoing). By all accounts, the period was difficult for families in the present study. Andrew and Gina Naicker related in a phone conversation that they continued to provide “the drug” to their 10 year-old son Griffin during this time, replacing it with Boost meal-replacement and telling him that the company had changed the formulation. “I simply can’t bear to break the news to

¹⁵⁰ On this point, see McGuire (2011).

¹⁵¹ In itself, this was a remarkable achievement for a company of its size without a larger pharmaceutical partner. The figure of 96 patients is obtained from the trial’s listing on <http://www.clinicaltrials.gov>.

him,” Gina explained, having seen improvements in his strength and cognitive function while in both the placebo-controlled and extension trials which they attributed to the drug. “He’s happy now,” she related through tears, “but I just don’t know what to tell him.” Other families also related stories of anguish at how to communicate the trial’s suspension and eventual termination to their children. I observed that families were less forthcoming in speaking about their experiences, as they grieved the potential loss not only of one experimental treatment, but also of the very notion of therapeutic possibility that ataluren represented.

During the intervening period, many of the children who participated in the initial trials would come off their feet and enter a wheelchair, while the company worked feverishly (by all accounts) to determine a course of action it could deliver upon. In a tense and emotional meeting between parents and company representatives that I attended as an observer, Pat Furlong (the leader of PPMD who had organized the meeting) emphasized that parents were invested in the trial not only as participants, but also “having invested their hearts in it too.” There has been such delay, she said, and it is heartbreaking and difficult for parents to see their boys decline knowing that there is something available that might help them. One father explained to company representatives that his son’s heart function (measured by ejection fraction, or how much blood the heart is pumping) had declined by 20% since discontinuing the drug a few months prior. He attributed this deterioration to stopping the drug, since his son’s heart function had been stable for the previous year while on it. Another father explained how he had to add more rubber bands to the assistive apparatus he had built to help his teenage son hold his arms up to feed himself, having recently lost the ability to eat independently. “Every month I add another rubber band,” the father explained to the group, gasping with frustration and emotion as tears ran down his beard. “That is how I’m measuring his decline.”

Another mother related to me that she did not understand why her son's decline was not treated as an "urgent" problem. "It's not just urgent," she said, "it's an emergency because he is getting worse each day, and that is strength and function that our son will not get back." It's interesting, she pointed out wryly, that a public health and drug regulatory apparatus was able to ramp up production of the swine flu vaccine and get it approved quickly in the face of an impending H1N1 crisis, but that in the case of her own personal public health crisis—that of her son—"the FDA is so utterly slow." Surprised at the muted public reaction of other parents' in the trial, this mother wondered whether this was a situation where "we need to be pushing, and not accepting—to be standing up for ourselves," she said, "but parents are already so depressed and worn out."¹⁵² More recently, a vocal patient advocacy movement has emerged demanding access to other investigational drugs that are perceived by parents (and many clinicians) to show benefit for DMD patients, but which face regulatory hurdles in demonstrating their efficacy through controlled clinical trials.¹⁵³

At the time of this writing, PTC Therapeutics has presented results from its extensive post-hoc analysis of data from the Phase 2b trial. The company argues that these data

¹⁵² These accounts are taken from my fieldnotes. I was also surprised at the restrained response by parents in public fora and online. It appeared that parents, finding themselves in a difficult position, were reluctant to "rock the boat." Some contemplated going public with their stories, but were cognizant that doing so might damage their relationship with the company in possession of a potentially useful treatment for their sons, and distract it from the work required to "move the drug forward." Many also seemed to appreciate that PTC was itself in a difficult position. Expressions of gratitude for the work the company had done, and hopeful wishes that they would continue their efforts to bring the drug to market for Duchenne patients, sat awkwardly beside parents' anxiety about how to best advocate on behalf of their child. Publically, at least, many parents expressed their faith that the company would do its best to plot a path forward. And yet, concern that PTC would, either by choice or by necessity, abandon its DMD program, were palpable. The situation reflected the multilayered tensions in rare disease parents' relationships with biopharma.

¹⁵³ Among many examples of such advocacy, with relation to Duchenne specifically see Seckler (2014); Jett Foundation (2014); TheRacetoYes.Org (2014). In relation to other diseases, see FasterCures (2014); Canadian Organization for Rare Disorders [CORD] (2013); Cinderella Therapeutics (2014). Presently "Right to Try" legislation mandating the provision of unapproved investigational drugs to seriously ill patients is being contemplated in several state legislatures in the United States. With regard to these lobbying efforts, see Servick (2014).

demonstrate that in fact ataluren *did* benefit those in the low-dose group, with a “refined” post-hoc analysis indicating that the low-dose group declined by 31.3 metres less than those on placebo, a finding that approaches conventional levels of statistical significance ($p = 0.0561$) (PTC Therapeutics Inc. 2014). The company has also presented post hoc analyses indicating that children in subgroups indicative of decline (i.e. those whose growth and development has slowed as the disease pathology begins to intensify) experience a much more substantial improvement in their 6MWD over those on placebo (a decline of 50 metres less than placebo for those in a “decline subgroup” and 68.2 metres less for those whose baseline 6MWD was <350 metres [a cutoff indicator of disease progression]) (ibid.). In various forums, they have also presented results suggesting the drug slowed the progression of the disease on a measure called “time to persistent 10% worsening,” and on a range of other secondary outcome measures and timed-function tests (Finkel et al. 2010). To the disappointment of many parents, the results of muscle biopsies taken during the trial have not been presented, and the company has disclosed that the majority of the samples were compromised as a result of variability in excision, storage, and shipping techniques (PTC Therapeutics Inc. 2013:99). As this dissertation goes to press, the company has just published the results of the Phase 2b trial in a peer-reviewed journal, arguing that its post-hoc analyses of the trial data support the drug’s efficacy (Bushby et al. 2014).

Indeed, those who believe in the drug’s efficacy have reason to be optimistic. PTC Therapeutics recently applied for a conditional marketing authorization with the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency—an approval pathway for promising drugs to treat serious diseases where no alternative treatment exists. After initially being rejected, the company announced on May 23, 2014 that an appeal of this decision had been successful, and approval to market ataluren in Europe (where it will be known

under its brand name Translarna) will soon be granted (Garde 2014). At the same time, the company has not been successful in convincing the United States Food and Drug Administration—whose review criteria and pathway for accelerated approval are more stringent—to allow it to file a New Drug Application (NDA) for approval on the basis of its Phase 2b trial results. Hoping to obtain more data demonstrating the efficacy of its drug, PTC has initiated a Phase 3 clinical trial at 58 sites in North America, South America, Europe, Israel, Asia and Australia, which it expects to complete in 2015. The implications of having the drug approved in Europe but not elsewhere in a globalized patient community with few alternatives for treatment are yet to be determined. The company has also not yet announced pricing, though its Chief Medical Officer recently claimed that the cost would be comparable to other drugs for orphan indications currently in the marketplace (i.e. in the hundreds of thousands of dollars per patient per year) (PTC Therapeutics Inc. 2014).

7.4 Conclusion

In this chapter I elaborated the outcome of the ataluren trials and how both the patient community and the company responded to a complex and rapidly changing set of circumstances. The stoppage of the trials was largely unexpected by families enrolled in them, suggesting that many parents were not aware of this possibility despite it having been explained to them in informed consent documents. It was apparent that many participants in the trials had come to expect therapeutic benefit even though the families understood that the reason for carrying out the study is to determine whether a new treatment is effective or not. The stoppage of the trials revealed how despite the best efforts of the professionals involved, in the end the boundary between treatment and research had very little meaning “on-the-ground.” It had been blurred not

only for patients, but also for physicians, research co-ordinators, company personnel, and anthropologists as well, many of whom described having become emotionally invested in the drug's success. As several neurologists remarked to me in the course of my research—and as the outcome of the trials described above demonstrates—informed consent is but a lofty ideal in the setting of lethal pediatric disease, where parents enter an unfamiliar, highly technical sphere in which emotions and hopes simmer and expectations are often unrealistic. While attention in the wake of the trials' suspension was focused on the topic of missed *statistical* significance, the events generated such profound disappointment within the Duchenne community that it was apparent the drug had attained a certain affective significance as well. Today, the trials are viewed in retrospect as but one step in a long and protracted development programme that is still ongoing. But at the time they symbolized much more, as they had come to represent the very possibility that this intractable disease could be modified by treatment and science—that an alternate future was possible.

Chapter 8: Conclusion to the Dissertation

I began the dissertation with a description of Paul Cassels piggybacking his 16 year-old son Jesse through a clinical trial study visit. Paul and Jesse had flown halfway across the country to participate in the ataluren trials many times during the previous nine months—a herculean feat in itself given his mobility limitations (Paul described having to enlist the pilots and luggage handlers to help him carry Jesse onto the plane). As a research subject, during each visit Jesse underwent numerous medical procedures over two days in hospital, including serial blood draws, urine analyses, physical therapy evaluations, a total of four surgical muscle biopsies, and (in a separate study) numerous MRIs. When the hospital nurses could not find a vein in Jesse’s arm to draw blood, I watched as the hospital’s vascular access team attended him with a needle and portable ultrasound machine, and began sticking him multiple times in his arm in an effort to find a viable vein.¹⁵⁴ “Sometimes they have to dig around a bit, and he’s been a bit of a pin cushion,” his father remarked. This was a regular occurrence as part of the study because the muscle supporting Jesse’s vasculature had deteriorated over the past three years, leaving scar tissue and fat in its place. As Jesse winced in pain with a team of nurses hovering over him, he spoke about his desire to contribute to a research project he saw as bigger than himself. “All of this will be worth it,” he said, “if it can help people who come after me. But it’s not a lot of fun.” His father had lost count of the number of blood draws Jesse had undergone, but surely he had given litres of his serum to the study.

¹⁵⁴ The vascular access team is a specialized team of nurses who handle difficult vascular procedures such as blood draws and IV placements. In addition to specialized training, they also have access to additional tools such as ultrasound for placing vascular lines.

When recalling it later, I realized the moment provided another metaphoric encapsulation of broader themes in this dissertation. As a drug development project for rare diseases rapidly gathers steam, researchers are “poking around” the bodies of children and teens, in an effort to identify and measure the efficacy of new compounds—to translate this knowledge into the clinic. They do so, in my experience, with largely noble but multi-layered intentions, and to be sure, within a market-based system that has historically privileged the interests of capital over patients (Hayden 2007; Dumit 2012; Petryna 2009; Rajan 2010b). But they are also constrained by the imperfection of the tools used to carry out clinical research with rare disease populations and the novelty of their use in this setting. Drug developers, advocates, regulators, and physicians are all feeling their way along as they proceed through unmarked biotechnical terrain. There are blurry pictures—images to guide clinical investigation (a previous natural history study here, a drug approved in similar conditions for a different disorder there)—but the dystrophic body, as it does for the nurses, presents a specialized set of challenges that can be difficult to overcome and involve extensive trial and error.

My goal in this thesis has been to contribute to deeper ethnographic understanding of patient-families’ stakes in this arena, the social and cultural currents that run through it, and the stories parents tell about their experiences within it. I have argued that closer attention to the narratives of parents—by collecting them alongside the formalized measures of the clinical trial, and by actively seeking the input and perspectives of patient-families outside of it—can offer insight that can help contextualize and personalise clinical research for rare diseases.

With this in mind, I elaborated the actors and methodological dimensions of the project in Chapter 2, and set out in Chapter 3 to examine the background illness experience in which families’ participation in clinical research is situated. Focusing on but a few aspects of the much

broader biographical disruption that such a diagnosis entails, I introduced the concept of “Stories of Waiting,” which I suggested are told by parents and can be used as an heuristic framework in other diseases to illuminate the context of their desire and hopefulness for science. I showed how these stories describe the often destructive impact of such waiting on family life, by examining the case of Garrett Petersen, and I suggested that they are likely to have important implications for how parents approach clinical research and make sense of their experiences within it. In order to make sense of the developmental context in which parents’ illness experiences are embedded, I introduced the notions of “Lost Milestones” and “Reversed Teleology.” Viewing parents’ narratives within this framework reveals how families are not only experiencing the loss of developmental milestones as a child progresses with Duchenne, but also an inversion of the very trajectory upon which family life is “supposed” to unfold, and which anchors notions of both personhood and good parenthood in North American popular culture. Lastly, I explored the scaffolds of “Duchenne as Culture,” examining how the emergence of a strong advocacy community of practice—and with it, a shared cultural orientation toward the disease—has both enhanced the resiliency of affected families in the community, and created its own dilemmas around the limits of parenthood in a globalized era of transnational health care. The rapidly expanding application of gene-based approaches to understanding and treating DMD, I suggested, has led to the emergence of Lucky Mutations and new biosocial contours within the patient community. In so doing, the recent biopharmaceutical focus on Duchenne has altered the illness experience by creating hope for treatment that is at present inequitably distributed among families, depending on the particular business case and scientific hurdles of each of the various genotypic mutations. Genomics has also created not

only new biosocial connections between families, but also fissures and divisions within the patient-advocacy movement.

