PERSPECTIVES ON THE TRANSLATIONAL TRAJECTORY OF NOVEL BIOTECHNOLOGIES FOR NEURODEGENERATIVE DISEASE

by

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Abstract

The translation of novel brain technologies from the bench to the bedside has been characterized by a tension between priorities to promote rapid access to experimental interventions and the utilitarian pursuit of their evaluation with rigorous and time-intensive research. Through three studies conducted within the scope of this dissertation, I focus on a central research question: *What are the perspectives of stakeholders about the translation of novel biotechnologies for neurodegenerative disease?*

Harnessing the strength of pragmatic neuroethics, I address this research question using both qualitative and quantitative analyses. In the first study, I explore the perspectives of patients with multiple sclerosis (MS) about the unproven but highly publicized chronic cerebrospinal venous insufficiency (CCSVI) intervention and the impact of its controversial trajectory on stem cell research. I find that patients are disappointed about the divestment of funds from other areas of research to support CCSVI trials, but maintain enduring hopes for future neurotechnological advancements, including stem cell research. In the second study, I examine how the news media represent timeframes for research and development of stem cell interventions for MS and other neurodegenerative diseases. I find that news articles celebrate the benefits of stem cell research with little context of its caveats. In contrast to prior studies, however, I discover that they also conscientiously convey caution about stem cell tourism and describe a lengthy trajectory between research and clinical availability of therapeutics. In the third study, I explore the perspectives of patients with MS and clinicians responsible for their care about the pace of research and development for stem cell interventions. Here I describe the urgency that patients

feel to access stem cell interventions and their desire to learn more about the research process. Clinicians suggest strategies for dialogue with their patients that can clarify translational timeframes and inform hopes. Overall, the findings bring together the voices of key stakeholders and support a commitment to socially minded translation of novel neurotechnologies for neurodegenerative disease.

Lay Summary

The development of new brain technologies follows a pathway of rigorous and time-intensive research that produces knowledge and protects research participants. At the same time, patients often seek opportunities to rapidly access therapies for incurable diseases. In this dissertation, I explore the perspectives of patients, clinicians, and the news media about the development of technologies for degenerative diseases of the brain. Findings bring forward new knowledge about these stakeholders' priorities, concerns, and informational needs, and support the importance of aligning the development of brain technologies with the values of the public.

Preface

This project was reviewed and approved by the University of British Columbia Behavioural Research Ethics Board, certificate number: H13-03275 and the Ottawa Health Science Network Research Ethics Board, certificate number: 20150282-01H. I identified the research questions in this dissertation and took the lead on study design, analysis, and synthesis. Several manuscripts that have been published or submitted for publication are integrated into the body of this dissertation:

1) **Benjaminy, S.**, Schepmyer, A., Illes, J.*, & Traboulsee, A.* Resilience, trust, and civic engagement in the post-CCSVI era. [under review; submitted July 2017].

This manuscript appears in Chapter 3. I conceptualized the study in collaboration with Prof. Judy Illes and Dr. Anthony Traboulsee. I took the lead on study design, analysis, synthesis, and manuscript writing. Dr. Andrew Schepmyer helped with data analysis and synthesis. All authors contributed to the final version of the manuscript.
*denotes co-lead authorship

2) **Benjaminy, S.**, Lo, C., & Illes, J. (2016). Social responsibility in stem cell research - Is the news all bad? *Stem Cell Reviews and Reports*, 12(3), 269-275.

This manuscript appears in Chapter 4. I conceptualized the study in collaboration with Prof. Judy Illes. I took the lead on study design, analysis, synthesis, and manuscript writing. Cody Lo

helped with data analysis and synthesis. All authors contributed to the final version of the manuscript.

3) **Benjaminy, S.**, Lo, C., Schepmyer, A., Traboulsee, A., & Illes, J. Perspectives about timeframes in stem cell research for multiple sclerosis. [under review; submitted December 2017].

This manuscript appears in Chapter 3. I conceptualized the study in collaboration with Prof. Judy Illes. I took the lead on study design, analysis, synthesis, and manuscript writing. Cody Lo and Dr. Andrew Schepmyer helped with data analysis and synthesis. All authors contributed to the final version of the manuscript.

4) **Benjaminy, S.**, & Traboulsee, A. (2017). At the crossroads of civic engagement and evidence-based medicine: Lessons learned from the chronic cerebrospinal venous insufficiency experience. In J. Illes (Ed.), *Neuroethics: Anticipating the future*. Oxford, UK: Oxford University Press.

Excerpts from this book chapter are integrated into Chapter 1, Chapter 4, and Chapter 6 of the dissertation. I contributed to conceptualization, synthesis, and took the lead on drafting the original book chapter. Dr. Traboulsee made conceptual contributions and was involved in drafting the original manuscript.

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List of Abbreviations

ALS	Amyotrophic lateral sclerosis
CCSVI	Chronic cerebrospinal venous insufficiency
EDSS	Expanded Disability Status Scale
ELSI	Ethical, legal, and social implications
ISSCR	International Society for Stem Cell Research
MS	Multiple sclerosis

Glossary

Agenda-setting – A theory that suggests that the media can lend salience to certain topics through selective coverage and emphasis.

Confirmability – A measure of rigour in qualitative research that demonstrates how the research findings are supported by the data.

Credibility – A measure of rigour in qualitative research that demonstrates consistency between research participants' expressions and the researcher's interpretations of data.

Dependability – A measure of rigour in qualitative research that demonstrates whether a study would yield similar findings, along with logical differences, if it were carried out in a similar context in the future.

Emic – An epistemological stance where knowledge is gathered from within a social group.

Epistemology – A branch of philosophy that describes the theory of knowledge and explores what is known and the rationalizations of justified belief.

Etic – An epistemological stance where knowledge is uncovered from outside a social group in an effort to maintain objectivity and avoid bias.

Framing – The use of simplified interpretive packages to influence public opinions about important issues.

Humanism – A philosophical tradition that grounds morality in the ever-evolving values of human beings.

Neuroethics – A field of biomedical ethics that is dedicated to exploring the ethical, legal, and social implications of developing brain technologies.

Ontology – A branch of philosophy that describes the nature of being, and of reality and truth.

Paradigm – A basic set of beliefs that shape the worldview of the researcher. These include the ontological, epistemological and methodological underpinnings of research.

Realism – The ontological belief that a single objective truth exists.

Regenerative medicine – A branch of translational science that focuses on engineering, replacing, repairing, or renewing cells, tissues, or organs that have been damaged as a result of trauma, disease, or congenital anomalies.

Relativism – The ontological belief that there are multiple realities and that various truths can co-exist.

Post-positivism – A philosophy and model of scientific inquiry that aims to capture an approximation of a single reality or truth.

Pragmatic neuroethics – A philosophical approach to neuroethics inquiry that emphasizes grounding ethics in empirical analyses rather than adhering to a set of *a priori* moral principles.

Science – For the purpose of this dissertation, the term science is defined as empirical inquiry and technology development.

Situationalism – The belief that the environment influences behaviour, including moral action, that is context-specific.

Social constructivism – A philosophy and model of inquiry that aims to co-create subjective realities and embraces bias.

Stem cell research – An area of research that falls under the umbrella of regenerative medicine and offers the potential to propagate cells that can divide and differentiate to serve specialized functions, replenish tissues and organs, and act as repair systems for the body.

Stem cell tourism – A colloquial term used to describe clinics that offer untested, unapproved, and unregulated interventions that are often marketed as *bona fide* stem cell therapies.

Theoretical saturation – A phase of qualitative data analysis where continued sampling and data analysis do not reveal additional major themes. Operationally, theoretical saturation indicates that adequate data have been collected, and that no new themes are emerging.

Transferability – A measure of rigour in qualitative research that describes the degree to which study results can be applied to populations outside of the study sample.

Translation – The process of moving research and development of novel interventions into market approved and clinically applicable treatments.

Translational pace – The rate of advancement or progress in the translation of research to clinical practice.

Translational timeframes – Estimations of the time it will take to reach discrete goals in translation.

Trustworthiness – The predominant measure of rigour in qualitative research that is characterized by credibility, confirmability, dependability, and transferability.

Acknowledgements

I would like to acknowledge the contributions of the research participants who generously gave their time and shared their insights with me. Without them, this dissertation would not have been possible.

I extend my infinite gratitude to my supervisor, Prof. Judy Illes, for her unwavering support and investment in my training. I am very fortunate to have a mentor who sees the success of her students as an extension of her own. Thank you to Dr. Anthony Traboulsee, my co-supervisor, who opened many doors for professional development and allowed me the flexibility to explore my research interests. To my committee members, Prof. Mary Anne Bobinski and Dr. Harold Atkins, thank you for providing key insights and guidance throughout my doctoral studies.

To the members of the National Core for Neuroethics, my academic home, thank you for the support and friendship along the way. An especially big thank you goes to Cody Lo who worked alongside me on many of the projects embedded in this dissertation. I would also like to thank Dr. Andrew Schepmyer for his contributions to data analysis, and Michelle Eisner and Marjorie Bowman for facilitating participant recruitment.

Throughout my doctoral journey, I was fortunate to have an opportunity to pursue a clinical ethics fellowship in collaboration with Providence Health Care and Provincial Health Services Authority in Vancouver. This training opportunity has been incredibly formative and has left an indelible mark on my identity as a bioethicist. I would like to thank my clinical ethics mentors:

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I am forever indebted to Prof. Tania Bubela, whose ongoing mentorship since the days of my Master's degree has shaped my worldviews as a researcher and gave me the boldness to aim high. I would not have considered pursuing doctoral studies if it were not for her guidance.

To my family, especially my parents, Pessy and Benny Benjaminy, thank you for encouraging me to be a lifelong learner and for teaching me the value of perseverance. To my brother, Nir Benjaminy, whose dedication to our grandparents allowed me to focus on my graduate studies. Niko, my four-legged support, has been by my side since my first year of university. He warmed my feet and offered cuddles through long days and nights of studying. To my partner, Jacob Ballen—whose kindness, generosity, and compassion are sources of inspiration and comfort—thank you for the patience and sacrifice that enabled me to complete my doctoral training.

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To my loving grandparents, Rachel and Baruch Tessler (Z”L), whose legacy of generosity and devotion lives on.

Chapter 1: Introduction

1.1 Biotechnology Development at the Intersection of Science and Society

The development of novel biotechnologies is as much a social enterprise as a scientific venture. Indeed, contemporary formulations of science are increasingly adopting a participatory stance with an unprecedented number of government and private research funding priorities that encourage knowledge translation (Canadian Institutes of Health Research, 2005). Initiatives that promote reciprocal and porous dialogue at the intersection of science and society are bolstered by a rich variety of empirical approaches. These include community-based participatory action research, deliberative democracy, and consensus conferences, among others (Stilgoe, Lock, & Wilsdon, 2014). New media, particularly Web 2.0 platforms (e.g., blogs, YouTube, Twitter, Facebook, wikis), are also democratizing science and allowing members of the public to actively create content rather than passively absorb information (Robillard & Wright, 2017). These platforms are now reforming traditional models of top-down science communication and introducing additional avenues for citizens to directly contribute to debates about science and policy.

Developing biotechnologies at the frontier of science and society are captivating public interest and attention with a complex landscape of hope and anticipation. Kimmelman (2010), for example, explains, "decisions to pursue the development of novel interventions are propelled by beliefs about promise rather than current realities" (p. 155). Hope garners public enthusiasm and support for research, which in turn influences research agendas and mobilizes funding for

scientific pursuits. Indeed, hope is a necessary and natural component of biotechnological development (Hedgecoe, 2004).

The Gartner Hype Curve is one leading model of public anticipation for innovation in science and technology (Figure 1.1). This curve demonstrates the typical trajectory of social expectations along the continuum of technology development. Notably, the curve features a peak of inflated expectations as a new technology begins to capture public attention, and a trough of disillusionment before reaching a plateau of productivity that is characterized by market adoption of a new technology.

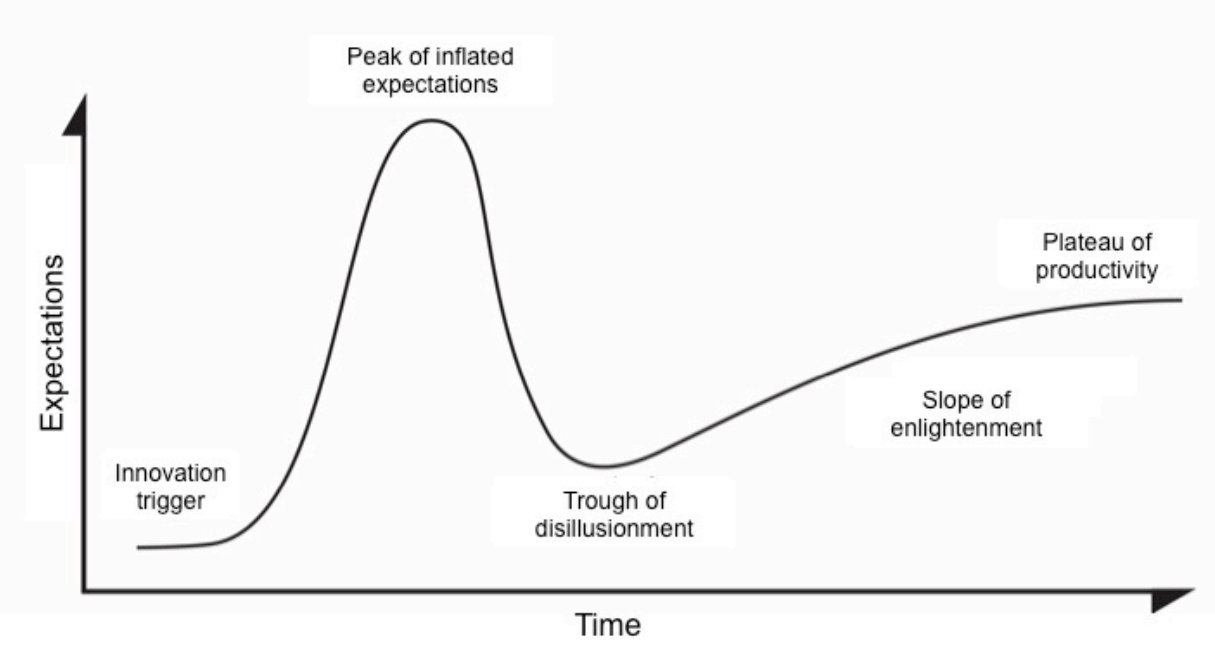

Figure 1.1 Gartner Hype Curve illustrating the key phases of public expectations along the continuum of technology development.

Figure from (Gartner Inc., 2017).

It has been suggested that public anticipation for new biotechnologies is often reinforced by a tendency to overemphasize the benefits of research and downplay the associated caveats and risks in both the popular media and the scientific literature (Caulfield & Condit, 2012). This tendency sometimes culminates in science hype, a sustained exaggeration of the benefits of research, which can have negative implications on developing biotechnologies (Holtzman, 1999). Hype can create patterns of hyperbolic hope and subsequent disappointment, and can thereby widen the amplitude between the peak of inflated expectations and the trough of disillusionment on the Gartner Hype Curve. This phenomenon may result in several negative implications on technology translation from the bench to the bedside. Inflated hopes, particularly those of patients, may compromise the integrity of informed consent in the context of enrolling clinical trials (Benjaminy, MacDonald, & Bubela, 2014; Kimmelman, 2010), and may contribute to therapeutic misconception whereby study participants conflate the goals of research and clinical care (Appelbaum, Roth, & Lidz, 1982). High hopes may create an unsustainable translational domain for novel biotechnologies, causing disillusionment among clinicians, despair among patient communities, a loss of public trust, and industry disengagement (Downey & Geransar, 2008; Ogbogu, 2006; Petersen, 2009). Hype can misinform the public and occlude opportunities for accessible and informed participation in science and policy debates. Moreover, hype can lead to confusion about the readiness of experimental products for clinical uptake, and may drive public pressures for the premature application of unproven biomedical interventions (Caulfield, Sipp, Murry, Daley, & Kimmelman, 2016; Daley, 2012; Petersen & Krisjansen, 2015).