In Chapter 4, I suggested that a more nuanced focus on the paths parents take to the clinical trial (and by extension the ways that parents make decisions about participation in it, a topic I plan to take up in later publications), can help to restore our attention to the idiosyncrasy of parents' illness experiences prior to the trial, the knowledge and experience they bring to it, and the various stakes they have invested in it. In this regard, I elaborated a typology of three archetypal "types" of parents that I encountered during my research by examining three case studies in depth—the Connected, Semi-Connected, and Actively Unconnected Parent, and the different pathways these families took to the trial. I pointed out that accounting for parents' illness experiences prior to the trial is important because, like the narratives of waiting they tell, these experiences undergird the social context in which parents interpret their experiences and perceptions of efficacy while participating in research, and yet their significance is often overlooked in clinical trials that take equivalence and comparability between cases for granted. I also suggested that discussion of parents' paths to the trial can serve to highlight inequities in the distribution of opportunities to participate in clinical research, and thus in opportunities to access promising new therapies.

In Chapters 5 and 6, I took up parents' experience in the trial and pointed to the ways they navigate its uncertainty. In examining this experience, I used Van Gennep's concept of liminality to explore how the trial unsettles taken-for-granted social roles, as parents find themselves uncertain of the parameters of their new hybrid role as caregivers, patients, and research subjects. Parents must adjust to new methods of keeping time, adapt to the rhythms of the trial protocol, and incorporate the routines of study and laboratory visits into their lives, all

while living on the edge of uncertainty as to whether their child will be safe on the drug and able to continue in the trial. For parents and clinicians alike, the trial truncates and constrains the clinical relationship, as site-investigators and research personnel attempt to maintain the integrity of the trial and avoid inducing placebo response, and parents seek information during a “blackout period” in which communication and therapeutic emplotment are constrained.

It is in this setting that parents construct their “Narratives of Efficacy,” a concept I introduced and elaborated in Chapter 6. There, I presented three cases to explore how parents developed their own sense of whether the study drug they were administering to their children was having any effect. They do this, I argued, by cobbling their own observations of their child’s strength, function, and behaviour in everyday life, and incorporating the observations of others. These narratives are important, I suggested, because they provide insight into the relationship between parents hopes and expectations for an investigational therapy and their perceptions of its efficacy. They also contain information about how a treatment affects family life, extending our ability to understand the nuanced and personalised ways that quality-of-life may be enhanced by an effective treatment and/or constrained by its absence. Finally, I suggested that parents’ narratives of efficacy offer a window for exploring what constitutes an acceptable treatment response in return for the tradeoffs of participating in research—a matter which is inescapably connected to their individual circumstances. Understanding parents’ narratives of efficacy can assist us to learn more about how they approach questions of risk/benefit and make decisions about treatment (a question of immediate importance to regulators, patients and drug discoverers alike [Peay et al. 2014a; Daugherty et al. 2014; FDA Center for Drug Evaluation and Research 2014b; PPMD 2014a]). They may also extend our evaluation of potential treatment effects to domains that might not be anticipated, including their

impact on notions of identity and on caregivers' wellbeing, and aid in the development of new outcome measures. I have sought to provide examples of how such narratives can be collected and used, the richness of the information they contain, and their range of content. But I have also pointed to some of their limitations, suggesting that narratives are inherently partial and grounded in individualized accounts of reality, and that parents' accounts do not obviate the need for standardized, controlled methods to quantify and assess efficacy.

A few limitations of the present study are worth noting. First, this study was limited to Canadian and American families, most of whom were pursuing or taking investigational treatments for DMD (mainly ataluren). As I discussed earlier, the experience of these parents likely differs substantially from those unable to access the highly-resourced neurological settings in which clinical trials for Duchenne occur. Restricting the study to North America also means that even within the multi-sited Phase 2b trial itself, the experiences of families attending sites in Europe and Australia likely varied due to differences in culture, health policy, and medical practice. As I mention in Chapters 3 and 4, I have also not explored in depth the experiences of families unable to participate in this type of clinical research, including those with mutations for which a gene-specific therapy has not yet been clinically tested, those who are unable to complete the outcome measures currently used in trials for DMD (such as the 6MWT), or those who otherwise do not meet the eligibility criteria for trial participation. The experiences and perspectives of such families is in urgent need of attention. Lastly, as discussed in Chapter 2, this study's focus on the experiences of patient-families means that the perspectives of other actors—including drug development professionals, research personnel, and site-investigators—are not fulsomely represented in the dissertation, and are thus worthwhile avenues for further ethnographic inquiry.

The findings of the dissertation suggest several theoretical and practical trajectories for further research, especially as many of the processes currently occurring in DMD are also taking place (or can be anticipated to take place) in other rare diseases and cancers. Theoretically, my thesis addresses questions about the nature of biosociality and presents some of the first evidence of the impact of genomics and the market dynamics of personalised medicine on biosociality within a clinically defined community. This finding has important theoretical implications by pointing to the need to broaden our perspective on what aspects of “bio” shape biosociality, as I discussed in Chapter 3. As genomic science rapidly expands the multiple ways in which genetic mutations and mechanisms may be therapeutic targets, we might ask in future research how such targeting not only arrays different relationships within patient communities, and also creates new forms of identification that commingle with already-existing social contours, allegiances, and relationships of support. Further ethnography might also address how the shifting relevance of these forms of biological differentiation within patient communities affects the group as a whole after a trial concludes. As scientific, market, and regulatory forces stratify patient communities by distributing eligibility for trials unevenly, what happens to these communities—from which parents derive much of their support—when such trials fail (as some inevitably will), and social divisions persist? In a disease with such a high emotional burden, the inequitable distribution of therapeutic possibility can weigh heavily on relationships of support for both “lucky” trial participants and those without access to such opportunities. These issues are likely to be further compounded by the high (and likely unsustainable) costs of drugs for orphan diseases and inconsistencies in decisionmaking by insurance payors, which are already creating both global and intra-national disparities in access to promising new treatments (e.g. Iskrov and Stefanov 2014; Biehl and Petryna 2011; see also Biehl 2007).

I have shown how the social context in which clinical research is conducted is of considerable importance, but is often overlooked and elided from the planning and execution of clinical trials, and in the dissemination of trial results. In pointing to the challenges of developing, validating, and employing outcome measures in rare disease and the ways that these outcome measures may miss key aspects of the qualitative changes in families' experiences, this ethnography lends support to demands to expand the use of innovative approaches for evaluating the safety and efficacy of investigational medicines, including the use of patient-centred outcome measures, patient-registry data, and qualitative research (e.g. FasterCures 2014; Rapport et al. 2013). Practically, I hope to have demonstrated with this thesis that patients' and caregivers' narratives are worth collecting, analysing, and understanding if we are to create an environment for drug development that better accounts for their perspectives and experiences. Qualitative research can supplement, contextualize, and fill gaps in understanding created by near-exclusive reliance on quantitative measures used in clinical research.

I have also examined the liminality created for boys, families, and clinicians during the clinical trial. The conditions of the trial create precarious emotional, social, and clinical situations for the participants and clinicians. We might note the need for enhancing the emotional and psychological support of parents navigating a difficult illness experience, both within the setting of the clinical trial and beyond it. In relating their experiences, parents and neurologists referred frequently to a shortage of professional help for parents in coping with their child's diagnosis, managing its impact on their lives, responding to the burden of care it creates, and dealing with its impact on siblings (Bluebond-Langner 1996). Within the trial itself, parents described experiencing significant anxiety related to the liminal nature of their experience and to a lack of information and support with which to make sense of their observations. In some cases,

the trial sponsor's requirement that parents not discuss their experience in the trial with others, combined with the burden on friendships between "lucky trial participants" and families without such opportunities described earlier, led to feelings of social isolation and loneliness during a period of extreme stress. Ironically, this occurs at precisely the moment when parents are undergoing a profoundly difficult experience as research subjects, by literally offering their children to science for experimental research. Trial sponsors seeking to improve research subjects' experiences in their trials (and thus to enhance recruitment and retention), may wish to consider how support for parents' emotional needs within the trial could be improved. Such initiatives might include written information and/or orally presented material about the common issues faced by parents in the trial and how to cope with them, the provision of counselling support, and educational initiatives to prepare and "train" parents in their approach to the trial. The outcome of the ataluren trials and the devastating effect of their closure—both on parents in the trial and the wider Duchenne community—demonstrate a need for more careful thinking about how families might be better prepared for this potential outcome and how they might be supported after a trial ends with disappointing results. These efforts are notably lacking in high-stakes clinical research and yet the accounts of parents point to both a need for them and their potential utility.

Finally, I hope this dissertation will contribute to debates about the stakes patients have in clinical research for serious and rare diseases, and to greater recognition of their labours and sacrifices in producing scientific knowledge (Cooper and Waldby 2014). Trial sponsors, clinical investigators and patient-families all agree, by and large, on the objective of the therapeutic enterprise—that is, they share a common desire to produce new treatments in a space where they are seen as desperately lacking. Each set of actors has different stakes in the game (among them,

a child's survival and quality of life, concern for one's patients, academic prestige, return on investment), but the clinical trial functions in part to align the interests of these diverse groups toward achieving a mutual goal—market approval for a treatment that works. Such utopian narratives of parental and industry co-operation in drug development circulate within the clinical trial itself, in patient-advocacy literature and discourse, and in parents' descriptions of their labours as both creators and participators in clinical research.

And yet as this dissertation shows, things are much more complicated and dynamic. In reality, the various actors have different interests and objectives, and approach the trial with different cultural backgrounds, knowledge sets, and prior experience. Despite their prominence in discourse and advocacy, patients and families remain secondary actors in an industry-centred drug-development paradigm that often privileges the needs of capital over the needs of patients. Decisions about which treatments to pursue and advance through preclinical and clinical testing, how to measure their effects, whether and how to bring them to market, and what to charge for them are still made with little or no input from patients despite their tremendous stake in their outcome (Bartfai and Lees 2013). Efforts to engage patients in research and to account for their preferences are presently a “hot topic” in both industry and regulatory circles, and there is emerging consensus that if we are to improve both health care delivery and investigational research, we must do a better job of incorporating patients' views and priorities. It is my hope that this ethnography will serve as an example of one way among many to develop our understanding of the everyday significance of therapeutic research in patients' lives, and the depth of their contributions to it.

References

Abadie, Roberto

2010 *The Professional Guinea Pig: Big Pharma and the Risky World of Human Subjects*. Durham, NC: Duke University Press.

Abbott, David, John Carpenter, and Kate Bushby

2012 Transition to Adulthood for Young Men with Duchenne Muscular Dystrophy: Research from the UK. *Neuromuscular Disorders* 22(5): 445–446.

Abelson, Reed

2008 Advocating a Treatment, but Denied Access to It. *The New York Times*, July 17. <http://www.nytimes.com/2008/07/17/business/17dystrophy.html>, accessed December 14, 2013.

Agarwal, Gina, and Valorie A. Crooks

2008 The Nature of Informational Continuity of Care in General Practice. *British Journal of General Practice* 58(556): e17–e24.

Anand, Geeta

2006 *The Cure: How a Father Raised \$100 Million – and Bucked the Medical Establishment – in a Quest to Save His Children*. New York: Regan Books.

Anderson, Bo

1970 Book Review: *The Ritual Process*. By Victor W. Turner. *Acta Sociologica* 13(4): 281.

Anderson, J. L., S. I. Head, C. Rae, and J. W. Morley

2002 Brain Function in Duchenne Muscular Dystrophy. *Brain* 125(1): 4–13.

Angell, Marcia

2005 *The Truth About The Drug Companies: How They Deceive Us And What To Do About It*. New York: Random House LLC.

Angelmar, Reinhard, and Philip C. Berman

2007 Patient Empowerment and Efficient Health Outcomes. *Financing Sustainable Healthcare in Europe: New Approaches for New Outcomes*. http://elibrary.zdrave.net/document/EU/Commission%20of%20the%20EC/eure324972771_en.pdf#page=139, accessed February 4, 2014.

Anonymous Parent

2013 My BRAVE Story: The Concept of Risk vs. Reward Has Changed for Me. PPMD Community Blog. <http://community.parentprojectmd.org/profiles/blogs/my-brave-story-the-concept-of-risk-vs-reward-has-changed-for-me>, accessed December 30, 2013.