Optimism combined with medical need often drive advocacy for rapid access to developing biotechnologies. This drive is demonstrated by trends such as the rise of medical tourism and by recent initiatives such as the Right to Try movement that calls for opportunities to promote access to experimental interventions outside of clinical trials (Burkett, 2007; Darrow, Sarpatwari, Avorn, & Kesselheim, 2015; Servick, 2014). At the same time, the translation of experimental interventions to clinically available therapeutics requires a rigorous and often lengthy process of evaluation. This process that begins with pre-clinical studies, transitions through exploratory and confirmatory clinical trials, and ends with market approval and uptake by health care systems is a utilitarian pursuit (Emanuel, Wendler, & Grady, 2000). It protects research participants, generates important knowledge that drives future innovation, and is also necessary in order to maintain public trust in the safety and efficacy of approved therapeutics and their competitiveness on the global market (Kimmelman & London, 2015; London, Kimmelman, & Emborg, 2010). Striking a balance between the conflicting priorities of access and evaluation is an age-old struggle, and a pervasive motif in contemporary biotechnology translation (Rettig, 2007).

1.2 Regenerative Medicine: A Complex Translational Biotechnology Landscape

The field of regenerative medicine is a branch of translational science that focuses on engineering, replacing, repairing, or renewing cells, tissues, or organs that have been damaged as a result of trauma, disease, or congenital anomalies (Atala, Lanza, Thomson, & Nerem, 2010). At the forefront of regenerative medicine, stem cell research offers the potential to propagate cells that can divide and differentiate to serve specialized functions, replenish tissues and organs, and act as repair systems for the body.

Few areas of research have been the subject of as much public debate and generated as much enthusiasm as stem cell research (Caulfield et al., 2009). Indeed, the field of regenerative medicine has been the focus of hope for many stakeholders including patient groups, clinicians, politicians, policymakers, the media, and funding agencies. Public discourse has emphasized the potential to combat currently incurable diseases by way of stem cell interventions. At the same time, prominent social concerns and policy barriers to the applications of stem cell research, particularly research involving embryonic tissue and induced pluripotent stem cells, parallel public excitement about the biotechnology (Caulfield et al., 2009). In addition, public controversies surrounding the integrity of stem cell research and its clinical applications have undermined legitimate scientific progress (Resnik, Shamoo, & Krimsky, 2006).

Studies suggest that the news media have played a role in shaping and reflecting public dissonance about stem cell research by representing both stories of promise and highlighting ethical controversies (Rachul, Zarzeczny, Bubela, & Caulfield, 2010). Research also suggests that media communications have also widened the translational gap between public expectations for immediate therapeutic applications of stem cell research and the clinical reality of limited treatment options for many diseases—a common occurrence among emerging biotechnologies (Evans, Kotchetkova, & Langer, 2009; Sung & Hopkins, 2006; Wilde, Bonfiglioli, Meiser, Mitchell, & Schofield, 2011). This gap is particularly prominent in the realm of neurological diseases, as media communications disproportionally focus on the applications of stem cell therapeutics in the neurosciences despite the relatively few clinical trials addressing neurological conditions (Bubela et al., 2012).

Gaps in pharmaceutical applications, patient need, and financial catalysts have contributed to the strong translational ethos in the field of regenerative medicine (Maienschein, Sunderland, Ankeny, & Robert, 2008). In recent years the field has seen movements to promote the rapid translation of stem cell research. Such strategies have been anchored in variable levels of regulatory protections. For example, Japan has recently implemented a conditional approval framework for regenerative medicine products that is characterized by abbreviated clinical research pathways and relies on continuous post-market surveillance to demonstrate indices of efficacy for clinically available stem cell therapeutics (Cyranoski, 2013; Sipp, 2015). Other movements have been motivated by an impetus for deregulation (Yusuf, 2010). These include the off-shoring of clinical research from jurisdictions of rigid oversight to ones with more relaxed regulatory mechanisms, and the provision of unproven and unregulated stem cell interventions through clinical platforms, a phenomenon colloquially termed *stem cell tourism* (Caulfield et al., 2009; Hyun, 2010; Ryan, Sanders, Wang, & Levine, 2009).

Medical tourism has presented a salient challenge in the field of regenerative medicine. Stem cell clinics most often, although not exclusively, operate from developing countries that have more limited regulatory mechanisms than, for example Canada or the United States. They commonly provide services to patients from industrialized countries and often advertise their services direct to consumers through web sites that overemphasize therapeutic benefits, present experimental interventions as *bona fide* treatments, downplay risks of harm, and charge significant fees (Einsiedel & Adamson, 2012; Lau et al., 2008; Petersen & Seear, 2011; Regenberg, Hutchinson, Schanker, & Mathews, 2009). These clinics often base their interventions on limited or no pre-

clinical data, limited evidence of safety and efficacy, and often fail to follow up with patients in the long-term to capture adverse events (MacReady, 2009). Serious adverse events, including meningitis, blindness, and cancer, have been reported in patients who have undergone unregulated stem cell procedures abroad (Amariglio et al., 2009; Dobkin, Curt, & Guest, 2006, Kuriyan et al., 2017). While it is difficult to characterize the full extent of stem cell tourism, it is believed that over 700 clinics worldwide provide dubious stem cell interventions, and that thousands of patients receive such procedures every year (Einsiedel & Adamson, 2012; Ryan et al., 2009; Song, 2011). Stem cell tourism is particularly problematic in the case of neurodegenerative disease, as purveyors of unproven and unregulated stem cell interventions most commonly target patients with diseases of the brain (Lau et al., 2008). Premature and illegitimate forms of stem cell application, such as stem cell tourism, prey on patient urgency to access a therapy, undermine legitimate translational research, and reframe the rigorous and utilitarian process of scientific evaluation as an access hurdle.

In response to translational challenges in regenerative medicine, the International Society for Stem Cell Research (ISSCR) convened an expert task force to create guidelines for stem cell research and clinical translation. Initial guidelines were published in 2008, and were further revised in 2016 (International Society for Stem Cell Research, 2008, 2016). The ISSCR guidelines emphasize several ethical principles in the translation of stem cell interventions including the focus on beneficence and patient welfare, respect for research subjects, social justice, transparency, and maintenance of the integrity of stem cell research. Several of these principles are common to other prominent guidance for human subjects research (Canadian Institutes of Health Research, Natural Sciences & Engineering Research Council of Canada, &

Social Sciences & Humanities Research Council of Canada, 2014; Emanuel, Wendler, & Grady, 2000; National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research, 1978). The emphasis on transparency and integrity in the context of regenerative medicine may be particularly compelling given the rise of stem cell tourism. The ISSCR specifically condemns stem cell tourism and provides cautious guidance for the provision of regulated but unapproved stem cell interventions outside of clinical trials through innovative therapy platforms such as compassionate access or off-label use (International Society for Stem Cell Research, 2016). To promote transparency about stem cell research the ISSCR encourages researchers to engage with various members of the public, including patient communities that may have the greatest stakes in the development of novel stem cell biotechnologies. Recommendations for such engagement encourage reciprocal conversations with patient communities to identify their informational needs about the state of the art of research and to clarify uncertainties about the safety and efficacy of novel stem cell interventions (International Society for Stem Cell Research, 2016).

1.3 At the Interface of Regenerative Medicine and Neurotechnology

Neurological applications have been a focus in regenerative medicine, with laboratory and early phase clinical trials for numerous diseases including stroke, spinal cord injury, Parkinson disease, and demyelinating diseases. Along with scientific advancement in this area, stem cell interventions for neurological diseases have raised prominent social and ethical concerns (Cote et al., 2017). The field of neuroethics aims to align neurotechnological innovation with societal values through dedicated attention to their ethical, legal, and social implications (ELSI) (Marcus, 2004). The brain is widely regarded as the seat of the mind, and is inextricably linked with

abstractions of individuality and personal identity (Leshner, 2005). It is therefore not surprising that new brain technologies that reside at the intimate frontier of personhood are compelling widespread public interest and engagement (Illes et al., 2005).

In this dissertation, I apply a pragmatic neuroethics framework (Racine, 2010) to explore the perspectives of relevant stakeholders about degenerative diseases of the brain that rob individuals of their mobility and cognitive function. An aging population has contributed to the high and growing prevalence of neurodegenerative diseases, and predictions that the global prevalence of neurodegenerative diseases will nearly double worldwide by 2030 are raising a significant public health challenge (Tofaris & Schapira, 2015). Currently most degenerative diseases of the brain cannot be cured, and the majority of treatment and clinical research are focused on disease modification or symptom management (Kiaei, 2013). Given this clinical need, development of biotechnologies that offer the prospect of new therapeutic avenues or even cures naturally elicits hope in patient communities that face debilitating and progressive disease. In recent years, there has been tremendous support for experimental interventions in the field of neurology with biotechnological development in areas such as neuroimaging, gene therapy, deep brain stimulation, optogenetics, nanotechnology, and stem cell research (Chatterjee & Farah, 2012; Einsiedel, 2009; Illes, 2017; Robillard, Lo, Feng, & Hennessey, 2016).

Here, I focus largely on stem cell research for neurodegenerative disease, an area that has been the subject of research and hope for multiple sclerosis (MS), amyotrophic lateral sclerosis, Parkinson disease, Alzheimer disease, and Huntington disease among others (Cote et al., 2017). I anchor the dissertation on MS specifically, a chronic and progressive neurological disease of the

brain and the spinal cord that affects more than two million individuals worldwide (Multiple Sclerosis International Federation, 2016). Its prevalence in Canada—at an estimated rate of 1 in 340 Canadians living with the disease—exceeds others internationally (Statistics Canada, 2017). In persons with MS, the immune system attacks myelinated axons in the central nervous system. This causes communication gaps between the brain and the rest of the body leading to a range of symptoms such as vision loss, fatigue, pain, sensory loss, spasticity, impaired mobility and cognitive deficits (Compston & Coles, 2008). Initially these symptoms may fluctuate. However, over time symptoms accumulate and become irreversible. Since the 1990s disease modifying drugs have decreased the frequency of new symptoms and delayed the onset of progressive decline. These treatments, however, only appear to benefit those at the earliest stages of the disease, and have little impact on improving or reversing chronic symptoms that impact quality of life (Goldenberg, 2012). The complex interaction between immunogenic predispositions and a variety of environmental triggers for the disease, especially the progressive forms, present challenges to finding a cure, and leave many patients severely disabled. Given this clinical need, MS has been an area of inquiry and hope in regenerative medicine since the 1990s. Early clinical trials focused on bone marrow transplantation approaches (Burt, Burns, & Hess, 1995). Contemporary clinical research approaches focus on autologous hematopoietic and mesenchymal stem cell applications (Atkins et al., 2016; Connick et al., 2012).

1.4 Dissertation Overview – Bridging Society, Regenerative Medicine, and Neurotechnology

In this dissertation, I aim to generate new knowledge that integrates the voices of patients, clinicians, and the media to further inform the development of stem cell research in a socially minded way. To this end, the following overarching research question anchors my work:

> *What are the perspectives of stakeholders about the translation of novel biotechnologies for neurodegenerative diseases?*

I elaborate on the central research question with the following sub-questions:

1. How are the perspectives of patients with multiple sclerosis (MS) about stem cell interventions influenced by advocacy and hype in biotechnology development? I use the case of the chronic cerebrospinal venous insufficiency research trajectory as a case study to answer this question.
2. How does the news media represent the timeframes associated with the research and development of stem cell interventions for neurodegenerative diseases?
3. What are the perspectives of patients with MS and clinician who care for them about the timeframes associated with the research and development of stem cell interventions?

This dissertation is formatted as a collection of independent but related manuscripts about stakeholder perspectives at the interface of regenerative medicine and neurotechnology development.

Following this introduction, I provide an overview of the methods and research design in Chapter 2. I begin with a discussion of the perspectives and experiences that shape my research

questions and study design. I elaborate on the ethical considerations for the research, particularly those associated with the inclusion of human participants. Finally, I provide details on the qualitative and quantitative methods used throughout the dissertation. Additional details about methods are further elaborated within chapters 3-5 that are stand-alone papers that have been published, submitted, or prepared for publication.

In Chapter 3 I focus on the perspectives of MS patients about the impact of advocacy, hype, and negative findings on biotechnology development. Through a qualitative descriptive study, I explore the impact of the chronic cerebrospinal venous insufficiency (CCSVI) research on MS patients' perspectives on contemporary stem cell research. The CCSVI experience generated both hope and skepticism, galvanized substantial international attention, and was heavily criticized for privileging public pressure over empirical evidence. In the aftermath of excitement about this surgical intervention for MS that has recently yielded negative findings in early-phase clinical trials, I explore patient perspectives about stem cell research, an analogous non-pharmaceutical biotechnology that has been the subject of hope in the MS community for nearly three decades.

In Chapter 4 I characterize the perspectives represented in the news media about the translation of stem cell research. The media are the most accessible source of information about science in the public sphere, the media have long served as a prominent means for civic engagement in biotechnology (Bubela et al., 2009). The media operate at the interface between scientific communities and lay publics, including patient communities, and thus serve as key gatekeepers of information between science and the society. News media not only inform the public about

advancements in stem cell biotechnologies, but also shape and reflect public priorities and concerns about translational research (Benjaminy & Traboulsee, 2017). In this chapter I focus on media portrayals of timeframe projections, descriptions of clinical trial phases and sample sizes, checkpoints and hurdles for translation, and descriptions of availability of stem cell interventions abroad (Benjaminy, Lo, & Illes, 2016).

In Chapter 5 I explore the perspectives of patients with MS and clinicians responsible for their care about the timeframes associated with the translation of stem cell research. Through a series of semi-structured interviews and a qualitative descriptive analytic approach, this study reveals receptivity to stem cell interventions for MS, estimations of timeframes associated with the clinical implementation of stem cell interventions, and accelerators and barriers to the translation of this research trajectory. This chapter concludes with a proposal for clinical communication strategies that aims to contextualize and clarify translational timeframes and promote informed hope about biotechnology development.

In Chapter 6 I bring together each arm of my dissertation research into a set of observations, conclusions, recommendations, and directions for future research. I build on results to: (1) suggest a model of informed hope (Figure 6.1) that aims to modify the cycle of inflated expectations and disappointment in biotechnology development, and (2) expand on existing scholarship about the tension between public demand for rapid access to experimental interventions and the lengthy evaluation process of clinical translation.

Chapter 2: Research Methods

In this chapter, I provide an overview of the methods used in this dissertation and their theoretical underpinnings. I begin by summarizing the research questions that guide the dissertation. I then provide a statement of personal perspectives that situates my role as a researcher in this body of work. I outline key ethics considerations in conducting human subjects research, and the theoretical and methodological grounding of the research.

2.1 Research Questions

Throughout this dissertation, my goal is to answer the following research question:

> *What are the perspectives of stakeholders about the translation of novel biotechnologies for neurodegenerative diseases?*

As a case example, I focus on stem cell biotechnologies that have been an avenue of research and of hope in the sphere of neurodegenerative diseases over the past 30 decades. Three sub-questions elaborate the answers to the central research question:

1. How are the perspectives of patients with multiple sclerosis (MS) about stem cell interventions influenced by advocacy and hype in biotechnology development? I use the chronic cerebrospinal venous insufficiency research trajectory as a case example to answer this question.
2. How does the news media represent the timeframes associated with the research and development of stem cell interventions for neurodegenerative diseases?
3. What are the perspectives of patients with MS and clinician who care for them about the timeframes associated with the research and development of stem cell interventions?

2.2 Statement of Personal Perspectives

In this section, I reflect on my worldviews and biases that contour this dissertation. To begin, I consider the view that the qualitative researcher is often regarded as the instrument of research. Traditional views that regard the researcher as an objective collector of facts have been widely criticized by qualitative scholars and have established the contemporary opinion that "all researchers bring their own preconceptions and interpretations to the problem being studied, regardless of the methods used" (Patton, 1999, p. 1204). Researchers often construct meaning rather than find meaning in their data, thus rendering an implicit interdependency between the researcher, the method, and the data (Mauthner & Doucet, 2003). Methodologists and scholars assert that methodological coherence, or the congruence between the researcher's epistemological and ontological stances, the research questions, the methods, and analyses utilized in the study (Mayan, 2016), is fundamental to ensuring rigour in qualitative research (Morse, Barrett, Mayan, Olson, & Spiers, 2002). Moreover, researchers may subtly influence the perspectives of their study participants (Cox & Starzomski, 2004). Denzin and Lincoln describe the term research paradigm as "a basic set of beliefs that guide action" and shape the worldview of the researcher (Denzin & Lincoln, 2011, p. 91). As such, the ontological, epistemological, and methodological propensities of the researcher influence the configuration of the research stance (Laudan, 1984; Morgan, 2007).

Epistemology describes the branch of philosophy that is dedicated to the theory of knowledge and the process by which knowledge is created or acquired, validated, and justified (Mayan, 2016). My epistemological stance is influenced by a variety of traditions and experiences to

which I have been exposed. My background in molecular genetics forms the basis of my understanding of empirical research in a post-positivist approach. The post-positivist approach, compared to a positivist approach that seeks objective truth and reality, acknowledges that empirical methods have inherent limitations and therefore can only deliver an approximation of reality (Denzin & Lincoln, 2011). In keeping with this position, I also use principles from social constructivist inquiry that aims to explore a subjective truth and embraces bias (Creswell, 2006; Crotty, 1998). As my research is grounded in curiosity about the experiences and perspectives of research participants, I aim to espouse an *emic* stance that encourages research within a social group—in contrast to *etic* traditions that maintain social distance between the researcher and the researched (Olive, 2014). My desire to understand the perspectives of research participants thus lends itself to well to exploratory and inductive qualitative research inquiry (Chenail, 1997). , I accommodate this seemingly epistemological muddle of conflicting approaches by incorporating a predominantly social constructivist approach with elements of post-positivist methods.

Ontology describes the nature of being, and of reality and truth (Mayan, 2016). I define my ontological perspective as relativist. I believe that reality is individually constructed, and that therefore multiple perspectives on realities and truths can co-exist. I aim to explore the truths of the research participants in my studies through conversations about their perspectives, and analyze these perspectives using an inductive an open-minded methodological approach.

As a believer in science and medicine, I am an optimist. Indeed, over the course of my doctoral studies I have developed hopes for the timely development of biotechnologies that tackle diseases of the brain, particularly stem cell interventions. Whether my hopes have been

influenced by bearing witness to patient narratives that often describe the challenges of living with progressive neurodegenerative disease, or by my involvement with professional organizations such as the Stem Cell Network, Canada, I recognize that there is a possibility that my views may influence participants during the research process. I regard this possibility with great responsibility, and have engaged in activities that promote reflexivity throughout the research process in an attempt to mediate the influence of my perspectives on research participants. For example, in the data collection stage, I avoided asking leading questions or imposing my beliefs upon research participants. After every interview, I created memos about my impressions and lingering questions, and reflected on how interview data aligns with or departs from my assumptions. During the data analysis process, I initially coded data line-by-line, and used active language such as gerunds to ensure that participant narratives closely inform the interpretation of study findings. Finally, I engaged in a member checking exercise on all qualitative data, to ensure that the synthesized results authentically represent research participants' views.

2.3 Ethics Review

This dissertation includes human subjects research and adheres to guidelines of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Canadian Institutes of Health Research et al., 2014). All studies presented here were reviewed by the University of British Columbia Behavioural Research Ethics Board (BREB) and approved under certificate H13-03275. The Ottawa Health Science Network Research Ethics Board (20150282-01H) reviewed the study presented in Chapter 3. Additionally, all research was reviewed and received operational approval by Vancouver Coastal Health Research Institute. All research participants

gave informed consent (Appendix B) to participate in the studies described in this dissertation. Research participants were informed that the study is voluntary and that participation would not impact their clinical care. Given the sensitive nature of some of the studies, participants were encouraged to disclose as little or as much information as they wished during the interview process. They were also invited to review interview transcripts, recant statements, and withdraw from the study prior to publication. To protect participants' privacy, all transcripts of interview data were assigned alphanumeric codes, de-identified, and stored in a secure locked cabinet in the office of my supervisor, Dr. Judy Illes. All data will be retained for a minimum of 5 years after the publication of the studies described in this dissertation and subsequently destroyed.

2.4 Theoretical Framework

In this dissertation, I harness the strength of *pragmatic neuroethics* as a theoretical grounding. Neuroethics is a burgeoning field dedicated to exploring the ethical, legal, and social implications of developing neurotechnologies. It aims to align "the exploration and discovery of neurobiological knowledge with human value systems" (Illes, 2007, p. S57). Pragmatic neuroethics emphasizes the importance of empirical analyses over *a priori* sets of moral principles, and proactive, solution-oriented inquiry over reactive measures to adverse phenomena or events (Racine, 2010). It is rooted in the pragmatist tradition that was championed in the late 1800s by philosophers such as Charles Sanders Peirce, William James, John Dewey, and George Herbert Mead. Pragmatism is a *humanist* tradition that grounds morality in the ever-evolving values of human beings. Pragmatism emphasizes *situationalism* and calls for descriptions of context that shape moral action, including the implications of social systems that guide dynamic formulations in ethics. It also promotes challenging common morality based on scientific

knowledge and advancing the understanding of ethical behaviour in the context of practical, real-world circumstances. In line with the fundamental rejection of dogmatic adherence to normative moral principles, pragmatism welcomes the application of knowledge from a diversity of moral theories (Fins, 2008; Racine, 2008, 2010).

The field of neuroethics has brought a contemporary emphasis on pluralism to the application of the pragmatist tradition. Pragmatic neuroethics underscores the importance of multidirectional and inclusive deliberations at the intersection of science and society (Illes et al., 2005). This approach calls for incorporating the perspectives of relevant and diverse stakeholders about the ethical and social issues that arise with developing neurotechnologies, with the aim of applying such evidence to inform best practices in ethics (Racine, Bell, Di Pietro, Wade, & Illes, 2011).

Racine et al. (2011) argue that the comprehensive application of a pragmatic neuroethics approach should include the voices of affected individuals with the aim of informing the development of biomedical research with key social considerations. In this dissertation, I apply a pragmatic neuroethics lens to an inquiry that aims to integrate the perspectives of key stakeholders in developing biotechnologies for neurodegenerative disease. I explore the values, priorities, and concerns of potential end-users of novel neurotechnologies, such as patients and clinicians, through an inductive approach that honours the unique narratives of research participants. I also survey discourse in the public sphere through a media analysis that aims to deliver new knowledge on narratives about science that both shape and reflect societal perspectives about developing neurotechnologies.

Pragmatism, much like other philosophical theories, has limitations. The pluralistic orientation central to the pragmatist tradition has been criticized as being overly relativistic. Indeed, critics argue that the pragmatist tradition regards opposing or divergent positions on the same issue as equally good (Rorty, 1980). Objections rooted in a realist ontological stance, which privilege an objective truth or moral course of action over others are at odds with the pragmatist tradition for its relativistic stance. Moreover, the rejection of the pragmatic commitment to normative moral principles has been challenged in the context of "inalienable human rights", which critics argue should be universally protected (Rorty, 1999). These are a few key limitations of the pragmatist tradition. A comprehensive critique is found in Rescher (2012).

2.5 Methods

I utilize two overarching approaches to address the primary research questions: (1) qualitative descriptive inquiry (Chapter 3, Chapter 5); and, (2) media analysis (Chapter 4).

2.5.1 Qualitative Descriptive Inquiry

2.5.1.1 Overview

Qualitative research is a methodological approach that encompasses a variety of research traditions. Generally, qualitative inquiry aims to gather or interpret an in-depth understanding of human experience. It is often utilized in circumstances where little is known about an area of focus, and thus, necessitates an inductive stance and a bottom-up approach (Richards & Morse, 2012). In Chapter 3 and Chapter 5, I use a descriptive qualitative method, as described by Sandelowski (2000). This method lends itself well to studies that aim to explore and characterize rich phenomena of interest, but that do not focus on generating an abstract interpretive outcome,

such as a conceptual advance or theoretical contribution (Sandelowski, 2000). Qualitative descriptive studies are characterized as a form of *naturalistic inquiry* (Lincoln & Guba, 1985). In naturalistic studies the researcher does not manipulate variables, does not utilize *a priori* theoretical frameworks to shape analysis, and allows phenomena to unfold naturally (Willems, 1967). Qualitative descriptive inquiry is often not grounded in a theory or philosophical spin, and is particularly amenable for solution-oriented research that aims to answer practical questions for application in real-world settings (Sandelowski, 2000). Qualitative descriptive studies are also less structured than other traditions of qualitative inquiry (e.g., phenomenology, grounded theory, ethnography) that are based on well-established methodological frameworks. Instead, qualitative descriptive studies are often eclectic and borrow from a variety of qualitative traditions in an effort to accommodate a pragmatic approach. In this thesis, I incorporate several features from the tradition of grounded theory into my qualitative descriptive inquiry including the use of a constant comparative approach that seeks similarities and differences within and between interview transcripts to characterize recurring phenomena and unique variations, and the use of theoretical saturation (when no new themes emerge from additional data analysis) as an indicator of sufficient sampling (Charmaz, 2014).

A common limitation of qualitative studies is the generalizability of the findings. The data represent the perspectives of a small number of research participants and represent their views at a snapshot in time. The data therefore do not provide generalizable accounts. The data also do not provide reliable accounts that can be replicated with precision in the future. Instead, the research aims to be transferable as discussed in section 2.5.1.6. For a comprehensive discussion

of the limitations of qualitative descriptive research within the context of specific studies in this dissertation, see sections 3.6, 5.6, and 6.3.

2.5.1.2 Sampling and Recruitment

For the studies described in Chapter 3 and Chapter 5, I recruited individuals who have MS (patients) and clinicians responsible for their care (clinicians). The inclusion criteria for patients were: a diagnosis of MS; age ≥19 years; ability to provide informed consent; and, ability to speak English. The inclusion criteria for clinicians were: an MD degree; clinical practice that involves care for individuals with MS; age ≥19 years; ability to provide informed consent; and, ability to speak English.

I used both convenience and purposive sampling approaches to recruit research participants. A convenience approach is a sampling technique where research participants are selected on the basis of accessibility and proximity to the researcher (Neuman, 2011). I recruited both patients and clinicians using this sampling technique. Patients were recruited using advertisements on Canadian patient advocacy websites, on the National Core for Neuroethics website, and through MS clinics (Appendix A.1, Appendix A.2). Clinicians were recruited through an MS-specific clinical listserv. In addition to this convenience approach, I used a purposive sampling approach to target additional clinicians. A purposive sampling approach is characterized by a selective and non-random targeting of research participants (Blackstone, 2012). I used this approach to send personal e-mail invitations to MS specialists throughout Canada (Appendix A.3, Appendix A.4). Specialists were identified through academic publications, memberships in professional societies, and affiliation with major clinical and academic centers.

Qualitative research is often characterized by an in-depth analysis of a small sample of research participant data. Small sample sizes are aligned with the goal of maintaining close association with research participants, and achieving an analysis that accounts for depth rather than breadth of research participant perspectives (Crouch & McKenzie, 2006). Instead of striving to collect a representative account of participant experiences through large sample sizes that would yield generalizable results, qualitative studies aim to establish theoretical saturation. Theoretical saturation is generally achieved in sample sizes of 15-20 participants, depending on the homogeneity of the sample size (Guest, Bunce, & Johnson, 2006). In this dissertation, I interviewed 20 MS patients and 15 clinicians responsible for their care. Clinicians represented more homogenous perspectives than the patients, perhaps because of commonalities in training and a shared discipline. Theoretical saturation for this cohort was therefore achieved following 15 interviews. Twenty interviews with patients were needed to reach theoretical saturation.

2.5.1.3 Data Collection

I conducted a series of in-depth semi-structured interviews with research participants. I developed interview guides (Appendix C) using previous studies of patient perspectives about novel biotechnologies (Benjaminy et al., 2014; Illes, Reimer, & Kwon, 2011). Interview guides were structured to include open-ended questions to elicit rich descriptions of the phenomena of interest and allow research participants an opportunity to direct important elements of the narrative (Kvale & Brinkmann, 2009). Semi-structured interviews allow for a balance of organization in the conversation as well as flexibility necessary for the emergence of participant-driven narratives. As standard in qualitative research, when participants' narratives diverge from

the initial interview guide, participant priorities to direct the conversation. Data collection and analysis were concurrent and iterative. This strategy enables primary data interpretation to be challenged and further refined and developed through ongoing data collection (Mayan, 2016).

Interviews ranged from approximately 45 minutes to one hour in length. To accommodate participants and ensure inclusivity, I conducted interviews in-person or over the phone based on participant preference. In-person interviews took place in a private conference room at the University of British Columbia. All interviews were audio recorded.

2.5.1.4 Data management

Data management adhered to guidelines of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (Canadian Institutes of Health Research et al., 2014). Interviews were audio recorded and subsequently transcribed verbatim. To protect the privacy of research participants, transcripts were de-identified and names were replaced with alphanumeric codes. I used NVivo 11 software to organize and analyze the data. NVivo 11 is a qualitative data management software that allows the researcher to index segments of text to particular themes, link research notes and observations to coding, helps the researcher to query possible relationships between the themes, and provides an audit trail to document the analytical process (Bazeley & Jackson, 2013; Richards, 2014).

2.5.1.5 Data Analysis

I utilized a qualitative content analysis approach in data analysis, a common method in qualitative descriptive studies (Sandelowski, 2000). This method is a dynamic and iterative approach used to summarize and organize data. Unlike quantitative content analysis that approaches data through a rich framework of existing knowledge and often relies on an *a priori* set of coding categories to organize the data, qualitative content analysis addresses the data from the bottom up and seeks to develop coding categories for emergent concepts in the data (Mayan, 2016).

I began coding the data line-by-line, staying close to the narratives of research participants by using summarizing gerunds and assigning units of meaning that closely reflect the language used by research participants (Charmaz, 2014). After this initial coding process, I utilized a constant comparative approach to identify similarities and differences within and between transcripts to identify relationships between codes (Glaser & Strauss, 1967). This enabled me to organize recurring codes into coding categories and emergent higher order themes. Through deliberations with a second coder, I revisited initial codes to ensure that they were organized well within coding categories and themes, and formed a final codebook through a consensus approach. To ensure the dependability of the codebook, a subset of the transcripts was co-coded with a second researcher. Cohen's kappa coefficient was used to indicate inter-rater reliability (Neuendorf, 2016).

Following data analysis, I prepared summaries of synthesized data and sent them to research participants who agreed to be re-contacted. I invited research participants to comment on the

findings, ask questions, or challenge the interpretation of the data. I integrated participant feedback to ensure that the data authentically represent participant views (Carlson, 2010).