- Appadurai, Arjun
1986 *The Social Life of Things: Commodities in Cultural Perspective*. Cambridge
Cambridge University Press.
- Appelbaum, Paul S., Charles W. Lidz, and Thomas Grisso
2004 Therapeutic Misconception in Clinical Research: Frequency and Risk Factors. *IRB:
Ethics & Human Research* 26(2): 1–8.
- Appelbaum, Paul S., Charles W. Lidz, and Alan Meisel
1987 Informed Consent: Legal Theory and Clinical Practice.
http://escholarship.umassmed.edu/psych_cmhsr/119/, accessed July 10, 2014.
- Appelbaum, PS, LH Roth, DW Lidz, P Benson, and W Winslade
1987 False Hopes and Best Data: Consent to Research and the Therapeutic Misconception.
Hastings Center Report 17(2): 20–4.
- Applbaum, Kalman
2006 Pharmaceutical Marketing and the Invention of the Medical Consumer. *PLoS Medicine*
3(4): e189.
- Aronson, JK
2006 Rare Diseases and Orphan Drugs. *British Journal of Clinical Pharmacology* 61(3):
243–245.
- Auld, Douglas S., Scott Lovell, Natasha Thorne, et al.
2010 Molecular Basis for the High-Affinity Binding and Stabilization of Firefly Luciferase by
PTC124. *Proceedings of the National Academy of Sciences* 107(11): 4878–4883.
- Auld, Douglas S., Natasha Thorne, William F. Maguire, and James Inglese
2009 Mechanism of PTC124 Activity in Cell-Based Luciferase Assays of Nonsense Codon
Suppression. *Proceedings of the National Academy of Sciences* 106(9): 3585–3590.
- Aymé, Ségolène, Anna Kole, and Stephen Groft
2008 Empowerment of Patients: Lessons from the Rare Diseases Community. *The Lancet*
371(9629): 2048–2051.
- Balasegaram, Manica
2014 Drugs for the Poor, Drugs for the Rich—why the Current Research and Development
Model Doesn’t Deliver. *BMJ*. [http://blogs.bmj.com/bmj/2014/02/13/manica-balasegaram-
drugs-for-the-poor-drugs-for-the-rich-why-the-current-research-and-development-model-
doesnt-deliver](http://blogs.bmj.com/bmj/2014/02/13/manica-balasegaram-drugs-for-the-poor-drugs-for-the-rich-why-the-current-research-and-development-model-doesnt-deliver), accessed February 17, 2014.
- Barbot, Janine
2006 How to Build an “Active” Patient? The Work of AIDS Associations in France. *Social
Science & Medicine* 62(3): 538–551.

- Bartfai, Tamas, and Graham V. Lees
2013 *The Future of Drug Discovery: Who Decides Which Diseases to Treat?* Academic Press.
- Becker, Gaylene
1997 *Disrupted Lives: How People Create Meaning in a Chaotic World*. Berkeley: University of California Press.
- Beck, U.
1999 *Risk World Society*. Cambridge: Polity Press.
- Beekman, C., J. Testerink, S. Giannakopoulos, et al.
2013 P.13.12 An Objective Method for Immunofluorescence Analysis of Dystrophin Levels in Muscle from DMD Patients in Clinical Studies. *Neuromuscular Disorders* 23(9–10): 812.
- Beeson, Diane
1997 Nuance, Complexity, and Context: Qualitative Methods in Genetic Counseling Research. *Journal of Genetic Counselling* 6(1): 21–43.
- Behar, Ruth, and Deborah A. Gordon
1995 *Women Writing Culture*. Berkeley: University of California Press.
- Bell, Catherine
1992 *Ritual Theory, Ritual Practice*. Oxford: Oxford University Press.
- Bernard, H. Russell
2006 *Research Methods in Anthropology: Qualitative and Quantitative Approaches*. Lanham, MD: Altamira Press.
- Bharadwaj, Aditya
2012 Enculturating Cells: The Anthropology, Substance, and Science of Stem Cells. *Annual Review of Anthropology* 41(1): 303–317.
2014 Experimental Subjectification: The Pursuit of Human Embryonic Stem Cells in India. *Ethnos* 79(1): 84–107.
- Bhatt, Dr Arun
2010 Evolution of Clinical Research: A History Before and Beyond James Lind. *Perspectives in Clinical Research* 1(1): 6.
- Bianchi, Maria Luisa, Doug Biggar, Kate Bushby, et al.
2011 Endocrine Aspects of Duchenne Muscular Dystrophy. *Neuromuscular Disorders* 21(4): 298–303.
- Biehl, João Guilherme
2007 *Will to Live: AIDS Therapies and the Politics of Survival*. Princeton: Princeton University Press.

Biehl, João, and Adriana Petryna

2011 Bodies of Rights and Therapeutic Markets. *Social Research: An International Quarterly* 78(2): 359–386.

Bish, Lawrence T., Mark Yarchoan, Meg M. Sleeper, et al.

2011 Chronic Losartan Administration Reduces Mortality and Preserves Cardiac but Not Skeletal Muscle Function in Dystrophic Mice. *PLoS ONE* 6(6): e20856.

Bluebond-Langner, Myra

1996 *In the Shadow of Illness : Parents and Siblings of the Chronically Ill Child*. Princeton: Princeton University Press.

Bodenheimer, T, K Lorig, H Holman, and K Angus

2002 Patient Self-Management of Chronic Disease in Primary Care. *JAMA: The Journal of the American Medical Association* 288(19): 2469–2475.

Boone, Philip M., Wojciech Wiszniewski, and James R. Lupski

2011 Genomic Medicine and Neurological Disease. *Human Genetics* 130(1): 103–121.

Bosk, Charles L.

2008 Irony, Ethnography, and Informed Consent. *In What Would You Do?: Juggling Bioethics and Ethnography*. Chicago: University of Chicago Press.

Boulos, Maged NK, Steve Wheeler, Carlos Tavares, and Ray Jones

2011 How Smartphones Are Changing the Face of Mobile and Participatory Healthcare: An Overview, with Example from eCAALYX. *BioMedical Engineering Online* 10(1): 24.

Bourdieu, Pierre

1984 *Distinction: A Social Critique of the Judgement of Taste*. Cambridge, MA: Harvard University Press.

Bourgois, Philippe

2003 *In Search of Respect: Selling Crack in El Barrio*. Cambridge: Cambridge University Press.

Bourgois, Philippe I., and Jeffrey Schonberg

2009 *Righteous Dopefiend*. Berkeley: University of California Press.

Bowker, Geoffrey C., and Susan Leigh Star

1999 *Sorting Things Out: Classification and Its Consequences*. Cambridge, MA: MIT Press.

Bregman, A M

1980 Living with Progressive Childhood Illness: Parental Management of Neuromuscular Disease. *Social Work in Health Care* 5(4): 387–408.

- Britton, Annie, Martin McKee, Nick Black, et al.
1999 Threats to Applicability of Randomised Trials: Exclusions and Selective Participation. *Journal of Health Services Research & Policy* 4(2): 112–121.
- Brody, H., and F. G. Miller
2011 Lessons From Recent Research About the Placebo Effect--From Art to Science. *JAMA: The Journal of the American Medical Association* 306(23): 2612–2613.
- Browner, C
2010 Neurogenetic Diagnoses: The Power of Hope and the Limits of Today's Medicine. London: Routledge.
- Brown, Ian
2011 *The Boy in the Moon: A Father's Journey to Understand His Extraordinary Son*. New York: St. Martin's Press.
- Bury, M.
1982 Chronic Illness as Biographical Disruption. *Sociology of Health and Illness* 13: 451–68.
- Bushby, Katharine, Richard Finkel, David J Birnkrant, et al.
2010a Diagnosis and Management of Duchenne Muscular Dystrophy, Part 1: Diagnosis, and Pharmacological and Psychosocial Management. *The Lancet Neurology* 9(1): 77–93.
2010b Diagnosis and Management of Duchenne Muscular Dystrophy, Part 2: Implementation of Multidisciplinary Care. *The Lancet Neurology* 9(2): 177–189.
- Bushby, Katharine, Richard Finkel, Brenda Wong, et al.
2014 Ataluren Treatment of Patients with Nonsense Mutation Dystrophinopathy. *Muscle & Nerve* 50(4): 477–487.
- Button, Katherine S., John P. A. Ioannidis, Claire Mokrysz, et al.
2013 Power Failure: Why Small Sample Size Undermines the Reliability of Neuroscience. *Nature Reviews Neuroscience* 14(5): 365–376.
- Callon, Michel
1986 Some Elements of a Sociology of Translation: Domestication of the Scallops and the Fisherman of St Brieuc Bay. In *Power, Action and Belief: A New Sociology of Knowledge?* John Law, Ronald Frankenberg, and Gordon Fyfe, eds. Pp. 196–233. *The Sociological Review*. London: Routledge & Kegan Paul.
- Callon, Michel, and Vololona Rabeharisoa
2004 Gino's Lesson on Humanity: Genetics, Mutual Entanglements and the Sociologist's Role. *Economy and Society* 33(1): 1–27.
2008 The Growing Engagement of Emergent Concerned Groups in Political and Economic Life Lessons from the French Association of Neuromuscular Disease Patients. *Science, Technology & Human Values* 33(2): 230–261.

Cameron, J.A., M.J. Bond, and S.C. Pointer

1996 Reducing the Anxiety of Children Undergoing Surgery: Parental Presence during Anaesthetic Induction. *Journal of Paediatrics and Child Health* 32(1): 51–56.

Canadian Organization for Rare Disorders [CORD]

2013. CORD Website. <http://www.raredisorders.ca>, accessed December 11, 2013.

Carroll, John

2014 The FDA vs. the Flash Mob: Hard Questions as Parents Demand Unproven Drugs. *FierceBiotech*. <http://www.fiercebiotech.com/story/fda-vs-flash-mob-hard-questions-parents-demand-unproven-drugs/2014-03-19>, accessed March 20, 2014.

CenterWatch

2001 An Industry in Evolution. Centerwatch Inc.

Centerwatch

2014 Centerwatch Website. www.centerwatch.com, accessed June 14, 2014.

Chalmers, Thomas C.

1981 The Clinical Trial. *The Milbank Memorial Fund Quarterly. Health and Society* 59(3): 324–339.

CIHR

2011 Canada's Strategy for Patient-Oriented Research - CIHR. <http://www.cihr-irsc.gc.ca/e/44000.html#a01>, accessed May 16, 2014.

Cinderella Therapeutics

2012 Cinderella Therapeutics: Ataluren Project. <http://www.cinderella-tx.org/k/en/n30773/cms/news/1238/Ataluren-project-completed.html>, accessed June 22, 2014.

2014 Cinderella Therapeutics Website. <http://cinderellatherapeutics.com/>, accessed July 9, 2011.

Clifford, James, and George E. Marcus

1986 *Writing Culture: The Poetics and Politics of Ethnography*. Berkeley: University of California Press.

ClinicalTrials.gov

2008 FAQClinicalTrials.gov - Clinical Trial Phases.

<http://www.nlm.nih.gov/services/ctphases.html>, accessed July 10, 2014.

CMAJ Editorial

2005 Vioxx: Lessons for Health Canada and the FDA. *Canadian Medical Association Journal* 172(1): 5–5.

Cohen, D., and J. Raftery

2014 Paying Twice: Questions over High Cost of Cystic Fibrosis Drug Developed with Charitable Funding. *BMJ* 348: 1445.

Collet, Jean-Paul, William McKellin, Sravan Jaggumantri, and Niranjana Kissoon

2014 Personalized Evidence of Treatment Effects for the Practice of Personalized Medicine: A New Model of Care. *BMC Health Services Research* 14(Suppl 2): P17.

Collins, Francis S.

2011 Reengineering Translational Science: The Time Is Right. *Science Translational Medicine* 3(90): 90cm17.

Collins, H. M., and Robert Evans

2002 The Third Wave of Science Studies: Studies of Expertise and Experience. *Social Studies of Science* 32(2): 235–296.

Committee on School Health

2003 Guidelines for the Administration of Medication in School. *Pediatrics* 112(3): 697–699.

Condin, Christopher J.

2005 The Changing Meaning of Gene Therapy: Exploring the Significance of Gene Therapy Research in the Narratives of Families with Duchenne Muscular Dystrophy. Master's Thesis, University of British Columbia Vancouver, Department of Anthropology.

Cook, Gareth

2004 Desperate Parents Chase a Stem-Cell Miracle - The Boston Globe. The Boston Globe. http://www.boston.com/yourlife/health/diseases/articles/2004/09/26/desperate_parents_chase_a_stem_cell_miracle/, accessed July 17, 2009.

Cooper, Melinda, and Catherine Waldby

2014 Clinical Labor: Tissue Donors and Research Subjects in the Global Bioeconomy. Durham: Duke University Press.

Cox, S.M., and W.H. McKellin

1999 There's This Thing in Our Family: Predictive Testing and the Construction of Risk for Huntington Disease. *Sociology of Health and Illness* 21(5): 622–646.

Cox, Susan M.

2003 Stories in Decisions: How At-Risk Individuals Decide to Request Predictive Testing for Huntington Disease. *Qualitative Sociology* 26(2): 257–280.