2.5.1.6 Trustworthiness

Rigour in qualitative research has come under considerable scrutiny from researchers who espouse positivist ontological stances that aim to capture a precise and unbiased depiction of reality in their research (Morse et al., 2002; Shenton, 2004; Silverman, 2006). Qualitative methodologists have made attempts to apply quantitative constructs of rigour, such as reliability and validity to qualitative inquiry (Golafshani, 2003; Long & Johnson, 2000). However, contemporary qualitative methodologists argue that unique measures of rigour in qualitative research respond more appropriately to its paradigmatic underpinnings and goals (Morse et al., 2002; Shenton, 2004). *Trustworthiness* is the predominant measure of rigour in qualitative research, and is characterized by: *credibility, confirmability, dependability, and transferability* (Lincoln & Guba, 1985).

Credibility is a measure of how accurately and comprehensively the researcher has described the phenomenon under inquiry (Lincoln & Guba, 1985). It is parallel to the quantitative measure of internal validity. I endeavored to maintain credibility in the construction of this dissertation by developing interview guides based on a thorough review of the literature, and in consultation with experts from my supervisory committee. Following transcription of every interview, I compared the original audio to the transcript version to verify accuracy and to ensure that each transcript was software-ready. I used NVivo 11 to generate an audit trail of the data analysis process (Welsh, 2002). All codebooks used to analyze the data were developed through iterative

deliberations with a second coder until consensus was reached. This deliberation process focused on distinctions between coding categories, as well as comprehensiveness of codes in describing the studied phenomena. Finally, once the data were analyzed and synthesized, I carried out a member checking exercise to ensure that my analysis reflected participants' views (Carlson, 2010).

Confirmability is parallel to the quantitative construct of objectivity. It is a measure of how well the research findings are supported by the data (Lincoln & Guba, 1985). To promote confirmability, I embedded quotes throughout Chapter 3 and Chapter 5 to give the reader a sense of participant narratives for each theme in the dataset. I used ellipses to shorten lengthy segments of data but ensured the abbreviation of segments did not omit important information or alter the meaning of quotes. I added parentheses in quotes to clarify details that were evident in the original narrative but missing when presented outside the original transcripts. Along with a second coder, I carefully reviewed all quotations in their original context prior to integrating into the final analysis.

Dependability is a measure of how well the study would yield similar findings, along with logical differences, if it were carried out in a similar context in the future (Shenton, 2004). Unlike reliability, the quantitative analog, dependability does not call for replication of study results. The investigator's observations and interactions with study participants are uniquely embedded into the context of the study and could never be entirely replicated (Shenton, 2004). To promote dependability, I provided a thick description of the study context as well as the

procedures of the research. These strategies include a description of recruitment strategies, research participants' characteristics, and data management and analysis.

Transferability describes the degree to which study results can be transferred outside of the study population (Lincoln & Guba, 1985). Unlike the parallel quantitative construct, generalizability, qualitative research does not aim to apply directly to populations outside of the study group. Since results of qualitative analyses are obtained from a small number of participants in a specific context, methodologists believe that qualitative research yields in depth description of phenomena but applying its findings and conclusions to other contexts and broad populations may be inappropriate (Shenton, 2004). To promote transferability, it is crucial to provide in-depth descriptions of the study context and procedures that allow future researchers to understand commonalities and differences between the current study and future investigations (Carlson, 2010). Indeed, strategies that promote transferability are linked with those aimed at ensuring dependability in qualitative inquiry (Shenton, 2004). I provided a detailed account of research context through description of study participant characteristics, inclusion and exclusion criteria, recruitment methods, data collection processes, interview length, location, as well as data analysis procedures.

2.5.2 News Media Analysis

2.5.2.1 Data Collection

Chapter 4 of this dissertation explores the landscape of communication about stem cell research in the news. I collected news articles from the United States (US), Canada (CA), and the United Kingdom (UK). These are three English-speaking countries that have registered the largest

numbers of stem cell clinical trials on ClinicalTrials.gov (National Institutes of Health, 2014). I collected news articles between 1991-2014, as media began to cover stories about stem cell interventions in 1991 (Bubela, Li, Hafez, Bieber, & Atkins, 2012). I developed customized search algorithms to capture news articles about stem cell clinical trials in media databases Factiva (US, UK) and Canadian Newsstand (CA). An initial search produced 339 articles (US n=174; CA n=59; UK n=106). After reading each article, I excluded all but original articles that discussed human stem cell interventions for neurodegenerative disease, resulting in 177 relevant articles (US n=83; CA n=29; UK n=65). This collection of news articles was further divided into two sets: a set of 94 articles that broadly focused on stem cell interventions for non-neurodegenerative disease, but still discussed neurodegenerative disease in a substantial way; and, a set of 83 articles that primarily focused on human stem cell interventions for neurodegenerative disease.

2.5.2.2 Data Analysis

I used a quantitative content analysis approach to characterize news article trends about stem cell research. Unlike the qualitative content analysis approach described above, a quantitative content analysis is used in instances where a wealth of knowledge and research exists about the phenomena of interest, and can guide the development of a deductive rather than inductive analytic approach (Neuendorf, 2016). I developed an *a priori* coding frame to analyze the content of the newspaper articles. The coding frame was informed by previous media analyses about biomedical research and health biotechnologies (Bates, 2005; Benjaminy & Bubela, 2014; Bubela & Caulfield, 2004; Caulfield et al., 2007; Holtzman et al., 2005; Illes et al., 2010; Racine, Bar-Ilan, & Illes, 2005; Racine, Waldman, Rosenberg, & Illes, 2010). The coding frame

(Appendix E) investigated timeframe projections, tone of projections, spokespeople who made projections, and public health claims in all the articles. I then coded the set of articles that primarily focused on human stem cell interventions for neurodegenerative diseases for additional constructs: dominant themes, descriptions of clinical trial phases and sample sizes, checkpoints and hurdles for translation, and descriptions of availability of stem cell interventions abroad. Along with a second coder, I performed Cohen's kappa tests on a subset of the articles to establish inter-coder reliability (Landis & Koch, 1977).

Chapter 3: Stem Cell Research in the Post CCSVI Era—Resilience, Trust, and Civic Engagement

3.1 Synopsis

Scientific and financial investments in chronic cerebrospinal venous insufficiency (CCSVI) research have been made to address both the hope for and skepticism over this interventional strategy for MS. Despite limited scientific evidence in support of the CCSVI hypothesis, the funding of clinical research was responsive to a demand by the public. I characterize patient perspectives about the CCSVI research trajectory, with particular attention to its impact on stem cell research, an analogous non-pharmaceutical intervention for MS. I conducted a series of semi-structured interviews with 20 MS patients across Canada who did not have CCSVI interventions. Interviews were analyzed for recurring themes and individual variations using the constant comparative approach. I found that participants had a critical view of the divestment of funds from stem cell research to support CCSVI trials, while retaining a sense of optimism about emerging evidence for stem cell interventions for MS. The unrealized hopes for CCSVI challenged the MS patient community, but did not undermine their resilience and optimism for developing therapeutic interventions. The narrative that unfolded highlights the importance of drawing a socially minded space for public participation in science.

3.2 Introduction

The chronic cerebrospinal venous insufficiency (CCSVI) hypothesis became a focus for multiple sclerosis (MS) research when a small study suggested that an angioplasty-like procedure would restore efficient haemodynamic flow, reduce iron deposits in the brain, and prevent related inflammation and myelin sheath attack (Zamboni et al., 2009; Zamboni et al., 2009). The hope for CCSVI was particularly pronounced in North America, where the MS community embarked on an unprecedented venture to secure investment in related research in hopes of a cure. Despite initial studies that challenged the CCSVI hypothesis (Doepp, Paul, Valdueza, Schmierer, & Schreiber, 2010; Traboulsee et al., 2014), the intervention—colloquially termed *liberation therapy*—was prevalent in the public sphere through wide-reaching anecdotal accounts of therapeutic gain in social media, and through advocacy efforts that pressured policy makers to mobilize access to the public (Pullman, Zarzeczny, & Picard, 2013).

In the current era of biomedicine in which models of public participation in science are embraced and a landscape of increasingly accessible social media is democratizing science, the voices of the public were heard. Indeed, despite widespread caution from experts, over $20 million were invested in CCSVI research in Canada and the United States (Pullman, Zarzeczny, & Picard, 2013). Severe adverse events and preventable fatalities from the CCSVI procedure were reported by others (Samson, 2010; Food and Drug Administration, 2015). Recent reports from a multi-site Canadian CCSVI clinical trial demonstrate negative results in 104 MS patients (Barton, 2017).

In an environment in which health research resources are taxed (Owens, 2015), investment in CCSVI research diverted both funding and attention from other areas of clinical inquiry. Here I

examine the lessons learned from the CCSVI research experience to understand the impact of the deviation in research on the perspectives of patients with MS and their trust in biotechnology. I focus on stem cell research in particular, an area of non-pharmaceutical inquiry that has been at the heart of hope in the MS community for nearly 30 years, and that has produced promising contemporary results through both hematopoietic and mesenchymal approaches (Atkins et al., 2016; Burt et al., 1995; Burt, 2017; Connick et al., 2012; Cote et al., 2017; Nash et al., 2017).

3.3 Methods

I recruited individuals with MS from across Canada, a country that has one of the highest rates of MS in the world, and where advocacy efforts for CCSVI research were particularly widespread and influential (Statistics Canada, 2017). I used a convenience sampling approach where research participants were recruited through online advertisements on patient advocacy group websites and through MS clinics. The time interval for participation was between May 2014 and August 2016. Inclusion criteria were: a diagnosis of MS; age ≥19 years; ability to provide informed consent; and, ability to speak English.

Following approval by the University of British Columbia Research Ethics Board (H13-03275) and the Ottawa Health Science Network Research Ethics Board (20150282-01H) and standard procedures for acquiring informed written consent (Appendix B), I conducted a series of in-depth semi-structured interviews. The interview guide (Appendix C) was informed by past studies of patient perspectives about novel biotechnologies (Benjaminy, MacDonald, & Bubela, 2014; Illes, Reimer, & Kwon, 2011). The overarching research question was: *What are the perspectives of*

MS patients about the CCSVI research trajectory, and how do these impact their views on stem cell research?

The interview guide was initially designed to focus on stem cell research, but, as prominent themes about the impact of CCSVI arose, I adapted the interviews to incorporate content that was responsive to participant priorities. This flexibility is consistent with the inductive approach described by Charmaz (2014) that accommodates the emic tradition of qualitative inquiry (Charmaz, 2014). I probed for familiarity with the CCSVI research trajectory, perspectives about CCSVI research and its impact, and perspectives about the promise of stem cell interventions as a potential therapeutic target for MS. I conducted all interviews over the phone or in person and took detailed field notes. I interviewed participants until no new major themes were identified from additional interviews and theoretical saturation was reached (Charmaz, 2014). Verbatim transcripts of interviews were made software-ready and managed using NVivo 11 qualitative analysis software. Analysis was conducted in conjunction with ongoing data collection.

Using standard qualitative inquiry methods and iterative and deliberative approach, in consultation with a second researcher, I developed a codebook that reflected the emerging phenomena and the hierarchy of themes and subthemes in the data set. Data were analyzed line by line for initial codes, which were then organized into major themes and subthemes through a constant comparative approach to characterize recurring phenomena and individual variations within and between transcripts (Charmaz, 2014). To ensure dependability of the primary codes, the second researcher coded 10% of the sample independently. A Cohen's kappa test performed on this sample yielded a coefficient of 0.92, indicating substantial inter-coder agreement

(Neuendorf, 2016). To ensure that the analysis of data represents the views of research participants, I provided all participants with synthesized study results representing major themes and illustrative quotes (Appendix D.1). I invited participants to comment on the data analysis and to provide feedback on our interpretation of the data. Three participants responded to this call and reported back that, in their opinion, the data analysis captured perspectives authentically. Respondents' suggestions to ensure diversity among illustrative quotes were integrated into the final analysis.

3.4 Results

I interviewed 20 individuals who have MS (Table 3.1). None of the participants received a CCSVI intervention. Seven participants had a stem cell transplant through the Ottawa Hospital. Interviews ranged between 23 minutes and 80 minutes in length, for a total of 13.9 hours of audio-recorded data for analysis. The final codebook consisted of four major themes and eight subthemes. I focus here on the four major themes – *grasping on to hope, costs of CCSVI research, enduring optimism, and lessons learned* (Table 3.2) – that were generated by participant narratives. Major themes were defined by their prominence and relevance to the objectives of the study. Themes were common to participants who had received stem cell interventions and those who had not.

Characteristic[a]	Number of participants (%)
Gender	
Male	7 (35)
Female	13 (65)
Age (years)	
19-30	6 (30)
31-40	4 (20)
41-50	5 (25)
51-60	3 (15)
61-70	2 (10)
Education	
Grade school	1 (5)
High school	4 (20)
College	8 (40)
University	4 (20)
Advanced degree (e.g., MD, PhD, JD)	3 (15)
MS sub-type	
Relapsing remitting	10 (50)
Primary progressive	1 (5)
Secondary progressive	7 (35)
Other variant	2 (10)
Time since MS diagnosis (years)	
0-5	5 (25)
6-10	5 (25)
11-15	6 (30)
16-20	3 (15)
21+	1 (5)
Sources of information about MS[b]	
Neurologist	20 (100)
Family physician	7 (35)
Other clinician	7 (35)
Internet forums	10 (50)
Internet health sites	12 (60)
Newspapers	5 (25)
Magazines	5 (25)
Television	6 (30)
Support groups	13 (65)
Other	10 (50)

[a]All participant characteristics information obtained directly from study participants, including MS sub-type
[b]Non-mutually exclusive categories

Table 3.1 Patient characteristics (n=20)

Themes and sub-themes	Description
Grasping onto hope Initial hopes Disappointment	Initial hopes and subsequent disappointment about chronic cerebrospinal venous insufficiency research in the multiple sclerosis community
Costs of chronic cerebrospinal venous insufficiency research Medical adverse events Divestment of research funds Limited efficacy Translational delays	Adverse implications of chronic cerebrospinal venous insufficiency research
Enduring optimism Caution in the wake of disappointment Forging onward with stem cell research	Retained optimism and continued support for stem cell research to address multiple sclerosis
Lessons learned	Knowledge gleaned from the chronic cerebrospinal venous insufficiency experience that may shape future scientific endeavours

Table 3.2 Emergent themes

3.4.1 Grasping onto Hope

Participants described the sense of hope in the MS community at the time that the CCSVI hypothesis was proposed. They articulated how hope motivated some MS patients to seek access to CCSVI interventions prior to sufficient testing, many times through clinics that offered unregulated interventions abroad, and often against medical advice.

> *There were a lot of people grasping on to hope... Desperation definitely played a part in it…A lot of people [were] willing to have the procedure [CCSVI] done prior to having North American testing done.*
>
> —Participant 8 (Female, relapsing remitting MS)

3.4.2 Costs of CCSVI Research

Participants described the disappointment that was felt in the MS community following premature access to the procedures, and the costs of CCSVI research. Many explained that the intervention did not yield lasting medical benefits, and some described the procedure as a temporary fix. Participants explained that those who experienced a temporary sense of wellness after CCSVI procedures felt the most disappointment.

> *I think people go for [CCSVI] and probably the most disappointment [is felt by] the people who have it and six months later they're right back to where they were.*
>
> —Participant 17 (Female, secondary progressive MS)

Participants described the adverse events endured by some individuals who received unregulated CCSVI interventions abroad, and were also critical about the financial investment in CCSVI research. These participants explained that funds which could have been invested in scientifically bolstered MS interventions, such as stem cell research, were spent on CCSVI research. A few participants were particularly critical about this divestment of resources, citing knowledge of scientific evidence that brought the CCSVI hypothesis into question prior to the funding of clinical trials.

> *It's just wasted money, especially when it's a disproved theory, when that money could have gone to better use to support research for the stem cell area.*
>
> —Participant 20 (Male, other MS variant)

Participants explained that the time spent on CCSVI research would have been better spent on other areas of inquiry, such as stem cell research. In addition, they worried that the lack of credibility associated with CCSVI research would infiltrate the public domain and undermine confidence among the MS community in the scientific enterprise. Participants suggested that this may necessitate more rigorous testing in the stem cell arena, and could result in delayed translation.

> *It makes me sad that it [CCSVI research] turned into such a fiasco cause…it'll [stem cell research] take longer and it'll take more proving…We wouldn't have to work so hard to prove [stem cell research] if we hadn't have shot ourselves in the foot with CCSVI first.*
>
> —Participant 14 (Female, other MS variant)

3.4.3 Enduring Optimism

Despite disappointment with CCSVI research, all participants still articulated optimism that stem cell research would yield a treatment for MS. However, optimism was guarded and cautious.

> *Five years ago it [CCSVI] came out and a lot of people saw it as a cure, and so everybody jumped on that bandwagon…So I didn't want to put all my cards on that table. And I'm at sort of that point with stem cell. I'm hopeful and eager to see what happens, but I'm not ready to jump into it.*
>
> —Participant 5 (Female, relapsing remitting MS)

Participants explained that optimism for stem cell research, unlike those that supported CCSVI research, are based in trusted science. They explained that this is why they continue to support stem cell research.

I think CCSVI was anecdotal…[stem cell research] has hard science behind it…they've been researching it for many years in relation to different uses.

—Participant 1 (Female, relapsing remitting MS)

Participants explained that they continue to support the development of research that tackles MS. Some acknowledged the uncertainty associated with medical research with the view that there are no guarantees in the pursuit of knowledge, and that scientists must move forward despite setbacks to find new treatment options.

It was a disappointment but…I knew it wasn't a guarantee…if it works it works and if it doesn't, well, let's go forward.

—Participant 6 (Male, secondary progressive MS)

3.4.4 Lessons Learned

Participants explained that society must reflect on the CCSVI experience to learn lessons about how to prioritize research in the future. They suggested that scientists ensure that research is safe before the public accesses it.

I would say that before you started treatment on the patient…you should be…sure that it's very safe to try it.

—Participant 12 (Male, secondary progressive MS)

They also suggested that scientists must promote social responsibility in science communication. They underscored the importance of public trust for the sustainability of the research enterprise, pointing to the joint responsibility of both the news media and scientists.

The media needs to be more responsible to what they present openly…That [CCSVI] was pretty devastating for people.

—Participant 11 (Female, secondary progressive MS)

…[scientists should] not to jump the gun and say…"we found a new cure for MS…come and try this", and then it doesn't work…because…people get their hopes up, and then…it's just going to damage the [community's] view of [research].

—Participant 20 (Male, other MS variant)

3.5 Discussion

The CCSVI story represents a historical moment in biomedicine that highlights the challenges of prioritizing a responsive and conscientious space for patient advocacy and public participation in science and policy. The MS community was faced with a profound dilemma: how to integrate genuine hope in the public sphere into science policy and funding priorities while also accounting for the absence of sufficient evidence-based data (Chafe, Born, Slutsky, & Laupacis, 2011; Pullman, Zarzeczny, & Picard, 2013). While the force of the CCSVI movement was exceptional, reminiscent perhaps only of few others such as the HIV movement in the 1980s (Buhles, 2011), the effect public endorsements for access to biomedical research have been a more frequent topic of discussion. They have implicated a wide range of applications, such as genetics and genomics research (Benjaminy, Kowal, MacDonald, & Bubela, 2015; Evans, Meslin, Marteau, & Caulfield, 2011), personalized medicine (Petersen, 2009), stem cell research (Benjaminy et al., 2016; Bubela et al., 2012; Kamenova & Caulfield, 2015), and neuroimaging

(Ariely & Berns, 2010; Illes et al., 2010). This literature repeatedly predicts the theoretical outcomes of sensationalism: it may render stakeholders hopeful and vulnerable to undue disappointment and distress (Hyun, 2013), and cycles of inflated expectations and subsequent disappointment may create unsustainable links in the chain of translation for novel biomedical research, disillusionment among clinicians, despair among patient communities, loss of public trust in science, and the disengagement of industry (Downey & Geransar, 2008; Ogbogu, 2006; Petersen, 2009). Few studies, however, have empirically examined the implications of these messages on patient communities who have great stakes in the investment and outcomes of the research (Master & Resnik, 2013). Even in the face of negative trials (Fayerman, 2017), the findings here are less disheartening: they point to community resilience and enduring optimism for research, including novel stem cell interventions. In contrast with MS patient narratives that unveil a lack of trust among those who chose to pursue unproven and unregulated stem cell interventions outside of their home countries for what is often referred to as medical tourism (Snyder, Adams, Crooks, Whitehurst, & Vallee, 2014), participants in this study retained their trust in science and urged the medical community to continue research efforts in the hopes of finding effective interventions for MS.

Contemporary formulations of science are increasingly moving towards more pluralistic approaches that encourage public participation in science. These include research methods that celebrate porous and reciprocal engagement between scientists and the public such as deliberative democracies and participatory action research, as well as government funding priorities that include knowledge translation, mobilization, and exchange initiatives that encourage engagement between scientists and the public (Tetroe et al., 2008). The imperative of

democratizing science is not only logical, but also socially conscientious, as the citizens who bear the costs and burdens of scientific advance should be informed and involved in its development and application (Illes et al., 2005). Moreover, public engagement in science and science policy aligns with the values of accountability and transparency, and is thought to be a tool for promoting public trust in technology development (Burgess, Tansey, & Einsiedel, 2009; Secko, Burgess, & O'Doherty, 2008).

This study demonstrates that public engagement in science, while an ethical imperative, is not without its challenges. In the CCSVI context, patient advocacy unveiled divergence between the scientific community that valued evidence-based medicine, and patient priorities for timely access to potentially life-saving interventions in the face of scientific uncertainty. These participant-drawn lessons reinforce the imperative for conscientious communication of advances in science and medicine. While participants advocated for social responsibility – in fact, a duty for scientists, clinicians, and the media to cautiously engage in top-down communication – they reflected considerably less about the MS community's roles and responsibilities in influencing views and policy. Yet, CCSVI research gained significant momentum by way of anecdotal accounts of patients who underwent the procedure through the social media platforms such as YouTube and the blogosphere (Chafe et al., 2011; Mazanderani, O'Neill, & Powell, 2013). Such public-generated endorsements led to significant political pressure that shaped science policy and mobilized funding for CCSVI clinical trials (Pullman, Zarzeczny, & Picard, 2013). Indeed, the CCSVI story demonstrates that patients are eager to engage, increase knowledge about their disease, and exchange advice with other patients (Antheunis, Tates, & Nieboer, 2013), but that much work remains to be done in closing a gap that still exists in supporting them well to do so.

3.6 Limitations

As is standard in the tradition of qualitative inquiry, this study has limitations. It cannot aim to be generalizable. Rather it yields transferable data that illustrate the perspectives of a sample of MS patients during the time at which this study was conducted. Clear trends in participant perspectives did not segregate by demographic criteria (e.g., MS subtype, gender, or education), or by whether or not they received a stem cell intervention. Such trends may be masked by the limited sample size in this study or by the self-selection element in the recruitment strategy. Moreover, the perspectives presented in this study only represent views of patients who did not receive CCSVI interventions. The data were collected over a two-year timeframe between 2014-2016 – an interval during which clinical trials for the CCSVI procedures were ongoing, but results still unknown. An exploration of perspectives after the results of the trial are published will reveal further important considerations for science policy.

3.7 Conclusion

Overall, MS patient community is resilient, hopeful, and trusting of ongoing developments in non-pharmaceutical biotechnology, including stem cell research. Participant perspectives draw attention to lingering challenges in translation of biomedical research from the bench to the bedside, including the imperative for carefully balancing civic engagement and scientific evidence. Indeed, the CCSVI research trajectory demonstrates that democratizing science is not without risks and challenges. The CCSVI experience serves as an opportunity for reflection, and enriches the field of bioethics with invaluable lessons about the complex relationship between science and society.

Chapter 4: Social Responsibility in Stem Cell Research—Is the News All Bad?

4.1 Synopsis

Transparent public discourse about translational stem cell research promotes informed hope about scientific progress and the sustainable development of biotechnologies. Using an *a priori* coding scheme, I surveyed articles from leading news media about stem cell interventions for neurodegenerative diseases (1991-2014) from United States (n = 83), Canada (n = 29), and United Kingdom (n = 65). While this analysis of translational contexts in the news demonstrates a lingering tendency to celebrate the benefits of research with little context of its caveats, in departure from many previous studies, the data also reveal conscientious reporting about stem cell tourism and timeframe estimates for the development of relevant therapeutics.

4.2 Introduction

The media have come under enormous scrutiny over the past years for the way that they cover the translation of biotechnology, and stem cell interventions in particular. Whether the focus is print or online news, study after study has provided data about hyperbolic reporting of the benefits of biotechnology with little context of its risks, limitations or timeframes for application (Benjaminy & Bubela, 2014; Kamenova & Caulfield, 2015; Lau et al., 2008; Racine et al., 2010). It would seem from past research that the problem is ubiquitous and indiscriminate to technology type and phase of research and development. I sought to understand this reporting phenomenon in the particularly acute case of neurodegenerative diseases that not only rob

affected individuals of their mobility and cognitive function, but for which the success for novel therapeutics becomes more urgent due to disease progression.

Is the news all bad? I find that the answer is no. Through an analysis of representations of discrete stages in the stem cell research process, regulatory checkpoints and hurdles in clinical translation, and timeframe projections for the clinical application of stem cell biotechnologies in news articles, I find evidence of socially responsible reporting in the stem cell arena for neurological diseases that has been seldom reported (Table 4.1).

Why should stem cell scientists care? Online and print media provide the most accessible information about health and science to the public. The media operate at the interface between scientific communities and the public, and thus serve as key gatekeepers of information between science and the society (Smith & Wakefield, 2005). The media may exert a substantial influence over public perspectives and opinions of controversial biotechnologies through deliberate reporting techniques (Nelkin, 1995). Two interrelated methods are prominently used in science reporting: agenda-setting and framing. Agenda-setting theory posits that the media can lend salience to certain topics through selective coverage. Media outlets cover certain issues with greater prominence (e.g., front-page news) or frequency to direct public attention to certain issues while omitting others (McCombs & Shaw, 1972). In a similar capacity, frames, or simplified interpretive packages, are used to direct public opinions about important issues. Frames help audiences organize and process complex information by drawing attention to some considerations surrounding controversial topics while downplaying others (Scheufele, 1999). In this manner, the media not only tell people what to think about (agenda-setting), but also shape

how people think about scientific controversies (framing). While the media engage in deliberate processes to direct public attention and opinions, there is a reciprocal exchange between popular media portrayals and public priorities. Indeed, public priorities and concerns also direct media attention just as media coverage shapes public discourse. Science reporting about research and medicine both shapes and reflects public discourse while promoting public understanding of science and participation in science policy. Simply stated, the integrity and sustainability of public and industry support for stem cell research and development, therefore, hinges on transparent and conscientious representations of translational medicine in the media that celebrate the promise of scientific discovery and ground hopes for health innovation in scientific realities.

Socially responsible representations of translational contexts	Opportunities for socially responsible representations
• Qualitative timeframes with accurate estimates for clinical implementation • Condemnation of unregulated stem cell interventions	• Mention of sample sizes in clinical research • Portrayal of clinical trial phases and their goals • Representations of hurdles and checkpoints to clinical implementation • Descriptions of timeframes to clinical implementation

Table 4.1 Summary of socially responsible representations and opportunities to promote social responsibility in news articles about stem cell research

4.3 Methods

Clinical translation of stem cell research has raised much hope for the treatment of a myriad of currently incurable diseases. While the strong translational ethos in the stem cell arena has contributed to the rise of registered clinical trials, the majority remain in early phases aimed at establishing indexes of safety (Li, Atkins, & Bubela, 2013). The earliest year of media coverage about stem cell interventions for neurological diseases was 1991. Using customized search algorithms to create a sample, I mined media databases Factiva (US, UK) and Canadian Newsstand (CA) from that year through 2014, and retrieved 177 unique news articles (US n=83; CA n=29; UK n=65) relevant to the analysis of interest. I examined the pool both as a whole, and as two independent sets: a set of 94 articles broadly focused on stem cell interventions for non-neurodegenerative diseases that still discussed neurodegenerative diseases in a substantial way; and, a set of 83 articles primarily focused on human stem cell interventions for neurodegenerative diseases.

Using an *a priori* coding scheme informed by other studies of health biotechnologies (Holtzman et al., 2005; Racine et al., 2005), I investigated timeframe projections, tone of projections, spokespeople who made projections, and public health claims in all the articles. I then coded the set of articles that primarily focused on human stem cell interventions for neurodegenerative diseases for additional constructs: dominant themes, descriptions of clinical trial phases and sample sizes, checkpoints and hurdles for translation, and descriptions of availability of stem cell interventions abroad (Table 4.2). Cohen's kappa tests on a random 14% of the articles yielded k scores in the range of 0.64-1.00 with a mean score of 0.84, indicating substantial inter-coder reliability (Landis & Koch, 1977). To stratify codes by country I graphed the variables of interest

by country. This visualization showed that news articles tend to cover local clinical trials more frequently than out-of-country trials. However since this phenomenon was not central to the research question about timeframes, I report trends across the dataset rather than stratified on a per country basis. Finally, I carried out a cross comparison of projected quantitative media timeframes for the implementation of stem cell research with outcomes published in ClinicalTrials.gov.

Coding categories	News articles with secondary focus on neurodegeneration n (%)	News articles with primary focus on neurodegeneration n (%)	Total news articles analyzed n (%)
Tone of future projections			
Positive	46 (49)	42 (51)	88 (50)
Neutral	18 (19)	11 (13)	29 (16)
Negative	7 (7)	2 (2)	9 (5)
Not mentioned	23 (24)	28 (34)	51 (29)
Timeframe projections			
Yes	29 (31)	45 (54)	74 (42)
No	65 (69)	38 (46)	103 (58)
Spokespeople making timeframe projection			
Media reporter		36 (43)	55 (31)
Public sector researcher	19 (20)	3 (4)	11 (6)
Biotechnology company	8 (9)	1 (1)	2 (1)
representative	1 (1)	2 (2)	2 (1)
Clinician	0 (0)	3 (4)	4 (2)
Other	1 (1)	45 (46)	103 (58)
Not applicable	65 (69)		
Public health claims			
Yes	63 (67)	40 (48)	103 (58)
No	31 (33)	43 (52)	74 (42)
Dominant themes	N/A		
Celebration of progress		50 (60)	50 (60)
Economic development		11 (13)	11 (13)
Human interest stories		11 (13)	11 (13)
Other		11 (13)	11 (13)
Description of clinical trial phases/goals*	N/A		
Not mentioned		21 (25)	21 (25)
Safety		15 (18)	15 (18)
Phase I		8 (10)	8 (10)
Safety and Efficacy		8 (10)	8 (10)
Phase I/II		1 (1)	1 (1)
Efficacy		24 (29)	24 (29)
Phase II		3 (4)	3 (4)
Not applicable		15 (18)	15 (18)
Sample sizes	N/A		
Yes		33 (40)	33 (40)
No		38 (46)	38 (46)
Not applicable		12 (14)	12 (14)
Hurdles and checkpoints for translation	N/A		
Yes		37 (45)	37 (45)
No		46 (55)	46 (55)
Availability of stem cell interventions abroad	N/A		
Yes		26 (31)	26 (31)
No		57 (69)	57 (69)

[a]Non-mutually exclusive categories

Table 4.2 Summary of main coding categories

4.4 Results and Discussion

4.4.1 Celebrating Progress

Sixty percent of the articles celebrate progress in stem cell research, and depict its potential for neurodegenerative diseases. Articles discuss such progress most prominently in the contexts of Parkinson disease, multiple sclerosis, amyotrophic lateral sclerosis, and Batten disease. For example:

> "To date, adult cells have produced 72 treatments of human diseases, ranging from cancer and diabetes to lupus and multiple sclerosis, with new findings every week" (Spatz, 2006).