Cuccia, Justine G.

2012 Compassionate Use: Balancing Compassion and Risk in Clinical Trials. White Paper. ACE Group. http://www.acegroup.com/usen/assets/ace_compassionate_care_whitepaper.pdf, accessed October 10, 2012.

- Curry, Leslie A., Ingrid M. Nembhard, and Elizabeth H. Bradley
2009 Qualitative and Mixed Methods Provide Unique Contributions to Outcomes Research. *Circulation* 119(10): 1442–1452.
- Cyrulnik, Shana E, Robert J Fee, Abigail Batchelder, et al.
2008 Cognitive and Adaptive Deficits in Young Children with Duchenne Muscular Dystrophy (DMD). *Journal of the International Neuropsychological Society: JINS* 14(5): 853–861.
- Daugherty, Sarah E., Sarita Wahba, Rachael Fleurence, et al.
2014 Patient-Powered Research Networks: Building Capacity for Conducting Patient-Centered Clinical Outcomes Research. *Journal of the American Medical Informatics Association* 21(4):583-586
- Davis, J. Michael, and David J. Svendsgaard
1990 U-Shaped Dose-response Curves: Their Occurrence and Implications for Risk Assessment. *Journal of Toxicology and Environmental Health* 30(2): 71–83.
- Davis, Lennard J.
2006 *The Disability Studies Reader*. New York: Taylor & Francis.
- Devereux, Eoin
1996 Good Causes, God's Poor and Telethon Television. *Media, Culture & Society* 18(1): 47–68.
- Downing, NS, NJ Aminawung, ND Shah, HM Krumholz, and JS Ross
2014 Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutic Agents, 2005-2012. *JAMA: The Journal of the American Medical Association* 311(4): 368–377.
- Dubowitz, Victor
2002 Therapeutic Possibilities in Muscular Dystrophy: The Hope versus the Hype. *Neuromuscular Disorders* 12(2): 113–116.
2004 Therapeutic Efforts in Duchenne Muscular Dystrophy: The Need for a Common Language between Basic Scientists and Clinicians. *Neuromuscular Disorders* 14(8-9): 451–455.
- Dumit, Joseph
2012 *Drugs for Life: How Pharmaceutical Companies Define Our Health*. Durham: Duke University Press.
- Den Dunnen, Johan T.
2014 Leiden Muscular Dystrophy Pages. www.dmd.nl, accessed February 6, 2014.
- Eagle, Michelle, Simon V Baudouin, Colin Chandler, et al.
2002 Survival in Duchenne Muscular Dystrophy: Improvements in Life Expectancy since 1967 and the Impact of Home Nocturnal Ventilation. *Neuromuscular Disorders: NMD* 12(10):

926–929.

Ecks, Stefan

2008 Global Pharmaceutical Markets and Corporate Citizenship: The Case of Novartis' Anti-Cancer Drug Glivec. *BioSocieties* 3(2): 165–181.

Einsiedel, Edna F., and Hannah Adamson

2012 Stem Cell Tourism and Future Stem Cell Tourists: Policy and Ethical Implications. *Developing World Bioethics* 12(1): 35–44.

Ejiogu, Ngozi, Jennifer H. Norbeck, Marc A. Mason, et al.

2011 Recruitment and Retention Strategies for Minority or Poor Clinical Research Participants: Lessons From the Healthy Aging in Neighborhoods of Diversity Across the Life Span Study. *The Gerontologist* 51(suppl 1): S33–S45.

Epping-Jordan, J. E., S. D. Pruitt, R. Bengoa, and E. H. Wagner

2004 Improving the Quality of Health Care for Chronic Conditions. *Quality and Safety in Health Care* 13(4): 299–305.

Epstein, Steven

1995 The Construction of Lay Expertise: AIDS Activism and the Forging of Credibility in the Reform of Clinical Trials. *Science, Technology & Human Values* 20(4): 408–437.

1996 *Impure Science: AIDS, Activism, and the Politics of Knowledge*. Berkeley: University of California Press.

2009 *Inclusion: The Politics of Difference in Medical Research*. Chicago: University of Chicago Press.

Ernst & Young

2006 Contract Research: Contracted for Trouble? *R&D Directions* 12(5).

Etkin, Nina L.

1992 “Side Effects”: Cultural Constructions and Reinterpretations of Western Pharmaceuticals. *Medical Anthropology Quarterly* 6(2): 99–113.

Faden, Ruth R., Tom L. Beauchamp, and Nancy M. King

1986 A History and Theory of Informed Consent. <http://www.popline.org/node/354450>, accessed July 10, 2014.

Faircloth, Charlotte

2013 *Militant Lactivism?: Attachment Parenting and Intensive Motherhood in the UK and France*. Oxford: Berghahn Books.

Farmer, Paul

1999 *Infections and Inequalities*. Berkeley: University of California Press.

2004a The Anthropology of Structural Violence. *Current Anthropology* 45(3): 305–325.

2004b Rethinking Medical Ethics: A View From Below. *Developing World Bioethics* 4(1): 17–41.

2005 *Pathologies of Power: Health, Human Rights, and the New War on the Poor*. California Series in Public Anthropology. Berkeley: University of California Press.

2013 Clinical Trials and Global Health Equity. *The Lancet Global Health Blog*. <http://globalhealth.thelancet.com/2013/07/08/clinical-trials-and-global-health-equity>, accessed May 16, 2014.

FasterCures

2014 FasterCures Website. <http://www.fastercures.org/>, accessed June 26, 2014.

FDA Center for Drug Evaluation and Research

1998 Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. <http://www.fda.gov/downloads/Drugs/.../Guidances/ucm078749.pdf>, accessed March 31, 2013.

2014a Guidance for Industry: Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM381352.pdf>, accessed July 7, 2014.

2014b Prescription Drug User Fee Act (PDUFA) - Enhancing Benefit-Risk Assessment in Regulatory Decision-Making. <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>, accessed June 25, 2014.

Feero, W. Gregory, Alan E. Guttmacher, and Francis S. Collins

2010 Genomic Medicine: An Updated Primer. *New England Journal of Medicine* 362(21): 2001–2011.

Felling, Rita

2010 Behind My Smile. <http://behindmysmile-raf.blogspot.ca/2010/03/i-watched-as-some-joggers-passed-my.html>, accessed June 22, 2014.

Finkel, Richard S.

2010 Readthrough Strategies for Suppression of Nonsense Mutations in Duchenne/Becker Muscular Dystrophy: Aminoglycosides and Ataluren (PTC124). *Journal of Child Neurology* 25(9): 1158–1164.

Finkel, Richard S., Kevin M. Flanigan, Brenda Wong, et al.

2013 Phase 2a Study of Ataluren-Mediated Dystrophin Production in Patients with Nonsense Mutation Duchenne Muscular Dystrophy. *PLoS ONE* 8(12): e81302.

Finkel, R., B. Wong, K. Bushby, et al.

2010 Results of a Phase 2b, Dose-Ranging Study of Ataluren (PTC124®) in Nonsense Mutation Duchenne/Becker Muscular Dystrophy (nmDBMD). *Neuromuscular Disorders*. 20: 656.

- Finkler, Kaja, Cécile Skrzynia, and James P Evans
2003 The New Genetics and Its Consequences for Family, Kinship, Medicine and Medical Genetics. *Social Science & Medicine* 57(3): 403–412.
- Fishbane, Simcha
1995 Contemporary Bar Mitzvah Rituals in Modern Orthodoxy. *In* *Ritual and Ethnic Identity: A Comparative Study of the Social Meaning of Liturgical Ritual in Synagogues*. Jack N. Lightstone and Frederick B. Bird, eds. Pp. 155–168. Waterloo, ON: Wilfrid Laurier University Press.
- Fisher, Jill A.
2006 Co-Ordinating “Ethical” Clinical Trials: The Role of Research Coordinators in the Contract Research Industry. *Sociology of Health & Illness* 28(6): 678–694.
2008 *Medical Research for Hire: The Political Economy of Pharmaceutical Clinical Trials*. New Brunswick, N.J: Rutgers University Press.
- Flanigan, Kevin M., Ermelinda Ceco, Kay-Marie Lamar, et al.
2013 LTBP4 Genotype Predicts Age of Ambulatory Loss in Duchenne Muscular Dystrophy. *Annals of Neurology* 73(4): 481–488.
- Flanigan, Kevin M., Thomas Voit, Xiomara Q Rosales, et al.
2013 Pharmacokinetics and Safety of Single Doses of Drisapersen in Non-Ambulant Subjects with Duchenne Muscular Dystrophy: Results of a Double-Blind Randomized Clinical Trial. *Neuromuscular Disorders*. 24(1): 16–24.
- Ford, Jean G., Mollie W. Howerton, Gabriel Y. Lai, et al.
2008 Barriers to Recruiting Underrepresented Populations to Cancer Clinical Trials: A Systematic Review. *Cancer* 112(2): 228–242.
- Forrest, Christopher B., Ronald J. Bartek, Yaffa Rubinstein, and Stephen C. Groft
2011 The Case for a Global Rare-Diseases Registry. *The Lancet* 377(9771): 1057–1059.
- Foucault, Michel
1975 *The Birth of the Clinic: An Archaeology of Medical Perception*. New York: Vintage Books.
1994 *The Order of Things: An Archaeology of the Human Sciences*. New York: Vintage Books.
- Frank, Arthur W.
1995 *The Wounded Storyteller: Body, Illness, Ethics*. Chicago: Chicago University Press.
- Frankenberg, R.
1988 “Your Time or Mine?” An Anthropological View of the Tragic Temporal Contradictions of Biomedical Practice. *International Journal of Health Services: Planning, Administration, Evaluation* 18(1): 11–34.

Franklin, Sarah

1995 Science as Culture, Cultures of Science. *Annual Review of Anthropology* 24: 163–184.

Franklin, Sarah, and Celia Roberts

2006 *Born and Made : An Ethnography of Preimplantation Genetic Diagnosis*. Princeton: Princeton University Press.

Franson, T.R., and H.L. Peay

2013 Benefit-Risk Assessment in Rare Disorders: The Case for Therapeutic Development in Duchenne Muscular Dystrophy as the Prototype for New Approaches. Parent Project Muscular Dystrophy (PPMD). <http://www.parentprojectmd.org/br>, accessed February 13, 2014.

Freedman, Benjamin

1987 Equipoise and the Ethics of Clinical Research. *The New England Journal of Medicine* 317(3): 141–145.

Fujimura, Joan H.

1996 *Crafting Science : A Sociohistory of the Quest for the Genetics of Cancer*. Cambridge, Mass.: Harvard University Press.

Fuks, Abraham, Charles Weijer, Benjamin Freedman, et al.

1998 A Study in Contrasts: Eligibility Criteria in a Twenty-Year Sample of NSABP and POG Clinical Trials. *Journal of Clinical Epidemiology* 51(2): 69–79.

Furlong, Patricia

2010a The “Female” Side of Duchenne. <http://community.parentprojectmd.org/profiles/blogs/the-female-side-of-duchenne>, accessed December 18, 2013.

2010b Katrina Revisited. <http://community.parentprojectmd.org/profiles/blogs/katrina-revisited>, accessed November 25, 2011.

2013 Finger Pointing Exercise.

http://community.parentprojectmd.org/profiles/blog/show?id=1187424%3ABlogPost%3A166067&commentId=1187424%3AComment%3A166133&xg_source=activity, accessed June 13, 2013.

Garde, Damian

2014 PTC Soars as EU Changes Its Tune on the DMD-Treating Ataluren. *FierceBiotech*. <http://www.fiercebiotech.com/story/ptc-soars-eu-changes-its-tune-dmd-treating-ataluren/2014-05-23>, accessed June 25, 2014.

Garro, L.C.

1992 Chronic Illness and the Construction of Narratives. *In Pain as Human Experience: An Anthropological Perspective*. Mary-Jo DelVecchio Good, ed. Pp. 100–137. Berkeley: University of California Press.