Other articles focus on economic development (13%) that hail the potential for capital gains though investment in stem cell enterprises, and human-interest stories (13%) that highlight the importance of stem cell research by featuring the voices of advocates of stem cell technologies including hopeful patients, families, and clinicians.

I also observe celebrations of progress in 58% of all the articles that make explicit public health claims, and assert that stem cell biotechnologies will produce therapeutic solutions for a diversity of ailments:

> "Stem cell therapy is already regarded by scientists as having huge potential for treating a range of diseases and disabilities including Alzheimer's and heart problems" (Goodchild, 2007).

Descriptions of clinical trial stages provide some context about the progress of clinical research that aims to produce such public health benefits (Figure 4.1) For example; safety is a focus of discussion for news articles that describe ALS clinical trials. Efficacy is more commonly discussed in news articles that about MS and Batten disease clinical trials. The sample sizes of human subjects in clinical trials are mentioned in 40% of articles about clinical research. Overall, the prominent celebration of progress in the stem cell sphere is consistent with previous studies that indicate an over-emphasis of the benefits of developing biotechnologies (Kamenova & Caulfield, 2015; Racine et al., 2010). It presents a continuing opportunity for future reporting that focuses on contextual details in translation, including descriptions of clinical trial phases, their goals, and the numbers of research participants in human studies.

4.4.2 Never Say Never

The prominent celebration of progress in the stem cell arena calls for commensurate context about when the benefits of this research trajectory might be realized. As such, socially responsible communications about the promise of stem cell research ought to be followed by details about timeframes for translation, be it the discrete steps such as the commencement of clinical trials or end-goals like clinical implementation. The majority (58%) of articles do not make timeframe projections about the research and development of stem cell interventions for neurodegenerative diseases, and none of the articles discuss the possibility that stem cell therapies may never be realized. These findings highlight an opportunity to promote social responsibility in media communications through additional context about timeframes and through the stipulation of statistics that emphasize the high attrition rate in clinical research (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014). Most of the timeframe projections

are qualitative in nature (71%), and offer vague estimates for the implementation of stem cell research (Figure 4.2). The majority of estimates are modest claims and suggest that clinical implementation of stem cell research will be realized in the distant future. For example:

> "…the practical application of this theory has been less than spectacular and any cures are in the *distant future*" (Martinuk, 2009).

Eight percent of the articles make explicit quantitative projections (Table 4.3). Thirty-three percent of these were actualized within the estimated timeframes and 40% were not. The accuracy of the remaining estimates cannot be determined because their projected timeframes have not yet been reached.

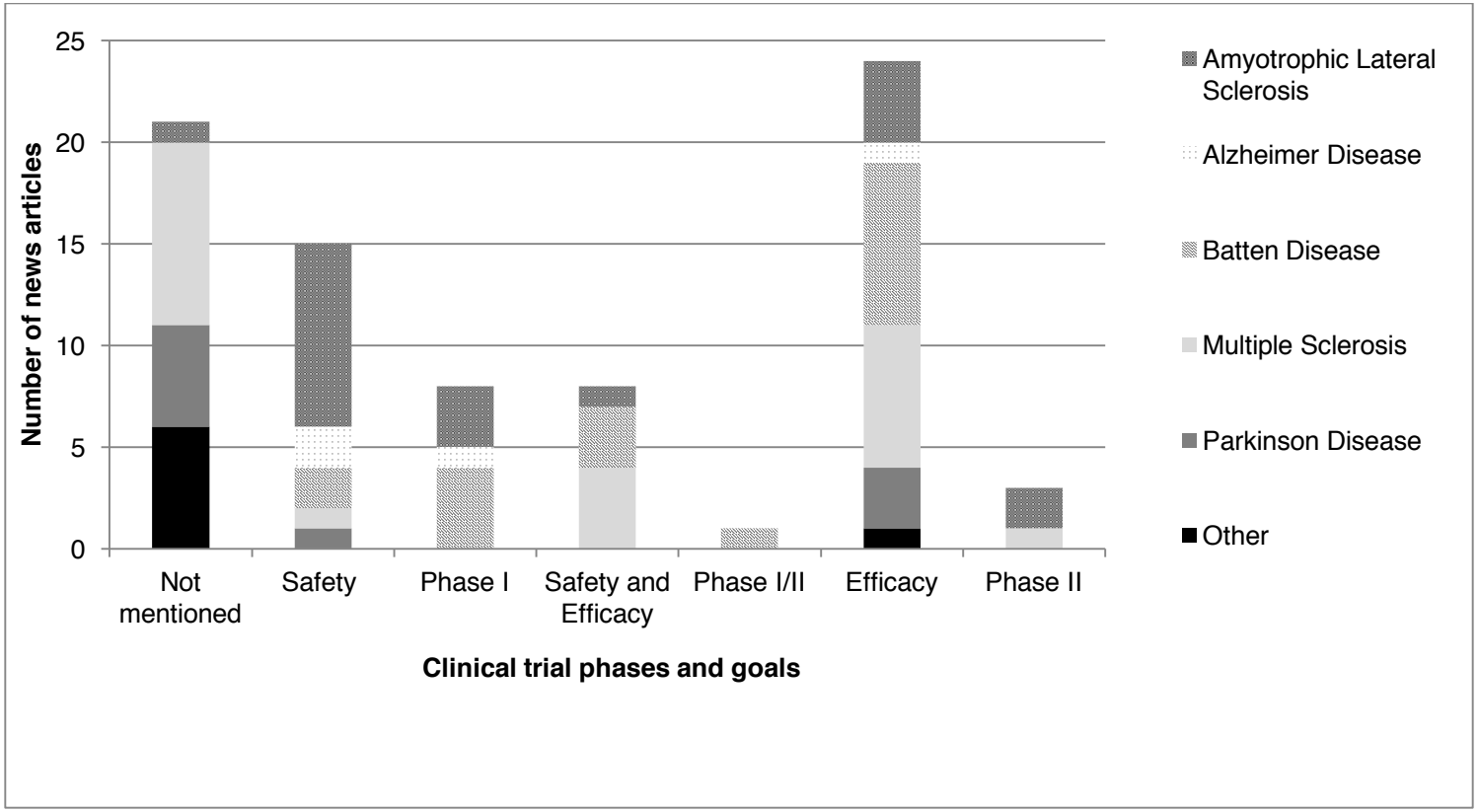

Figure 4.1 Clinical trial phases and goals in news articles about stem cell clinical trials stratified by disease

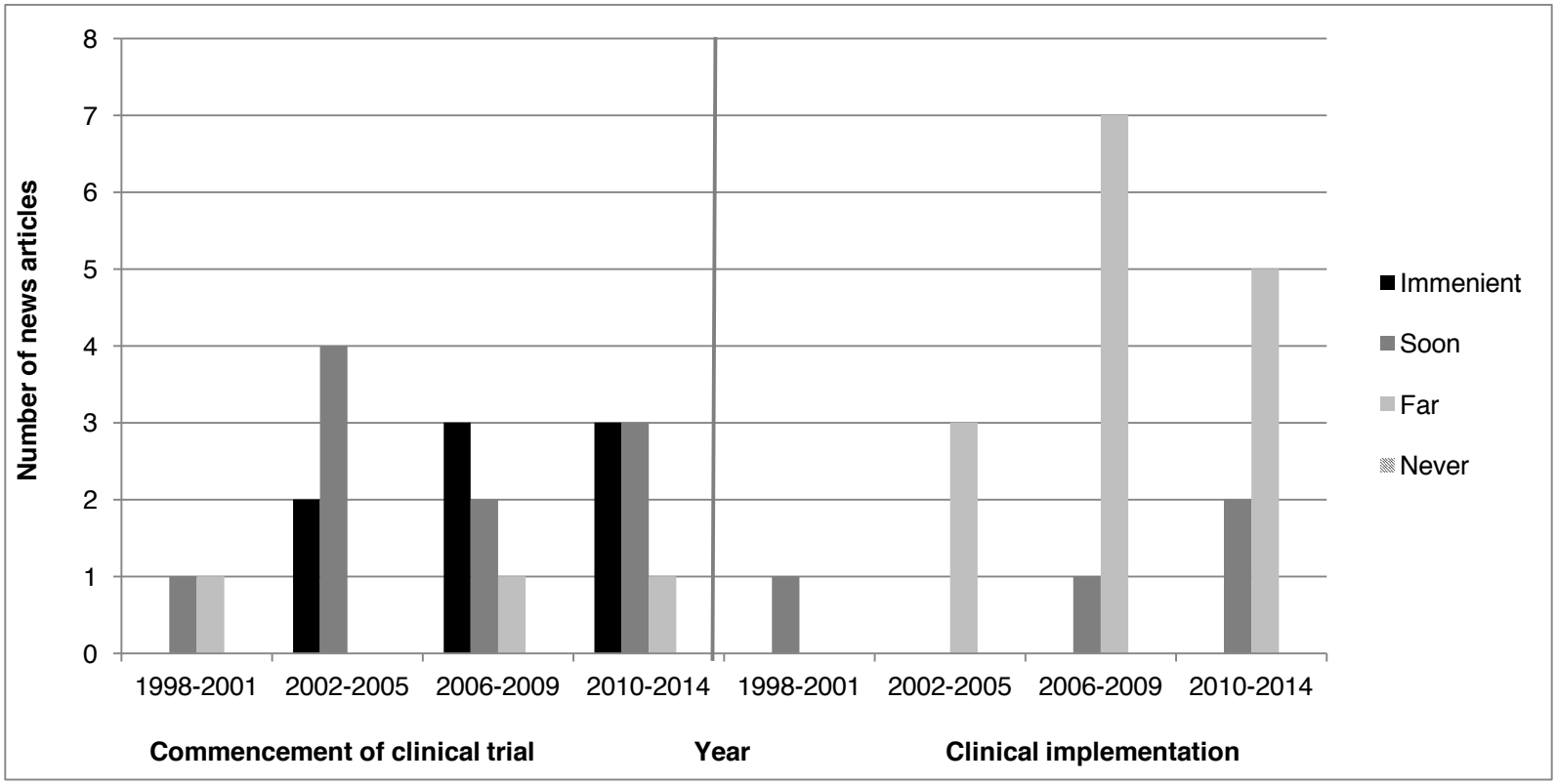

Figure 4.2 Qualitative timeframe projections for the commencement of stem cell clinical trials (n=21; left), and clinical implementation of stem cell interventions (n=19; right). Results are stratified by the year of news article publication.

Media timeframe projection	Projected outcome in context	Outcome	Projection met in estimated timeframe?
"The U.S. Food and Drug Administration approved Phase II of the clinical trial, which is overseen by U-M neurologist Dr. Eva Feldman… Surgeries could begin by the end of the summer" (Kozlowski, 2013).	Phase II trial for amyotrophic lateral sclerosis will commence by the end of summer 2013.	Phase II neural stem cell trial for amyotrophic lateral sclerosis began in May 2013 (NCT01730716).	Yes.
"Cutting-edge stem cell treatment to repair the damage caused by multiple sclerosis is to…start in February with people who have long standing MS… it'll be the first phase two trial of any repair therapy in MS" (Mathias, 2011).	Phase II mesenchymal stem cell trial for multiple sclerosis will commence in 2012.	Phase I/II mesenchymal stem cell trial for MS began in 2013 (NCT01606215).	No.
"Repair to MS-related nerve damage using stem-cell therapy is I think, five to 10 years away" (Kinder, 2009).	Stem cell therapies will become standard of care for MS by 2019.	To be determined.	To be determined.

Table 4.3 Illustrative comparisons between newspaper timeframe projections and outcomes of stem cell clinical interventions for neurodegeneration

News reporters make 74% of the timeframe projections in the sample; experts such as researchers and clinicians make the minority (18%) of these estimations. Other stakeholders such as representatives of biotechnology companies and affected individuals accounted for the remainder. This finding deviates from previous reporting trends that showcase expert opinions of trusted clinicians and researchers (Benjaminy & Bubela, 2014; Critchley, 2008; Kamenova & Caulfield, 2015). I cannot speculate, however, whether reporters are paraphrasing the timeframe estimates of experts or making *de novo* timeframe projections.

4.4.3 Checkpoints and Hurdles

The regulatory and political milieu in which stem cell research is positioned may impact the pace of therapeutic development. Indeed, the political environment that historically followed stem cell research has focused as much on its social controversies as on its scientific potential, and has been addressed through heightened oversight that promotes social accountability (Caulfield et al., 2015). Forty-five percent of the articles mention such checkpoints and hurdles (Figure 4.3), and these are prominently explored in the political context of embryonic stem cell research, e.g.:

> "The California initiative was largely an effort to sidestep restrictions on federal financing of human embryonic stem cell research imposed by the Bush administration, which objects to the destruction of human embryos that is necessary in harvesting the stem cells" (Pollack, 2004).

A minority of articles discuss other checkpoints and hurdles to the translation of stem cell research, such as government health regulations, ethics board review, barriers to benefit-sharing including patents and intellectual property. Additional details about regulatory hurdles and checkpoints may serve to clarify the position of stem cell research endeavors along the translational continuum and contextualize the prominent celebration of progress I describe above.

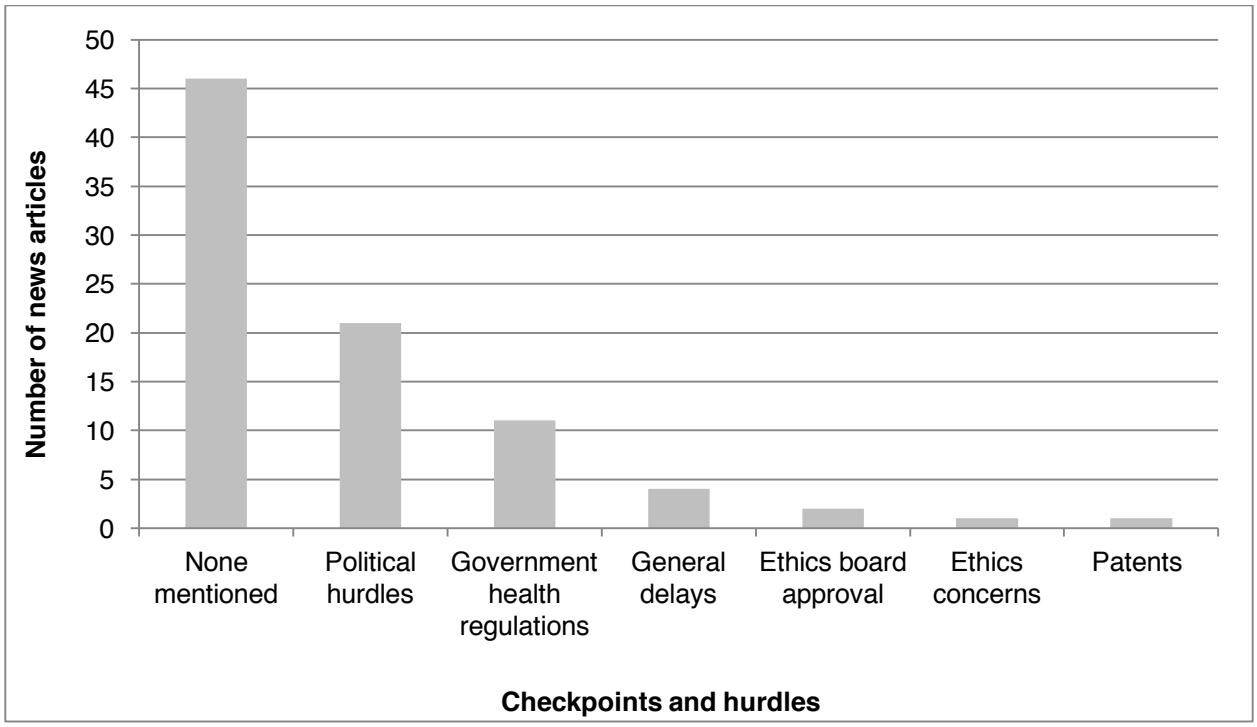

Figure 4.3 Representations of regulatory checkpoints and hurdles to clinical implementation of stem cell research for neurodegeneration

4.4.4 Lured Away from Regulated Clinical Realities

With stem cell tourism on the rise, countless opportunities to access unapproved and unregulated stem cell interventions are available abroad, with purveyors most commonly targeting patients with neurological diseases (Lau et al., 2008). Thirty one percent of the articles discuss stem cell interventions abroad. The tone of the articles about stem cell interventions abroad is largely negative (69%) or neutral (23%). Indeed, 73% of relevant articles explicitly state that the interventions are unapproved, a nuanced proxy for unproven, and unregulated.