- Garro, Linda C.
2000 Remembering What One Knows and the Construction of the Past: A Comparison of Cultural Consensus Theory and Cultural Schema Theory. *Ethos* 28(3): 275.
- Garro, Linda C., and Cheryl Mattingly
2000 Narrative as Construct and Construction. *In* Narrative and the Cultural Construction of Illness and Healing. Cheryl Mattingly and Linda C. Garro, eds. Pp. 1–49. Berkeley: University of California Press.
- Gaudine, Alice, Marilyn Sturge-Jacobs, and Mary Kennedy
2003 The Experience of Waiting and Life During Breast Cancer Follow-Up. *Research and Theory for Nursing Practice* 17(2): 153–168.
- Geertz, Clifford
1973a The Interpretation of Cultures: Selected Essays. New York: Basic Books.
1973b Thick Description: Toward an Interpretive Theory of Culture. *In* The Interpretation of Cultures: Selected Essays Pp. ix, 470. New York: Basic Books.
- Van der Geest, S., S.R. Whyte, and A. Hardon
1996 The Anthropology of Pharmaceuticals: A Biographical Approach. *Annual Review of Anthropology* 25: 153–178.
- Van Gennep, Arnold
1909 The Rites of Passage. Chicago: University of Chicago Press.
- George, S. L.
1996 Reducing Patient Eligibility Criteria in Cancer Clinical Trials. *Journal of Clinical Oncology* 14(4): 1364–1370.
- Gershon, Richard C., Nan Rothrock, Rachel Hanrahan, Michael Bass, and David Cella
2010 The Use of PROMIS and Assessment Center to Deliver Patient-Reported Outcome Measures in Clinical Research. *Journal of Applied Measurement* 11(3): 304–314.
- Giacomini, Mita K., and Deborah J. Cook
2000 Users' Guides to the Medical Literature: XXIII. Qualitative Research in Health Care A. Are the Results of the Study Valid? *JAMA: The Journal of the American Medical Association* 284(3): 357–362.
- Gibbon, Sahra, and Carlos Novas, eds.
2008 Biosocialities, Genetics and the Social Sciences: Making Biologies and Identities. London: Routledge.
- Gibbons, Michael, Camille Limoges, Helga Nowotny, et al.
1994 The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies. Beverly Hills: Sage.

- Gibson, Barbara E, Bhavnita Mistry, Brett Smith, et al.
2013 Becoming Men: Gender, Disability, and Transitioning to Adulthood. *Health* 18(1): 95–114.
- Gibson, Barbara E., Nancy L. Young, Ross E.G. Upshur, and Patricia McKeever
2007 Men on the Margin: A Bourdieusian Examination of Living into Adulthood with Muscular Dystrophy. *Social Science & Medicine* 65(3): 505–517.
- Gibson, Barbara E, Hilde Zitzelsberger, and Patricia McKeever
2009 “Futureless Persons”: Shifting Life Expectancies and the Vicissitudes of Progressive Illness. *Sociology of Health & Illness* 31(4): 554–568.
- Goffman, Erving
1963 *Stigma: Notes on the Management of Spoiled Identity*. Englewood Cliffs, N.J.: Prentice-Hall.
- Good, B.J.
1994 *Medicine Rationality and Experience*. Cambridge: Cambridge University Press.
- Good, B.J., and M.J.D.V. Good
1994 In the Subjunctive Mode: Epilepsy Narratives in Turkey. *Social Science & Medicine* 38(6): 835–42.
- Good, Mary-Jo Delvecchio, Byron J. Good, Cynthia Schaffer, and Stuart E. Lind
1990 American Oncology and the Discourse on Hope. *Culture Medicine and Psychiatry* 12: 43–63.
- Govoni, Alessandra, Francesca Magri, Simona Brajkovic, et al.
2013 Ongoing Therapeutic Trials and Outcome Measures for Duchenne Muscular Dystrophy. *Cellular and Molecular Life Sciences: CMLS* 70(23): 4585–4602.
- Grant, Adrian
2004 Stopping Clinical Trials Early. *BMJ* 329(7465): 525–526.
- Grelotti, D. J., and T. J. Kaptchuk
2011 Placebo by Proxy. *BMJ* 343(aug11 2): d4345–d4345.
- Griggs, Robert C., Mark Batshaw, Mary Dunkle, et al.
2009 Clinical Research for Rare Disease: Opportunities, Challenges, and Solutions. *Molecular Genetics and Metabolism* 96(1): 20–26.
- Guess, Harry A., Arthur Kleinman, John Kusek, and Linda Engel
2002 *The Science of the Placebo: Toward an Interdisciplinary Research Agenda*. London: BMJ Books.

Gupta, A., and J. Ferguson

1997a *Anthropological Locations: Boundaries and Grounds of a Field Science*. J. Ferguson, ed. Berkeley: University of California Press.

1997b *Discipline and Practice: "The Field" as Site, Method, and Location in Anthropology*. In *Anthropological Locations: Boundaries and Grounds of a Field Science*. A. Gupta and J. Ferguson, eds. Pp. 1–46. Berkeley: University of California Press.

Guttmacher, Alan E., and Francis S. Collins

2003 Welcome to the Genomic Era. *New England Journal of Medicine* 349(10): 996–998.

Habermas, Jürgen

1984 *The Theory of Communicative Action: Reason and the Rationalization of Society*. Boston: Beacon Press.

Hacking, Ian

1975 *The Emergence of Probability*. Cambridge: Cambridge University Press.

1990 *The Taming of Chance*, vol.17. Cambridge: Cambridge University Press.

Hallowell, N.

1999 *Doing the Right Thing: Genetic Risk and Responsibility*. In *Sociological Perspectives on the New Genetics*. P. Conrad and J. Gabe, eds. Malden, MA: Blackwell Publishers.

Hamburg, Margaret A., and Francis S. Collins

2010 The Path to Personalized Medicine. *New England Journal of Medicine* 363(4): 301–304.

Hammersley, Martyn, and Paul Atkinson

2007 *Ethnography: Principles in Practice*. New York: Routledge.

Hannerz, Ulf.

2003 Being There... and There.... and There! Reflections on Multi-Sited Ethnography. *Ethnography* 4(2): 201–216.

Harkness, Sara, Catherine Raeff, and Charles M Super

2000 *Variability in the Social Construction of the Child*. San Francisco: Jossey-Bass.

Harkness, Sara, and Charles M. Super

1996 *Parents' Cultural Belief Systems: Their Origins, Expressions, and Consequences*. New York: Guilford Press.

2006 Themes and Variations: Parental Ethnotheories in Western Cultures. In *Parenting Beliefs, Behaviors, and Parent-Child Relations: A Cross-Cultural Perspective*. Kenneth M. Rubin and Ock Boon Chung, eds. Pp. 61–79. New York: Taylor & Francis.

Hayden, Cori

2007 Taking as Giving Bioscience, Exchange, and the Politics of Benefit-Sharing. *Social Studies of Science* 37(5): 729–758.

Hays, Sharon

1996 *The Cultural Contradictions of Motherhood*. New Haven: Yale University Press.

Health Canada

2012 *Health Products and Food Regulatory Modernization* - Health Canada.

<http://www.hc-sc.gc.ca/ahc-asc/activit/strateg/mod/index-eng.php>, accessed May 16, 2014.

Heath, Deborah, Rayna Rapp, and Karen-Sue Taussig

2004 *Genetic Citizenship. In A Companion to the Anthropology of Politics*. David Nugent and Joan Vincent, eds. New York: Blackwell Publishing.

Hedgecoe, Adam

2004 *The Politics of Personalised Medicine : Pharmacogenetics in the Clinic*. Cambridge: Cambridge University Press.

Henderson, G. E., L. R. Churchill, A. M. Davis, et al.

2007 *Clinical Trials and Medical Care: Defining the Therapeutic Misconception*. *PLoS Medicine* 4(11): 1735–1738.

Henricson, Erik, Richard Abresch, Jay J. Han, et al.

2012 *Percent-Predicted 6-Minute Walk Distance in Duchenne Muscular Dystrophy to Account for Maturation Influences*. *PLoS Currents* 4: RRN1297.

Herper, Matthew

2007 *Stopping the Nonsense*. *Forbes*, August 31.

<http://www.forbes.com/forbes/2007/0917/072.html>, accessed December 14, 2013.

Hoffman, Eric P., and Edward M. Connor

2013 *Orphan Drug Development in Muscular Dystrophy: Update on Two Large Clinical Trials of Dystrophin Rescue Therapies*. *Discovery Medicine* 16(89): 233–239.

Hoffmaster, B.

1992 *Can Ethnography Save the Life of Medical Ethics?* *Social Science & Medicine* 35(12): 1421–1431.

Houyez, François, Chantal Bélorgey, Arielle North, Etelka Czondi, and Michele Lipucci di Paola

2012 *Compassionate Use Programmes for Rare Diseases: Proposals for Actions*. *Orphanet Journal of Rare Diseases* 7(Suppl 2): A28.

Hughes, Virginia

2010 *When Patients March in*. *Nature Biotechnology* 28(11): 1145–1148.

Hunt, Linda M.

2000 *Strategic Suffering: Illness Narratives as Social Empowerment Among Mexican Cancer Patients. In Narrative and the Cultural Construction of Illness*. Cheryl Mattingly and Linda C.

- Garro, eds. Pp. 88–107. Berkeley: University of California Press.
- Hyden, Lars-Christer
1997 Illness and Narrative. *Sociology of Health & Illness* 19(1): 48–69.
- ICH Harmonised Tripartite Committee
1996 Guideline on Good Clinical Practice E6(R1). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf, accessed December 6, 2013.
- Ingstad, Benedicte, and Susan Reynolds Whyte
1995 Disability and Culture. Berkeley: University of California Press.
- Interagency Advisory Panel on Research Ethics
2010 TCPS 2—2nd Edition of Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. <http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/>, accessed March 19, 2014.
- Ioannidis, John P. A.
2005 Why Most Published Research Findings Are False. *PLoS Med* 2(8): e124.
- Iskrov, Georgi, and Rumen Stefanov
2014 Post-Marketing Access to Orphan Drugs: A Critical Analysis of Health Technology Assessment and Reimbursement Decision-Making Considerations. *Orphan Drugs: Research and Reviews*: 1.
- Jadad, Alejandro R., and Murray W. Enkin
2008 Bias in Randomized Controlled Trials. *In* *Randomized Controlled Trials: Questions, Answers and Musings* Pp. 29–47. Hoboken, NJ: John Wiley & Sons.
- Jett Foundation
2014 The Jett Foundation Website. <http://jettfoundation.org/>, accessed June 26, 2014.
- Johnson, Mary
2000 The “Care” Juggernaut. *The Ragged Edge*.
<http://www.raggededgemagazine.com/1100/1100aft1.htm>, accessed July 16, 2014
- Kamangar, Farin, Graça M. Dores, and William F. Anderson
2006 Patterns of Cancer Incidence, Mortality, and Prevalence Across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World. *Journal of Clinical Oncology* 24(14): 2137–2150.
- Kaufert, Patricia A.
1998 Women, Resistance and the Breast Cancer Movement. *In* *Pragmatic Women and Body Politics*. Patricia A. Kaufert and Margaret Lock, eds. Cambridge: Cambridge University Press.

- Keating, Peter, and Alberto Cambrosio
2011 *Cancer on Trial: Oncology as a New Style of Practice*. Chicago: University of Chicago Press.
- Kemp, Evan Jr.
1981 Aiding the Disabled: No Pity Please. *The New York Times*, September 3.
<http://www.nytimes.com/1981/09/03/opinion/aiding-the-disabled-no-pity-please.html>,
accessed February 5, 2014.
- Kenneson, Aileen, and Janet Kay Bobo
2010 The Effect of Caregiving on Women in Families with Duchenne/Becker Muscular Dystrophy. *Health & Social Care in the Community* 18(5): 520–528.
- Kesselheim, Aaron S., Jessica A. Myers, and Jerry Avorn
2011 Characteristics of Clinical Trials to Support Approval of Orphan vs Non-Orphan Drugs for Cancer. *JAMA: The Journal of the American Medical Association* 305(22): 2320–2326.
- Kinali, Maria, Virginia Arechavala-Gomeza, Lucy Feng, et al.
2009 Local Restoration of Dystrophin Expression with the Morpholino Oligomer AVI-4658 in Duchenne Muscular Dystrophy: A Single-Blind, Placebo-Controlled, Dose-Escalation, Proof-of-Concept Study. *The Lancet Neurology* 8(10): 918–928.
- Kirmayer, Laurence J.
2000 Broken Narratives: Clinical Encounters and the Poetics of Illness Experience. *In* *Narrative and the Cultural Construction of Illness and Healing*. Cheryl Mattingly and Linda C. Garro, eds. Pp. 153–180. Berkeley: University of California Press.
- Kleinman, Arthur
1986 *Social Origins of Distress and Disease: Depression, Neurasthenia, and Pain in Modern China*. New Haven: Yale University Press.
1988 *The Illness Narratives: Suffering, Healing and the Human Condition*. New York: Basic Books.
1997 Anthropology of Bioethics. *In* *Writing at the Margin: Discourse Between Anthropology and Medicine* Pp. 41–67. Berkeley: University of California Press.
1999 Moral Experience and Ethical Reflection: Can Ethnography Reconcile Them? A Quandary for "the New Bioethics. *Daedalus* 128(4): 69–97.
2013 From Illness as Culture to Caregiving as Moral Experience. *New England Journal of Medicine* 368(15): 1376–1377.
- Kleinman, Arthur, and Joan Kleinman
1991 Suffering and Its Professional Transformation: Toward an Ethnography of Experience. *Culture, Medicine, and Psychiatry* 15: 275–302.
- Koenig, M., E.P. Hoffman, C.J. Bertelson, et al.
1987 Complete Cloning of the Duchenne Muscular Dystrophy (DMD) cDNA and Preliminary

Genomic Organization of the DMD Gene in Normal and Affected Individuals. *Cell* 50: 509–17.

Kominski, Gerald F.

2013 *Changing the U.S. Health Care System: Key Issues in Health Services Policy and Management*. New York: John Wiley & Sons.

Labov, W., and J. Waletzky

1967 Narrative Analysis: Oral Versions of Personal Experiences. *Journal of Narrative and Life History* 7: 3–28.

LaDonna, Kori A.

2011 A Literature Review of Studies Using Qualitative Research to Explore Chronic Neuromuscular Disease. *Journal of Neuroscience Nursing* 43(3): 172–182.

Laidlaw, James

2000 A Free Gift Makes No Friends. *Journal of the Royal Anthropological Institute* 6(4): 617–634.

Lakoff, Andrew

2002 The Mousetrap: Managing the Placebo Effect in Antidepressant Trials. *Molecular Intervention* 2(2): 72–76.

2006 *Pharmaceutical Reason: Knowledge and Value in Global Psychiatry*. Cambridge: Cambridge University Press.

LaMontagne, Lynda L., Joseph T. Hepworth, and Michele H. Salisbury

2001 Anxiety and Postoperative Pain in Children Who Undergo Major Orthopedic Surgery. *Applied Nursing Research* 14(3): 119–124.

Landsman, Gail

2003 Emplotting Children's Lives: Developmental Delay vs. Disability. *Social Science & Medicine* 56(9): 1947–1960.

Landsman, Gail H.

2009 *Reconstructing Motherhood and Disability in the Age of "Perfect" Babies*. New York: Routledge.

Landzelius, Kyra

2006 Introduction: Patient Organization Movements and New Metamorphoses in Patienthood. *Social Science & Medicine* 62(3): 529–537.

Langone, John

2000 When Friends and Family Fill Most of a Patient's Medical Needs. *New York Times*, October 26: F6.

- Latour, Bruno
1987 *Science in Action: How to Follow Scientists and Engineers through Society*. Cambridge, Mass.: Harvard University Press.
- Latour, Bruno, and Steve Woolgar
1979 *Laboratory Life: The Social Construction of Scientific Facts*. Beverly Hills: Sage Publications.
- Lave, Jean, and Etienne Wenger
1991 *Situated Learning: Legitimate Peripheral Participation*. Cambridge: Cambridge University Press.
- Lee, E.J., Faircloth, C., Macvarish, J., and Bristow, J., eds.
2014 *Parenting Culture Studies*. London: Palgrave Macmillan.
- LeVine, Robert A.
1977 *Child Rearing as Cultural Adaptation*. In *Culture and Infancy: Variations in the Human Experience*. P.H. Leiderman, ed. Pp. 15–27. Detroit: University of Michigan Press.
- LeVine, Robert Alan, Patrice M. Miller, and Mary Maxwell West
1988 *Parental Behavior in Diverse Societies*. San Francisco: Jossey-Bass.
- Lévi-Strauss, Claude
1966 *The Savage Mind*. Chicago: University of Chicago Press.
- Lichtenstein, Paul, Niels V. Holm, Pia K. Verkasalo, et al.
2000 *Environmental and Heritable Factors in the Causation of Cancer — Analyses of Cohorts of Twins from Sweden, Denmark, and Finland*. *New England Journal of Medicine* 343(2): 78–85.
- Lilford, R. J., J. G. Thornton, and D. Braunholtz
1995 *Clinical Trials and Rare Diseases: A Way out of a Conundrum*. *British Medical Journal* 311(7020): 1621–1625.
- Lock, Margaret
2013 *The Lure of the Epigenome*. *The Lancet* 381(9881): 1896–1897.
- Lock, Margaret, and Vinh-Kim Nguyen
2010 *An Anthropology of Biomedicine*. Malden, MA: Wiley-Blackwell.
- Lovato, Laura C., Kristin Hill, Stephanie Hertert, Donald B. Hunninghake, and JL Probstfield
1997 *Recruitment for Controlled Clinical Trials: Literature Summary and Annotated Bibliography*. *Controlled Clinical Trials* 18(4): 328–352.

- Lowes, Linda P, Lindsay N Alfano, Brent A Yetter, et al.
 2013 Proof of Concept of the Ability of the Kinect to Quantify Upper Extremity Function in Dystrophinopathy. *PLoS Currents* 5. <http://currents.plos.org/md/article/proof-of-concept-of-the-ability-of-the-kinect-to-quantify-upper-extremity-function-in-dystrophinopathy/>, accessed February 27, 2014.
- Lupton, Deborah
 1992 Discourse Analysis: A New Methodology for Understanding the Ideologies of Health and Illness. *Australian Journal of Public Health* 16(2): 145–150.
- Maanen, John Van
 2011 *Tales of the Field: On Writing Ethnography*. Chicago: University of Chicago Press.
- Mah, Jean K, Kathryn Selby, Craig Campbell, et al.
 2011 A Population-Based Study of Dystrophin Mutations in Canada. *The Canadian Journal of Neurological Sciences* 38(3): 465–474.
- Malik, Vinod, Louise R Rodino-Klapac, Laurence Viollet, et al.
 2010 Gentamicin-Induced Readthrough of Stop Codons in Duchenne Muscular Dystrophy. *Annals of Neurology* 67(6): 771–780.
- Malorye, Allison
 2008 Gunvalson Decision Sends Shockwaves through Industry. *Nature Biotechnology* 26: 1201–1202.
- Marcus, Amy Dockser
 2011 Families of Ill Children Try Drug Development.
<http://www.halotherapeutics.com/families-of-ill-children-try-drug-development-wsj-com>, accessed June 24, 2014.
- Marcus, George E.
 1995 Ethnography In/of the World System: The Emergence of Multi-Sited Ethnography. *Annual Review of Anthropology* 24: Pp. 95–117.
 1998 *Ethnography through Thick and Thin*. Princeton: Princeton University Press.
- Martin, Emily
 1998 Anthropology and the Cultural Study of Science. *Science, Technology and Human Values* 23(1): 24–44.
- Martin, Paul
 2001 Great Expectations: The Construction of Markets, Products, and User Needs during the Early Development of Gene Therapy in the USA. *In Technology and the Market: Demand, Users and Innovation*. Rod Coombs, ed. Northampton, Mass.: E. Elgar Publishers.

Martin, Paul A.

1999 Genes as Drugs: The Social Shaping of Gene Therapy and the Reconstruction of Genetic Disease. *Sociology of Health and Illness* 21(5): 517–538.

Mattingly, Cheryl

1994 The Concept of Therapeutic Emplotment. *Social Science & Medicine* 38(6): 811–822.

1998 *Healing Dramas and Clinical Plots : The Narrative Structure of Experience*. Cambridge: Cambridge University Press.

2010 *The Paradox of Hope: Journeys through a Clinical Borderland*. Berkeley: University of California Press.

Mattingly, Cheryl, and Linda C. Garro

2000 *Narrative and the Cultural Construction of Illness and Healing*. Berkeley: University of California Press.

Mauss, Marcel

1990 *The Gift: The Form and Reason for Exchange in Archaic Societies*. New York: W.W. Norton.

McBride, Ryan

2011 Genzyme Gives Back Drug Rights to PTC Therapeutics. *FierceBiotech*.

<http://www.fiercebiotech.com/story/genzyme-gives-back-drug-rights-ptc-therapeutics/2011-09-02>, accessed June 22, 2014.

McDonald, Craig M, Erik K Henricson, R Ted Abresch, et al.

2013 The 6-Minute Walk Test and Other Endpoints in Duchenne Muscular Dystrophy: Longitudinal Natural History Observations over 48 Weeks from a Multicenter Study. *Muscle & Nerve* 48(3): 343–356.

McElroy, Stuart P., Toshifumi Nomura, Leah S. Torrie, et al.

2013 A Lack of Premature Termination Codon Read-Through Efficacy of PTC124 (Ataluren) in a Diverse Array of Reporter Assays. *PLoS Biol* 11(6): e1001593.

McGuire, Marlene

2011 *Expensive Drugs for Rare Diseases: An Anthropological Analysis of the Cultural, Political, and Economic Dimensions of Metabolic Disease*. Master's Thesis. University of British Columbia, Vancouver, Department of Anthropology.
<https://circle.ubc.ca/handle/2429/39881>, accessed February 10, 2014.

McMillan, Hugh, Craig Campbell, and Jean Mah

2010 Duchenne Muscular Dystrophy: Canadian Paediatric Neuromuscular Physicians Survey. *The Canadian Journal of Neurological Sciences* 37(2): 195–205.

McPherson, Jan, and Rachel Conner

1996 *You Did It! Bothell, WA: Wright Group*.

McSherry, Christine

2013 The Jett Foundation » Email to Dr. Janet Woodcock from Abigail Alliance. Jett Foundation Blog. <http://jettfoundation.org/uncategorized/email-to-dr-janet-woodcock-from-abigail-alliance/>, accessed December 4, 2013.

Mendell, Jerry R, Louise R Rodino-Klapac, Zarife Sahenk, et al.

2013 Eteplirsen for the Treatment of Duchenne Muscular Dystrophy. *Annals of Neurology* 74(5): 637–647.

Miller, Anton, Christopher J. Condin, William McKellin, et al.

2009 Continuity of Care for Children with Complex Chronic Health Conditions: Parents' Perspectives. *BMC Health Services Research* 9(1): 242.

Miller, Franklin G., and Howard Brody

2003 A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials. *The Hastings Center Report* 33(3): 19.

Mishler, E.G.

1995 Models of Narrative Analysis: A Typology. *Journal of Narrative and Life History* 5: 87–123.

Moerman, Daniel E., and Wayne B. Jonas

2002 Deconstructing the Placebo Effect and Finding the Meaning Response. *Annals of Internal Medicine* 136(6): 471–476.

Murdoch, Charles E, and Christopher Thomas Scott

2010 Stem Cell Tourism and the Power of Hope. *The American Journal of Bioethics: AJOB* 10(5): 16–23.

Murphy, Robert Francis

1987 *The Body Silent*. New York: H. Holt.

Murphy, Robert F., Jessica Scheer, Yolanda Murphy, and Richard Mack

1988 Physical Disability and Social Liminality: A Study in the Rituals of Adversity. *Social Science & Medicine* 26(2): 235–242.

Nader, Laura

1972 Up the Anthropologist: Perspectives Gained from Studying Up. *In Reinventing Anthropology*. Dell Hymes, ed. Pp. 284–311. New York: Pantheon Books.

Newman, Harmony

2010 Cross-Cultural Framing Strategies of the Breastfeeding Movement and Mothers' Responses. *Vanderbilt University Dept of Sociology*.

Nguyen, Vinh-Kim

2010 *The Republic of Therapy: Triage and Sovereignty in West Africa's Time of AIDS*. Durham: Duke University Press.

Northouse, Laurel L., Tansey Rosset, Laurel Phillips, et al.

2006 *Research with Families Facing Cancer: The Challenges of Accrual and Retention*. *Research in Nursing & Health* 29(3): 199–211.

Novas, Carlos

2006 *The Political Economy of Hope: Patients' Organizations, Science and Biovalue*. *BioSocieties* 1(03): 289–305.

2009 *Orphan Drugs, Patient Activism and Contemporary Healthcare*. Quaderni. *Communication, Technologies, Pouvoir*(68): 13–23.

Ochs, Elinor, and Tamar Kremer-Sadlik, eds.

2013 *Fast-Forward Family*. Berkeley: University of California Press.

Olivier, Catherine, Bryn Williams-Jones, Beatrice Godard, et al.

2008 *Personalized Medicine, Bioethics and Social Responsibilities: Re-Thinking the Pharmaceutical Industry to Remedy Inequities in Patient Care and International Health*. *Current Pharmacogenomics and Personalized Medicine* 6(2): 108–120.

Orfali, M., L. Feldman, V. Bhattacharjee, et al.

2012 *Raising Orphans: How Clinical Development Programs of Drugs for Rare and Common Diseases Are Different*. *Clinical Pharmacology and Therapeutics* 92(2): 262–264.

O'Sullivan, BP, DM Orenstein, and CE Milla

2013 *Pricing for Orphan Drugs: Will the Market Bear What Society Cannot?* *JAMA: The Journal of the American Medical Association* 310(13): 1343–1344.

Panofsky, Aaron

2011 *Generating Sociability to Drive Science: Patient Advocacy Organizations and Genetics Research*. *Social Studies of Science* 41(1): 31 –57.

Parent Project Muscular Dystrophy (PPMD)

2013 *Grief and Loss Forum*. Parent Project Community.