In contrast to other literature that suggests that media representations of stem cell research are

hyped (Evans et al., 2009; Kamenova & Caulfield, 2015), I find scientifically and socially responsible examples of reporting. Indeed, distant qualitative timeframe estimations for the clinical availability of stem cell therapies (Figure 4.2) are consistent with the 10-14 year timeframe for experimental products to move along the translational trajectory from novel target to market approval, and the additional time necessary to account for health technology assessment and integration into health care systems and insurance regimens (Glassman & Sun, 2004). Additionally, the condemnatory stance of the media about stem cell clinics that offer unregulated interventions has been previously hidden from view. Set against the financial and marketing forces of illegitimate stem cell clinics (International Society for Stem Cell Research, 2016) that detract attention from the scientific unknowns of stem cell biotechnologies and reframe the issue as an access problem, the media provide valuable interpretation in the context of neurological diseases. Diverse methods and procedural approaches, in addition to variability in contextual details (e.g., different biotechnologies, focus on different disorders), may contribute to the polarity of results here to those of the past.

4.5 Limitations

The exclusive analysis of news media, rather than a focus on broader forms of media such as television and social media, is a limitation in this study. While broader media outlets are playing an increasingly prominent role in disseminating information about science and technology, news media has retained its agenda-setting role and serves to inform the content of other media platforms (Bubela et al., 2009; Holtzman et al., 2005). Additionally, I did not compare news media representations to scientific journal publications and therefore I cannot account for potential *errors of commission* or blatant inaccuracies in media content. On the other hand, the

study captures subtle, yet more common *errors of omission* in the form of missing context (Bubela & Caulfield, 2004). Customized search algorithms yielded an unexpectedly low sample size of US coverage in reference to the population size when compared with samples of Canadian and UK news articles. While standard search techniques in Factiva were used, the sample size may be due to syndication patterns in the US and the curated removal of duplicate content from the final analysis.

4.6 Conclusion

Reporters as well as scientists and clinicians who communicate with the media have the individual and collective responsibility to highlight incremental advances in biotechnology and detail the steps necessary to achieve clinical implementation of research efforts. These are details such as number of research participants in clinical trials, phases of clinical research and their goals such as establishing safety or efficacy, and regulatory steps such as ethics approval, market approval, and health technology assessment. There may well be work to be done to achieve these goals with greater reproducibility, but there is also evidence to note the socially responsible media representations of stem cell interventions that promote informed hope about scientific progress and the sustainable development of biotechnologies.

Chapter 5: Clinical Stakeholder Perspectives about Timeframes in Stem Cell Research for Multiple Sclerosis

5.1 Synopsis

The field of regenerative medicine has been visible to the public eye, and has spawned many hopes for therapeutic applications. Information about the pace of developments in related biotechnology, however, is less accessible than representations of its potential benefits. In this study, I explore the perspectives of patients with multiple sclerosis (MS) and clinicians responsible for their care about the timeframes associated with stem cell research. Findings demonstrate that patients have a limited understanding about the time that it takes for stem cell research to reach the clinic. At the same time, they desire to know more than they do about the translational process. Clinicians suggest strategies to address patients' questions about the pace of stem cell research, and to promote informed hope about experimental interventions.

5.2 Introduction

Stem cell research has experienced a great deal of public attention and excitement about potential therapeutic applications that have contributed to the hopes of researchers, clinicians, and patient communities alike (Wilson, 2009). Despite the anticipation of the benefits of stem cell research, progress has been slow and incremental, much like other forms of novel biotechnology (Glassman & Sun, 2004). Indeed, research has demonstrated that the application of stem cell biotechnologies often falls short of public expectations, and most acutely so in the sphere of neurologic disease compared to others (Bubela et al., 2012).

While the public eagerly awaits stem cell therapeutics (Evans et al., 2009), research suggests that comprehensive information about the pace of biotechnology development may be far less accessible than representations of its' potential benefits (Benjaminy et al., 2016; Kamenova & Caulfield, 2015). This has contributed to confusion in the public domain about the readiness of stem cell interventions for clinical uptake (Caulfield et al., 2016). Clear messaging about the timeframes associated with stem cell research may be particularly important given the strong momentum for translation in the field of regenerative medicine (Maienschein et al., 2008) and its premature clinical debut through unregulated stem cell tourism routes (Einsiedel & Adamson, 2012; Petersen, Munsie, Tanner, MacGregor, & Brophy, 2017; Ryan et al., 2009). An appreciation of translational context may be particularly helpful for patients with neurodegenerative disease, not only given the progressive nature of their illness and the limited therapeutic window for meaningful intervention, but also because purveyors of unproven interventions abroad predominantly target patients with diseases of the brain (Lau et al., 2008).

In this chapter I focus on MS, a disease that has been the subject of clinical inquiry in regenerative medicine since the late 1990s (Burt et al., 1995). While stem cell applications for MS have been the focus of hope for nearly three decades, and current research advances have resulted in human trials using both hematopoietic and mesenchymal approaches (Atkins et al., 2016; Connick et al., 2012), they have not yielded a widely available treatment to date. I therefore explore the perspectives of stakeholders in the MS community about the pace of this translational area and ask: *What are the perspectives of MS patients and clinicians responsible for their care about the timeframes associated with the research and development of stem cell*

interventions?

5.3 Methods

I recruited individuals with interests in MS from across Canada using a convenience sampling approach. I recruited affected individuals (patients) through online advertisements, on patient advocacy group websites, and through MS clinics. I recruited MS clinicians through advertisements on a professional list serve and through email invitations. The time interval for participation was between May 2014 and February 2017. Inclusion criteria for MS patients were: a diagnosis of MS; age ≥19 years; ability to provide informed consent; and, ability to speak English. The inclusion criteria for MS clinicians were: physician specializing in care for MS patients; age ≥19 years; ability to provide informed consent; and, ability to speak English.

Following approval by the University of British Columbia Research Ethics Board (H13-03275) and standard procedures for acquiring informed written consent, I conducted a series of in-depth semi-structured interviews. The interview guides were developed using previous studies of patient perspectives about novel biotechnologies (Benjaminy et al., 2014; Illes et al., 2011) and probed for familiarity with and receptivity to stem cell interventions for MS, estimations of timeframes associated with the clinical implementation of stem cell interventions, and accelerators and barriers to the translation of this research trajectory (Appendix C).

I conducted all interviews over the phone or in person and took detailed field notes. I interviewed participants until no new major themes emerged from additional interviews, operationally

marking theoretical saturation (Charmaz, 2014). Verbatim transcripts of interviews were verified for accuracy by comparison with original audio recordings, and then managed using NVivo 11 qualitative analysis software. I conducted analysis in conjunction with ongoing data collection in an effort to identify emergent phenomena and modified the interview guide to accommodate themes as they arose (Mayan, 2016).

Using standard qualitative content analysis methods and a deliberative approach (Sandelowski, 2000), I developed a codebook that reflected the emerging phenomena and the hierarchy of themes and sub-themes in the data set in consultation with a second researcher. The deliberations about the organization of the codebook were iterative until consensus was reached. Data were analyzed line by line initially, noting remarkable phenomena and primary codes. Similarities and differences were probed within and between transcripts, and primary codes were then organized into major themes and sub-themes through a constant comparative approach (Charmaz, 2014). To ensure dependability of the coding, the second researcher coded 10% of the sample. A Cohen's kappa test performed on this sample yielded a coefficient of 0.93 and 0.83 for the patient and clinician samples respectively, indicating substantial inter-coder agreement (Neuendorf, 2016). After coding was finalized, I analysed patient data to identify patterns corresponding with demographic information (e.g., age, gender, MS sub-type) using the NVivo query function. Responses that segregated by patterns in demographics are noted in the results.

I provided all participants who agreed to be re-contacted about the results of the study with synthesized study results representing major themes and illustrative quotes (Appendix D.2, Appendix D.3). I invited participants to comment on the data analysis and to provide feedback

on data interpretation. Twelve participants responded to this call (7 patients, 5 clinicians). Overall, participants indicated that the data represent their views authentically, and no major revisions were suggested. During this verification process, patients reinforced their ongoing hopes that stem cell research will soon yield new therapies for MS.

5.4 Results

Twenty patients (Table 5.1) and 15 MS clinicians (Table 5.2) were interviewed. None of the patients had received a stem cell intervention. Sample sizes are consistent with standard qualitative methods, which generally require 15-20 participants to reach theoretical saturation (Guest et al., 2006). The patient sample reflects a predominantly female distribution and a diversity of MS sub-types that is consistent with that of MS population in Canada (Orton et al., 2006). Interviews ranged between 12 minutes and 80 minutes in duration (mean interview duration was 31 minutes) for a total of 18 hours of audio-recorded data for analysis.

The final codebook consisted of 4 major themes – *receptivity*, *translational pace*, *accelerators and barriers to translation*, and *clinical communication strategies* – and 17 sub-themes that were generated by participant narratives (Table 5.3). The major themes were defined by their prominence and relevance to the objectives of the study. I discuss the themes in the order in which they were explored in the interview guide and in participant narratives. I integrate patient and clinician data and present sub-themes and quotations in the sequence that best represents the logic and flow of emerging narratives.

Characteristic[a]	Number of participants (%)
Gender	
Male	8 (40)
Female	12 (60)
Age (years)	
19-30	1 (5)
31-40	5 (25)
41-50	5 (25)
51-60	5 (25)
61-70	4 (20)
Education	
Grade school	0 (0)
High school	2 (10)
College	8 (40)
University	4 (20)
Advanced degree (e.g., MD, PhD, JD)	4 (20)
Unavailable	2 (10)
MS sub-type	
Relapsing remitting	11 (55)
Primary progressive	3 (15)
Secondary progressive	5 (25)
Other variant	0 (0)
Not sure	1 (5)
Time since MS diagnosis (years)	
0-5	6 (30)
6-10	4 (20)
11-15	5 (25)
16-20	4 (20)
21+	1 (5)
Sources of information about MS[b]	
Neurologist	18 (90)
Family physician	4 (20)
Other clinician	6 (30)
Internet forums	8 (40)
Internet health sites	15 (75)
Newspapers	6 (30)
Magazines	4 (20)
Television	9 (45)
Support groups	14 (70)
Other	10 (50)

[a]Information obtained directly from patients, including MS sub-type
[b]Non-mutually exclusive categories

Table 5.1 Patient characteristics (n=20)

Characteristic	Number of participants (%)
Gender	
Male	8 (53)
Female	7 (47)
Specialization	
Physiatry	3 (20)
Neurology	12 (80)

Table 5.2 Clinician characteristics (n=15)

Major themes and sub-themes	Description
Receptivity	General interest in, optimism about, and/or desire to access stem cell interventions.
Inquiries about stem cell research	
Optimism about stem cell research	
Desire to undergo stem cell intervention	
Translational pace	Perspectives about the pace of stem cell research and development.
Urgency to access stem cell interventions	
Questions about the pace and application of research	
Timeframe estimates	
Within therapeutic window	
Beyond therapeutic window	
Understanding of clinical trial phases	
Familiarity with stem cell sources	
Accelerators and barriers to translation	Factors that may speed up or slow down the pace of advancing stem cell research from the bench to the bedside.
Scientific hurdles	
Competition with pharmaceuticals	
Access challenges	
Ethical challenges	
Public awareness	
Clinical communication strategies	Clinical communication approaches to address patient inquiries about the pace of advancing stem cell research from the bench to the bedside.
Promoting informed hope	
Clarifying timeframes	

Table 5.3 Emergent themes

5.4.1 Receptivity

Patients expressed support of stem cell research. Some individuals with progressive or poorly controlled disease indicated a desire to undergo stem cell interventions.

> *I know about stem cell research…I absolutely believe in it and I absolutely support it… I'm quite optimistic about success for this in the future…if they [researchers] did a clinical trial I would absolutely participate.*
>
> — Patient 1 (Male, relapsing remitting MS)

Patients expressed optimism that stem cell research would someday produce a treatment option for MS. Many cited other recent advancements in the field of MS to support these views. Some patients drew examples from medical interventions that had successfully made the transition to the clinic after years of research.

> *I have great hopes that it [stem cell interventions] will be a very viable treatment for MS…there's so much research being done… oncology took a long time before they got to the transplant stage.*
>
> — Patient 13 (Female, relapsing remitting MS)

Likewise, many clinicians noted that patients are receptive to learning about stem cell research and often ask about developments in the field. The majority of inquiries focus on the most recent advancements in research and the potential therapeutic benefits of stem cell interventions. Some patients explained that they would not consider undergoing stem cell interventions at this time because their disease is stable. They explained that their MS is well controlled with pharmaceutical interventions and that stem cell applications might be risky. Some also explained that while they would not choose to have a stem cell intervention at the present time, they would

consider it if they were to experience more progressive disease or increased disability in the future.

> *When I hear you talking about stem cell clinical trials and their relation to MS, the first thing that comes to my mind is patients who are in wheelchairs, or…have permanent disability due to their MS…I imagine that [stem cell interventions] would be most relevant and most effective and most needed…by them.*
>
> — Patient 2 (Female, relapsing remitting MS)

On the other hand, clinicians explained that stem cells interventions, particularly mesenchymal and hematopoietic, would likely offer the most therapeutic benefit to young patients who have milder disease or are in earlier stages of the disease.

> *I think it [stem cell interventions] certainly shouldn't be given to patients who are too advanced in their disease, because there's fibrosis, astrocytosis that will block the multiplication of those cells. So it should be given fairly early and tried early in the disease course.*
>
> — Clinician 3 (Male, neurologist)

5.4.2 Translational Pace

Clinicians explained that urgency often motivates patients to ask questions about the pace of stem cell research, particularly with respect to their therapeutic windows. They also explained that their patients often express a sense of urgency to access stem cell interventions, particularly in light of the progressive nature of MS.

I think many of them [MS patients] feel a sense of urgency to do something about their disease… So I think that patients…know that time is brain and they want to get on board [with stem cell interventions] as fast as they can.

— Clinician 5 (Male, neurologist)

Clinicians explained that the stem cell tourism phenomenon underlies patients' inquiries about the timeframes for clinical application of stem cell interventions locally.