<http://community.parentprojectmd.org/forum/categories/grief-and-loss/listForCategory>, accessed December 19, 2013.

Passamano, Luigia, Antonella Taglia, Alberto Palladino, and Emanuela Viggiano

2012 *Improvement of Survival in Duchenne Muscular Dystrophy: Retrospective Analysis of 835 Patients*. *Acta Myologica* 31(2): 121–125.

Peay, H.L.

2013 *P.2.20 Prioritizing the Worries of Parents of Children with Duchenne Muscular*

Dystrophy Using Best-Worst Scaling. *Neuromuscular Disorders* 23(9–10): 755.

Peay, Holly L., Ilene Hollin, Ryan Fischer, and John F. P. Bridges

2014a A Community-Engaged Approach to Quantifying Caregiver Preferences for the Benefits and Risks of Emerging Therapies for Duchenne Muscular Dystrophy. *Clinical Therapeutics* 36(5): 624–637.

Peay, Holly L., Aad Tibben, Tyler Fisher, Ethan Brenna, and Barbara B Biesecker

2014b Expectations and Experiences of Investigators and Parents Involved in a Clinical Trial for Duchenne/Becker Muscular Dystrophy. *Clinical Trials* 11(1): 77–85.

Pegoraro, E., E. P. Hoffman, L. Piva, et al.

2011 SPP1 Genotype Is a Determinant of Disease Severity in Duchenne Muscular Dystrophy. *Neurology* 76(3): 219–226.

Peltz, Stuart W

2009 Gunvalson and PTC Therapeutics' Community Outreach. *Nature Biotechnology* 27(2): 121–122.

Peltz, Stuart W, Manal Morsy, Ellen M Welch, and Allan Jacobson

2013 Ataluren as an Agent for Therapeutic Nonsense Suppression. *Annual Review of Medicine* 64: 407–425.

Peterson, Kristin

2004 HIV/AIDS and Democracy in Nigeria: Policies, Rights, and Therapeutic Economies. Houston: Rice University Press.

Petryna, Adriana

2002 *Life Exposed: Biological Citizens after Chernobyl*. Princeton: Princeton University Press.

2005 Ethical Variability: Drug Development and Globalizing Clinical Trials. *American Ethnologist* 32(2): 183–197.

2009 *When Experiments Travel: Clinical Trials and the Global Search for Human Subjects*. Princeton: Princeton University Press.

Petryna, Adriana, Andrew Lakoff, and Arthur Kleinman

2006 *Global Pharmaceuticals: Ethics, Markets, Practices*. Durham: Duke University Press.

Phillips, Cassandra

2001 Re-Imagining the (Dis)Able Body. *Journal of Medical Humanities* 22(3): 195–208.

Phimister, Elizabeth G, W. Gregory Feero, and Alan E Guttmacher

2012 Realizing Genomic Medicine. *New England Journal of Medicine* 366(8): 757–759.

Pocock, S. J.

1992 When to Stop a Clinical Trial. *British Medical Journal* 305(6847): 235–240.

Pope, Catherine, and Nick Mays

1995 Qualitative Research: Reaching the Parts Other Methods Cannot Reach: An Introduction to Qualitative Methods in Health and Health Services Research. *BMJ* 311(6996): 42–45.

Pope, Catherine, Sue Ziebland, and Nicholas Mays

2000 Qualitative Research in Health Care: Analysing Qualitative Data. *BMJ* 320(7227): 114–116.

PPMD

2013 Parent Project Muscular Dystrophy (PPMD). <http://www.parentprojectmd.org>, accessed January 27, 2014.

2014a FDA Guidance on Duchenne - Parent Project Muscular Dystrophy.

http://www.parentprojectmd.org/site/PageServer?pagename=Advocate_fdaguidance, accessed July 9, 2014.

2014b PPMD President Participates on Patient Reported Outcomes Panel to Inform FDA Public Meeting - PPMD Community. <http://community.parentprojectmd.org/profiles/blogs/ppmd-president-participates-on-panel-at-engelberg-center-for-heal>, accessed July 16, 2014.

Price, Laurie

1987 Ecuadorian Illness Stories: Cultural Knowledge in Natural Discourse. *In* *Cultural Models in Language and Thought*. Dorothy C. Holland and Naomi Quinn, eds. Pp. 313–342. Cambridge: Cambridge University Press.

PriceWaterhouseCoopers

2009 The New Science of Personalized Medicine: Translating the Promise into Practice.

<http://pwchealth.com/cgi-local/hregister.cgi/reg/personalized-medicine.pdf>, accessed November 30, 2013.

Prior, Lindsay

2003 Belief, Knowledge and Expertise: The Emergence of the Lay Expert in Medical Sociology. *Sociology of Health & Illness* 25(3): 41–57.

Probstfield, JL, and RL Frye

2011 Strategies for Recruitment and Retention of Participants in Clinical Trials. *JAMA: The Journal of the American Medical Association* 306(16): 1798–1799.

PTC Therapeutics Inc.

2010 Summary of Ataluren Phase 2b Clinical Trial Results Presented at the American Academy of Neurology Meeting on April 16, 2010, Toronto. http://www.parentprojectmd.org/site/DocServer/2010-04-16_Final_Summary_of_Ataluren_Data_at_AAN.pdf?docID=9461, accessed June 20, 2014.

2013 Form S-1 Registration Statement Under the Securities Act of 1933. United States Securities and Exchange Commission EDGAR Website. http://www.sec.gov/Archives/edgar/data/1070081/000104746913006241/a2215112zs-1.htm#bg47601a_main_toc, accessed June 1, 2014.

- 2014 Webinar: Ataluren (Translarna) Update with PTC.
<http://community.parentprojectmd.org/events/webinar-ptc-update-on-translarna-ataluren>,
 accessed July 10, 2014.
- Puddephatt, Antony J, William Shaffir, and Steven W Kleinknecht
 2009 *Ethnographies Revisited: Constructing Theory in the Field*. New York: Routledge.
- Rabeharisoa, Vololona
 2003 The Struggle against Neuromuscular Diseases in France and the Emergence of the
 “Partnership Model” of Patient Organisation. *Social Science & Medicine* (1982) 57(11):
 2127–2136.
 2006 From Representation to Mediation: The Shaping of Collective Mobilization on Muscular
 Dystrophy in France. *Social Science & Medicine* 62(3): 564–576.
- Rabeharisoa, Vololona, and Michel Callon
 2002 The Involvement of Patients’ Associations in Research. *International Social Science
 Journal* 54(171): 57–63.
- Rabeharisoa, Vololona, Michel Callon, Angela Marques Filipe, et al.
 2014 From “Politics of Numbers” to “Politics of Singularisation”: Patients’ Activism and
 Engagement in Research on Rare Diseases in France and Portugal. *BioSocieties* 9(2):
 194–217.
- Rabinow, Paul
 1996a *Making PCR : A Story of Biotechnology*. Chicago: University of Chicago Press.
 1996b Artificiality and Enlightenment: From Sociobiology to Biosociality. *In* *Essays on the
 Anthropology of Reason*. Paul Rabinow, ed. Princeton: Princeton University Press.
 1997 *Science as Practice*. *In* *Cyborgs & Citadels : Anthropological Interventions in Emerging
 Sciences and Technologies*. Gary Lee Downey and Joseph Dumit, eds. Santa Fe, N.M.:
 School of American Research Press.
 1999 *French DNA : Trouble in Purgatory*. Chicago: University of Chicago Press.
- Radin, Patricia
 2006 “To Me, It’s My Life”: Medical Communication, Trust, and Activism in Cyberspace.
Social Science & Medicine 62(3): 591–601.
- Rajan, Kaushik Sunder
 2010a Experimental Values: Indian Clinical Trials and Surplus Health. *In* *A Reader in Medical
 Anthropology: Theoretical Trajectories, Emergent Realities*. Byron J. Good, Michael M. J.
 Fischer, Sarah S. Willen, and Mary-Jo DelVecchio Good, eds. Pp. 377–388. New York: John
 Wiley & Sons.
 2010b The Experimental Machinery of Global Clinical Trials: Case Studies from India. *In*
Asian Biotech: Ethics and Communities of Fate. Aihwa Ong and Nancy N. Chen, eds. Pp.
 55–80. Durham: Duke University Press.

- Rangel, Vanessa, Ann S. Martin, and Holly L. Peay
2012 DuchenneConnect Registry Report. PLoS Currents 4: RRN1309.
- Rapport, Frances, Mel Storey, Alison Porter, et al.
2013 Qualitative Research within Trials: Developing a Standard Operating Procedure for a Clinical Trials Unit. *Trials* 14(1): 54.
- Rapp, Rayna
1999 Testing Women, Testing the Fetus: The Social Impact of Amniocentesis in America. New York: Routledge.
2000 Extra Chromosomes and Blue Tulips: Medico-Familial Conversations. *In* Living and Working with the New Medical Technologies. Alberto Cambrosio, Margaret Lock, and Allan Young, eds. Pp. 184–208. Cambridge: Cambridge University Press.
- Rapp, Rayna, and Faye Ginsburg
2001 Enabling Disability: Rewriting Kinship, Reimagining Citizenship. *Public Culture* 13(3): 533–556.
- Rapp, Rayna, Deborah Heath, and Karen-Sue Taussig
2001 Genealogical Dis-Ease: Where Hereditary Abnormality, Biomedical Explanation, and Family Responsibility Meet. *In* Relative Values: Reconfiguring Kinship Studies. Sarah Franklin and Susan McKinnon, eds. Pp. 384–409. Durham: Duke University Press.
- Ray, Lynne D.
2003 The Social and Political Conditions That Shape Special-Needs Parenting. *Journal of Family Nursing* 9(3): 281–304.
- Reith, Christina, Martin Landray, P.J. Devereaux, et al.
2013 Randomized Clinical Trials — Removing Unnecessary Obstacles. *New England Journal of Medicine* 369(11): 1061–1065.
- Richards, M.
1996 Lay and Professional Understandings of Genetics and Inheritance. *Public Understanding of Science* 5: 217–30.
- Rose, Nikolas
2006 The Politics of Life Itself: Biomedicine, Power, and Subjectivity in the Twenty-First Century. Princeton: Princeton University Press.
- Rose, Nikolas, and Carlos Novas
2008 Biological Citizenship. *In* Global Assemblages: Technology, Politics, and Ethics as Anthropological Problems. Aihwa Ong and Stephen J. Collier, eds. New York: John Wiley and Sons.

Rothwell, Peter M

2005 External Validity of Randomised Controlled Trials: To Whom Do the Results of This Trial Apply?. *The Lancet* 365(9453): 82–93.

Rubinstein, Yaffa R., Stephen C. Groft, Ronald Bartek, et al.

2010 Creating a Global Rare Disease Patient Registry Linked to a Rare Diseases Biorepository Database: Rare Disease-HUB (RD-HUB). *Contemporary Clinical Trials* 31(5): 394–404.

Ruegg, Urs T

2013 Pharmacological Prospects in the Treatment of Duchenne Muscular Dystrophy. *Current Opinion in Neurology* 26(5): 577–584.

Sackett, David, Brian Haynes, Tom Marshall, and W. K. C. Morgan

1995 Evidence-Based Medicine. *The Lancet* 346(8983): 1171–1172.

Samson, André, E. Tomiak, J. Dimillo, et al.

2009 The Lived Experience of Hope Among Parents of a Child with Duchenne Muscular Dystrophy: Perceiving the Human Being Beyond the Illness. *Chronic Illness* 5(2): 103–114.

Sankar, Andrea

1986 Out of the Clinic Into the Home: Control and Patient-Physician Communication. *Social Science and Medicine* 22(9): 973–982.

Sarepta Therapeutics Inc.

2013 Press Release: Parent Project Muscular Dystrophy and Sarepta Therapeutics Join Forces on Genetic Testing Program for Patients With Duchenne Muscular Dystrophy. Marketwire. <http://www.marketwired.com/press-release/parent-project-muscular-dystrophy-sarepta-therapeutics-join-forces-on-genetic-testing-nasdaq-srpt-1842067.htm>, accessed February 13, 2014.

Scheper-Hughes, Nancy

1992 *Death without Weeping: The Violence of Everyday Life in Brazil*. Berkeley: University of California Press.

1995 The Primacy of the Ethical: Propositions for a Militant Anthropology. *Current Anthropology* 36(3): 409–440.

Schrans, D. G. M., D. Abbott, H. L. Peay, et al.

2013 Transition in Duchenne Muscular Dystrophy: An Expert Meeting Report and Description of Transition Needs in an Emergent Patient Population: (Parent Project Muscular Dystrophy Transition Expert Meeting 17–18 June 2011, Amsterdam, The Netherlands). *Neuromuscular Disorders* 23(3): 283–286.

Scully, Michele A., Valerie A. Cwik, Bruce C. Marshall, et al.

2013 Can Outcomes in Duchenne Muscular Dystrophy Be Improved by Public Reporting of

Data? *Neurology* 80(6): 583–589.

Seckler, Tracy

2014 Needless Delay for a Medicine That Could Save Kids' Lives. *Huffington Post*.
http://www.huffingtonpost.com/tracy-seckler/eteplirsen-duchenne_b_4904850.html,
accessed June 26, 2014.

Seemann, Natasha, Kathy Selby, Laura McAdam, et al.

2011 Symptomatic Dystrophinopathies in Female Children. *Neuromuscular Disorders* 21(3):
172–177.

Senior, Jennifer

2014 *All Joy and No Fun: The Paradox of Modern Parenthood*. New York: Ecco.

Servick, Kelly

2014 Patient Advocacy. “Right to Try” Laws Bypass FDA for Last-Ditch Treatments. *Science*
344(6190): 1329.

Sharp, Lesley A.

2000 The Commodification of the Body and Its Parts. *Annual Review of Anthropology* 29:
287–328.

Sherman, Rachel E., Jun Li, Stephanie Shapley, Melissa Robb, and Janet Woodcock

2013 Expediting Drug Development: The FDA's New “Breakthrough Therapy” Designation.
New England Journal of Medicine 369(20): 1877–1880.

Sherwin, Susan

1992 *No Longer Patient: Feminist Ethics and Health Care*. Philadelphia: Temple University
Press.

Shostak, Marjorie, and Nisa

2000 *Nisa, the Life and Words of a !Kung Woman*. Cambridge, Mass.: Harvard University
Press.

Shuchman, Miriam

2007 Commercializing Clinical Trials—Risks and Benefits of the CRO Boom. *The New
England Journal of Medicine* 357(14): 1365–1368.

Silverman, E.

2013 Off-Label Marketing: Free Speech or Illegal Promotion? *BMJ* 346: f320–f320.

Simpson, Christy

2004 When Hope Makes Us Vulnerable: A Discussion of Patient-Healthcare Provider
Interactions in the Context of Hope. *Bioethics* 18(5): 428–447.

Siren Interactive Inc.

2014 Navigating the Landscape of Compassionate Use. SirenSong.

<http://www.sireninteractive.com/sirensong/how-should-pharma-navigate-the-landscape-of-compassionate-use/>, accessed September 30, 2014.

Smart, Andrew, and Paul Martin

2006 The Promise of Pharmacogenetics: Assessing the Prospects for Disease and Patient Stratification. *Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences* 37(3): 583–601.

Smit, Christopher R.

2003 “Please Call Now, Before It’s Too Late”: Spectacle Discourse in the Jerry Lewis Muscular Dystrophy Telethon. *The Journal of Popular Culture* 36(4): 687–703.

Söderpalm, Ann-Charlott, Per Magnusson, Anne-Christine Ahlander, et al.

2007 Low Bone Mineral Density and Decreased Bone Turnover in Duchenne Muscular Dystrophy. *Neuromuscular Disorders* 17(11-12): 919–928.

Solomon, Andrew

2012 *Far from the Tree: Parents, Children and the Search for Identity*. New York: Scribner.

Soltanzadeh, Payam, Michael J. Friez, Diane Dunn, et al.

2010 Clinical and Genetic Characterization of Manifesting Carriers of DMD Mutations. *Neuromuscular Disorders* 20(8): 499–504.

Song, Priscilla

2010 Biotech Pilgrims and the Transnational Quest for Stem Cell Cures. *Medical Anthropology: Cross-Cultural Studies in Health and Illness* 29(4): 384 – 402.

2011 The Proliferation of Stem Cell Therapies in Post-Mao China: Problematizing Ethical Regulation. *New Genetics and Society* 30(2): 141–153.

Sontag, Susan

1978 *Illness as Metaphor*. New York: Farrar, Straus and Giroux.

Spurney, Christopher F, Carolina Tesi Rocha, Erik Henricson, et al.

2011 CINRG Pilot Trial of Coenzyme Q10 in Steroid-Treated Duchenne Muscular Dystrophy. *Muscle & Nerve* 44(2): 174–178.

Stanley, Alessandra

2011 Muscular Dystrophy Telethon Takes Steps Without Jerry Lewis. *The New York Times*, September 5. <http://www.nytimes.com/2011/09/06/arts/television/muscular-dystrophy-telethon-takes-steps-without-jerry-lewis.html>, accessed February 5, 2014.

Stewart, David J., Simon N. Whitney, and Razelle Kurzrock

2010 Equipoise Lost: Ethics, Costs, and the Regulation of Cancer Clinical Research. *Journal of*

Clinical Oncology: Official Journal of the American Society of Clinical Oncology 28(17): 2925–2935.

Stockdale, Alan

1999 Waiting for the Cure: Mapping the Social Relations of Human Gene Therapy Research. *Sociology of Health and Illness* 21(5): 579–596.

Temple, Robert

1982 Government Viewpoint of Clinical Trials. *Drug Information Journal* 16: 11–17.

Terry, Sharon F., Patrick F. Terry, Katherine A. Rauen, Jouni Uitto, and Lionel G. Bercovitch

2007 Advocacy Groups as Research Organizations: The PXE International Example. *Nature Reviews Genetics* 8(2): 157–164.

Testart, A.

1998 Uncertainties of the “Obligation to Reciprocate”: A Critique of Mauss. *In* Marcel Mauss: A Centenary Tribute. Wendy James, Marcel Mauss, and N. J. Allen, eds. New York: Berghahn Books.

TheRacetoYes.Org

2014 Race to Yes Petition Website. <http://theracetoyes.org/>, accessed June 26, 2014.

Thomson Reuters

2012 The Economic Power of Orphan Drugs. New York: Thomson Reuters.

http://thomsonreuters.com/business-unit/science/scripts/elqnow/elqRedir.htm?ref=/business-unit/science/pdf/orphan_drugs.pdf, accessed February 10, 2014.

2013 Review of Trends and Developments in Orphan Drug R&D. Life Sciences Connect.

<http://lsconnect.thomsonreuters.com/market-insight-a-review-of-the-trends-and-developments-in-orphan-drug-rd/>, accessed July 10, 2014.

Thorat, C., K. Xu, S. N. Freeman, et al.

2012 What the Orphan Drug Act Has Done Lately for Children With Rare Diseases: A 10-Year Analysis. *Pediatrics* 129(3): 516–521.

Timmermans, Stefan, and Marc Berg

2010 The Gold Standard: The Challenge of Evidence-Based Medicine and Standardization in Health Care. Philadelphia: Temple University Press.

Tirrell, Meg

2014 JP Morgan Dad Starts Biotech in Muscular Dystrophy Quest. Bloomberg, February 19.

<http://www.bloomberg.com/news/2014-02-20/jpmorgan-dad-starts-biotech-in-muscular-dystrophy-quest.html>, accessed March 3, 2014.

TREAT-NMD

2014 Registry of Outcome Measures - View A-Z. <http://www.researchchrom.com/masterlist>,

accessed February 27, 2014.

Tsilidis, Konstantinos K., Orestis A. Panagiotou, Emily S. Sena, et al.

2013 Evaluation of Excess Significance Bias in Animal Studies of Neurological Diseases. *PLoS Biology* 11(7): e1001609.

Tulloch, John, and Deborah Lupton

2003 *Risk and Everyday Life*. London: Sage.

Turner, Leigh

2008 Anthropological and Sociological Critiques of Bioethics. *Bioethical Inquiry* 6: 83–98.

Turner, Victor Witter

1967 Betwixt and between: The Liminal Period in Rites de Passage. *In* *The Forest of Symbols: Aspects of Ndembu Ritual* Pp. 23–59. Ithaca: Cornell University Press.

1969 *The Ritual Process: Structure and Anti-Structure*. The Lewis Henry Morgan Lectures. Chicago: Aldine.

United States Office for Human Research Protections (OHRP)

1991 Federal Policy for the Protection of Human Subjects ('Common Rule').

<http://www.hhs.gov/ohrp/humansubjects/commonrule/>, accessed March 19, 2014.

Usdin, Steve

2014 Hardy Case Shows Flaws in Compassionate Use System, Provides Catalyst for Change – BioCentury.com. *Biocentury.com*. <http://www.biocentury.com/biotech-pharma-news/cover-story/2014-03-31/hardy-case-shows-flaws-in-compassionate-use-system-provides-catalyst-for-change-a1>, accessed June 25, 2014.

Vertin, Betty

2014 My BRAVE Story: Three of Our Four Sons Have Duchenne Muscular Dystrophy. PPMD Community. <http://community.parentprojectmd.org/profiles/blogs/my-brave-story-three-of-our-four-sons-have-duchenne-muscular-dyst>, accessed June 22, 2014.

De Vruh, R., and J.M.H. de Haan

2013 WHO World Health Report 2013 Background Paper 6.19: Rare Diseases. World Health Organization (WHO). http://www.who.int/medicines/areas/priority_medicines/BP6_19Rare.pdf, accessed December 11, 2013.

Wagner, Kathryn R., Sherifa Hamed, Donald W. Hadley, et al.

2001 Gentamicin Treatment of Duchenne and Becker Muscular Dystrophy due to Nonsense Mutations. *Annals of Neurology* 49(6): 706–711.

Warner, Judith

2006 *Perfect Madness: Motherhood in the Age of Anxiety*. Reprint edition. New York: Riverhead Trade.

- Wästfelt, M., B. Fadeel, and J.-I. Henter
2006 A Journey of Hope: Lessons Learned from Studies on Rare Diseases and Orphan Drugs. *Journal of Internal Medicine* 260(1): 1–10.
- Webb, C L
2005 Parents' Perspectives on Coping with Duchenne Muscular Dystrophy. *Child: Care, Health and Development* 31(4): 385–396.
- Wehling, Peter
2011 The “Technoscientization” of Medicine and Its Limits: Technoscientific Identities, Biosocialities, and Rare Disease Patient Organizations. *Poiesis & Praxis* 8(2-3): 67–82.
- Weimer, Katja, Marco D. Gulewitsch, Angelika A. Schlarb, et al.
2013 Placebo Effects in Children: A Review. *Pediatric Research* 74(1): 96–102.
- Weisman, Mary Lou
2000 Intensive Care: A Family Love Story. Lincoln, Nebraska: Backinprint.com.
- Weisz, George, Alberto Cambrosio, Peter Keating, et al.
2007 The Emergence of Clinical Practice Guidelines. *Milbank Quarterly* 85(4): 691–727.
- Wendell, Susan
1996 The Rejected Body : Feminist Philosophical Reflections on Disability. New York: Routledge.
- WHO Council for international Organizations of Medical Sciences
2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects. Geneva: World Health Organization (WHO).
- Wieczorek, Aleksandra, Przemyslaw Rys, Iwona Skrzekowska-Baran, and Maciej Malecki
2008 The Role of Surrogate Endpoints in the Evaluation of Efficacy and Safety of Therapeutic Interventions in Diabetes Mellitus. *The Review of Diabetic Studies* 5(3): 128–135.
- Wiener, John
2011 The End of the Jerry Lewis Telethon—It's About Time. *The Nation*, September 2. <http://www.thenation.com/blog/163119/end-jerry-lewis-telethon-its-about-time>, accessed February 5, 2014.
- Wiles, Rose, Cheryl Cott, and Barbara E. Gibson
2008 Hope, Expectations and Recovery from Illness: A Narrative Synthesis of Qualitative Research. *Journal of Advanced Nursing* 64(6): 564–573.
- Winkler, Anne-Marie, and David Finegold
2008 Giving Patients a Say: How to Work with Patient Advocacy Groups. *Nature Biotechnology* 26(1): 1–4.

World Medical Association

2013 World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA: The Journal of the American Medical Association* 310(20): 2191–2194.

Wynne, Brian

1992 Sheep Farming after Chernobyl: A Case Study in Communicating Scientific Information. When Science Meets the Public: 43–68.

Yancey, A. K., A. N. Ortega, and S. K. Kumanyika

2006 Effective Recruitment and Retention of Minority Research Participants. *Annual Review of Public Health* 27: 1–28.

Yandell, Kate

2013 Drug Mechanism Questioned | The Scientist Magazine. *The Scientist*. <http://www.the-scientist.com/?articles.view/articleNo/36182/title/Drug-Mechanism-Questioned/>, accessed May 16, 2014.

Yewchuk, Lila, John Paul Morrison, and Scott Yewchuk

2012 Special Feature: Unsafe at School: Advocating for Children with Type 1 Diabetes. *BC Medical Journal* 54(5): 232–237.

Zingman, L. V., S. Park, T. M. Olson, A. E. Alekseev, and A. Terzic

2007 Aminoglycoside-Induced Translational Read-through in Disease: Overcoming Nonsense Mutations by Pharmacogenetic Therapy. *Clinical Pharmacology & Therapeutics* 81(1): 99–103.