The problem is, is that they're [patients] fully aware that there are people around the world that are willing to inject…stem cells into them and they're actually coming wanting a kind of an honest answer as to is this technology at the point where they can trust it enough to consider having something like this done to them? Or is this a money making process? And that's really what they want. They want to know is it available right now? Should they go off and get this right now?

— Clinician 2 (Male, neurologist)

They expressed difficulty responding to questions from their patients given the unpredictable nature of the research and development process.

I think when I tell them [patients]…that it's [stem cell interventions] experimental and they ask me…when do you expect it to come on the market or when is it going to be kind of standard treatment? But I myself don't know the answer.

— Clinician 1 (Male, physiatrist)

While acknowledging the uncertainty associated with the pace of research and development in the stem cell arena, some clinicians provided estimates for when stem cell interventions will be available as standard of care therapies. Estimates ranged from 5 to 25 years. Clinicians were

most optimistic about the translational pace of autologous hematopoietic stem cell approaches. Some had referred their patients to centres that provide the intervention through a special access programme following phase II clinical trials that demonstrated indexes of safety and efficacy. They provided more uncertain and distant timeframes for the clinical application of both mesenchymal and neural stem cell approaches for treating MS than for the application of hematopoietic approaches.

> *With the mesenchymal [approach]…we have to follow up with the study and see if there's…early data that suggests it's helpful. And then the restorative stuff [neural stem cell approach]…I think that we're twenty years out from…finding a process that works…But if there's strong proof of concept, it'll probably be another five years until you find something for all patients.*
>
> — Clinician 5 (Male, neurologist)

Likewise, patients provided estimates about the timeframes necessary for stem cell therapies to become widely available in MS clinics. Patient predictions were heterogeneous and ranged from 2 to 30 years. Some patients expressed hopes that stem cell therapies will be widely available in time to provide them with medical benefits. Others explained that by the time stem cell therapies will be available, their disease course would likely be too far progressed for them to benefit. Responses did not segregate by patient age or by MS sub-type.

> *I would like to think that there will be stem cell therapies available for me in my lifetime… you can never really predict what course your disease is going to take. So, I like to remain hopeful that my disease will stay sort of at the course it's at and stem cell therapies will help me at some point.*

— Patient 5 (Female, relapsing remitting MS)

I'm 60 and a cure might not be found in my lifetime, but hopefully it's going to be found for a kid. That's the way I look at it."

— Patient 12 (Male, secondary progressive MS)

Many patients explained that they know little about the translational process, and that this makes predicting timeframes for clinical application challenging.

I don't know how far along they [researchers] are with the research. I don't know what they've done or what the next steps are. I don't know what's involved.

— Patient 2 (Female, relapsing remitting MS)

Indeed, while many patients indicated a limited understanding of different stem cell sources and the stages of clinical research and their goals, they also expressed a desire to learn more about the research process.

How long does it - like say from start to finish [of the research process], how long does the process take to get stem cell done [approved for clinical use]?

— Patient 15 (Male, primary progressive MS)

5.4.3 Accelerators and Barriers to Translation

Patients and clinicians described similar factors that may speed up or slow down the translation of stem cell research from the bench to the bedside. The major factors were: scientific hurdles, competition with pharmaceuticals, financial considerations, access challenges, ethical considerations, and public awareness might impact the pace of the translational trajectory of stem cell research.

5.4.3.1 Scientific Hurdles

Both patients and clinicians discussed the scientific challenges that stem cell research will have to overcome. Clinicians explained that while regenerative medicine is often depicted as a cure. They explained that with hematopoietic stem cell transplantation, which has been the most studied regenerative medicine approach for MS, clinical research has demonstrated potential to halt the course of MS, but has not produced evidence of a cure. Clinicians expressed concern about the safety profile of stem cell interventions, particularly the risk of mortality associated with the hematopoietic approach. Both cohorts commented about the challenges of translating basic science advances into clinically available treatments.

> *It's always difficult to turn something that works in theory, or works in a lab, into…a treatment for individualized patients…part of the problem of treating MS…is it's such a different disease in everybody…the process that is needed to treat relapsing remitting [MS] is different than the process needed to treat primary progressive [MS].*
>
> — Patient 7 (Female, relapsing remitting MS)

5.4.3.2 Competition with Pharmaceuticals

Some patients expressed concerns about the incentives for the development of stem cell research in light of potentially more profitable pharmaceutical approaches for industry.

> *I think that the first thing [barrier] would be pharmaceutical companies because it's [stem cells] not a drug so they can't produce any kind of medication so they can't make money.*
>
> — Patient 20 (Male, primary progressive MS)

Clinicians commented on the landscape of pharmaceutical therapies that may present a reduced niche for stem cell interventions in the current market. To this end, clinicians explained that the risk/benefit profile of stem cell interventions must be weighed against that of pharmaceutical therapies.

> *...hematopoietic stem cell transplant is…a promising type of treatment but there is a lot of risk to it…it involves chemotherapy…and that puts the patient at risk for infections, hemorrhage, and death even. So, with that type of risk/benefit ratio we have a lot of effective medications that are coming down the pipeline that are much less risky, and I would be more inclined to offer that to a patient as opposed to the hematopoietic stem cells.*
>
> — Clinician 11 (Female, neurologist)

5.4.3.3 Financial Considerations and Access Challenges

One of the main challenges discussed was the need for more robust infrastructure to support stem cell transplantation approaches for MS. Patients were worried that given costs of the procedure and the likelihood that it would only be offered at a limited number of specialized centers, access to the stem cell interventions may be a challenge.

> *For people, depending on where they live, that [location] will be one barrier... if you were living in Newfoundland and had to go to Ottawa for transplant, that could be quite cost prohibitive because of the length of stay in the hospital.*
>
> — Patient 13 (Female, relapsing remitting MS)

Clinicians were concerned that developing the infrastructure necessary to support access to stem cell interventions may not withstand a cost-effectiveness analysis when compared with existing less expensive pharmaceuticals

> *...even if something becomes available, they might make it third or fourth line [therapy]...Do you know how much it costs to get a stem cell transplant?...it's like a quarter of a million dollars to do it... so cost will become a problem.*
>
> — Clinician 5 (Male, neurologist)

5.4.3.4 Ethical Considerations

Both patients and clinicians commented on lingering ethical considerations that arise with the use of stem cells in research. Participants in both cohorts noted that such ethical considerations are more salient in neural stem cell approaches that have used cells derived from fetal tissue.

> *...a lot of the cells that we use in the way of stem cell research was obtained from fetal tissue. And there's a lot of ethical, and if you like, moral and religious problems associated with that, which then became political and sort of stopped the area. I think developments in what they call mesenchymal stem cell research has improved that, but we still have a number of problems associated with it.*
>
> —Clinician 2 (Male, neurologist)

5.4.3.5 Public Awareness

Finally, while clinician narratives did not explore the sub-theme of public awareness, patients prominently suggested that to advance stem cell research to the bedside, advocacy and education

efforts must raise public awareness. They articulated that awareness would serve to address public concerns about and increase support for stem cell research.

> *I think there's a lack of knowledge… and if they [people] knew more, they'd have less fear about it [stem cell research].*
>
> — Patient 8 (Female, relapsing remitting MS)

5.4.4 Clinical Communication Strategies

Clinical communication strategies were not explored in patient interviews, but emerged as a major theme in clinician narratives. In response to patient interest and expressed sense of urgency to access interventions, clinicians suggested clinical communication approaches to address patient inquiries about stem cell research and elucidate the pace of research and development. Strategies focus on two main goals: promoting informed hope and clarifying timeframes for the clinical implementation of stem cell research.

5.4.4.1 Promoting Informed Hope

Clinicians expressed that it is important to help patients establish a sense of informed hope that is grounded in scientific promise and acknowledges the caveats of research. At the same time, clinicians explained that it is also essential to honour patient hope despite scientific uncertainty.

> *I try not to…create false hopes. I try to be fairly honest. But on the other hand you don't want to take all hope away from individuals. Patients…cling to hope and you want to…[promote] reasonable, realistic hopes. And I think that this is one area [stem cell research] that I personally believe is…eventually going to be helpful to them. So, I don't have a problem giving them that hope.*

— Clinician 2 (Male, neurologist)

Clinicians explained that it is important to help patients ground hopes not only in contemporary research efforts, but also to anchor expectations in current clinical realities. They described strategies for informing patients about the landscape of current therapeutic options, be it pharmaceutical interventions, physical or occupational therapy, and community supports, to help manage their disease while research is underway.

> *…it's…about not taking away their hope…but to explain to them that right now the focus is more on the things that we can do something about, like managing their spasticity, managing their pain, optimizing their functioning. And maintaining their body, ready for any potential cure that may come out of stem cell, not knowing when that is going to occur, but we need to maintain their bodies as best as possible to receive anything, should it happen.*
>
> — Clinician 4 (Female, physiatrist)

5.4.4.2 Clarifying Timeframes

Clinicians suggested that an approach that balances hope and sensationalism is most effective to clarify translational timeframes. This balance can be achieved by references to contemporary research and by grounding hopes in current scientific realities. They articulated that it is important to acknowledge the uncertainty of research. Consistent with a stance of epistemic humility, clinicians articulated that they should be upfront with their patients about the scientific uncertainty associated with stem cell research, particularly about whether stem cell therapies will be available within their therapeutic windows.

Although clinicians articulated their uncertainty about the trajectory of stem cell research for MS, they also reinforced the importance of engaging with patients about the process of research and associated timeframes. Clinicians indicated that patients are often not familiar with the stages of clinical trials. To this end, they suggested that dialogue could explore clinical trial phases, their goals, and the timeframes historically associated with each phase of clinical research.

> *I just explain it's kind of like any other medical intervention, you know. You have to have various like studies. You do the sort of open label early stuff to find out if the intervention's safe at all in the human body. And then you do the phase two study, which generally is shorter and has less patients and is generally supposed to show that there might be some effect…And then they do a larger…phase three studies, where we really get a sense of if the intervention works.*
>
> — Clinician 5 (Male, neurologist)

Clinicians indicated that it would be beneficial to highlight the heterogeneity of stem cell sources (e.g., hematopoietic, mesenchymal, neural) used in MS research, and to explain that research using different stem cell sources may be at different stages of development. Clinicians also suggested that it is important to highlight both the progress achieved in the stem cell arena and the challenges that remain. This includes discussion about the facilitators and barriers noted in section 5.4.3 and an exploration of completed and ongoing clinical trials.

> *We talk about that study [a phase I/II autologous hematopoietic clinical trial] and how it was published, how it was indicated for a very sort of small percentage of people and*

why and how it was helpful for that group. And then we talk about other stem cell work going on, and we usually talk about the study in Ottawa with the mesenchymal stem cell and how that works and why they would or wouldn't qualify.

— Clinician 14 (Female, neurologist)

Finally, clinicians suggested that it is helpful to direct patients to credible resources that have been reviewed by the scientific community in an effort to offset potentially misleading information about stem cell research in the public sphere.

5.5 Discussion

This qualitative study of MS patient and clinician perspectives about the timeframes associated with the research and development of stem cell interventions unveils four salient themes: *receptivity*, *timeframes*, *accelerators and barriers to translation*, and *clinical communication strategies*. Results reveal key differences in receptivity to stem cell interventions among MS patients, accelerators of the research process, and clinical communication strategies about the translational process.

5.5.1 Advancing a Commitment to Transparency in Translation

Recently revised International Society for Stem Cell Research (ISSCR) guidelines on the ethical translation of stem cell research emphasize the obligation that stem cell researchers ought to engage with the public about the benefits and risks of stem cell research in a socially responsible way (International Society for Stem Cell Research, 2016). The guidelines emphasize the value of transparency in the translation of stem cell interventions, and urge investigators to engage with

the public to address their concerns and informational needs. Several resources have been devoted to advancing this goal, with an emphasis on engaging with the public about the stem cell tourism phenomenon that has been condemned by the ISSCR (International Society for Stem Cell Research, 2008; Master & Caulfield, 2014). The findings here reinforce the ethical imperative of engaging with potential end-users of developing biotechnologies (Illes et al., 2011), and focuses on the unique challenge of clarifying timeframes for neurotechnology translation.

5.5.2 Negotiating Risk and Receptivity

The data suggest that MS patients are receptive to and interested in stem cell interventions. At the same time, clinician and patient viewpoints demonstrate reluctance about the use of stem cell interventions because of the associated risks. Indeed, both participant cohorts agreed that stem cell interventions would not be appropriate first line approaches given their risk profile compared with that of conventional pharmaceutical therapies. Nevertheless, clinical equipoise still remains as research comparing hematopoietic stem cell transplantation and pharmaceutical approaches is currently underway (National Institutes of Health & Northwestern University, 2017). This clinical trial aims to generate knowledge about the relative risks and benefits of hematopoietic stem cell interventions compared with standard of care pharmaceutical therapies.

A divergence between the receptivity of patients and clinicians exists with respect to the timing of stem cell transplantation. While many patients with stable disease indicated that they would be receptive to stem cell approaches if in the future they were to become severely debilitated, clinicians indicated that hematopoietic stem cell interventions would be more optimally suited

for patients who are younger, earlier in their disease course, and who experience less severe disability. Indeed, recent clinical trials using an autologous hematopoietic stem cell transplantation have found that patients who have milder disease (Multiple Sclerosis Severity score ≤8.3) experience more stabilization or improvement than individuals with more severe MS (Multiple Sclerosis Severity score >8.3) after transplant (Atkins et al., 2016), and that patients who are younger and undergo transplantation closer to the time of diagnosis have better outcomes than older patients (Muraro et al., 2013).

These findings are aligned with a study that explored the perspectives of patients with spinal cord injury. Patients with sub-acute spinal cord injury (injured between 1-7 months prior to the study) expressed hesitation to participate in stem cell clinical trials, while those with chronic injury (injured over 18 months prior to the study) expressed greater readiness to enroll in stem cell research (Illes et al., 2011). In the same study, patients with more severe disease (cervical spinal cord injury) were less receptive to stem cell interventions than patients with less severe disease (thoracic spinal cord injury) (Illes et al., 2011). In the present study, patient receptivity to stem cell interventions did not segregate by MS sub-type. This finding is consistent with a recent autologous hematopoietic stem cell clinical trial that showed no significant difference on the Expanded Disability Status Scale (EDSS) between patients with relapsing remitting MS and with those with secondary progressive MS after transplantation (Atkins et al., 2016). Differences in patient perspectives in the context of MS and spinal cord injury may be due to the progressive nature of MS compared with the more static nature of impairment in spinal cord injury.

5.5.3 Clarifying Timeframes in a Multi-Track Translational Landscape

Results unveil patients' desire to learn more about the translational process and the pace of research and development. A salient challenge in clarifying such research timeframes may be associated with the complex translational landscape in the stem cell arena. Models of science discovery and translation have been historically described as linear, consisting of a single-track path from preclinical studies, to exploratory clinical trials, confirmatory trials, and finally to market approval and clinical delivery (Kimmelman & London, 2015). By contrast, the contemporary landscape of translation in the stem cell arena is a far more complex, multi-track pipeline. This pipeline is characterized by several points of access to stem cell interventions from both within and outside of clinical trials (Hyun, 2010; Lindvall & Hyun, 2009). For example, stem cell interventions may be offered outside of clinical trials through regulated routes such as Health Canada's Special Access Programme and through unregulated avenues, such as stem cell tourism. Indeed, clinicians noted that patient inquiries about the local availability of stem cell treatments for MS are often fueled by marketing efforts for stem cell tourism. Findings about the heterogeneity of patient estimates for the clinical availability of stem cell applications are therefore not surprising given the diversity of routes to access stem cell interventions.

The challenge of clarifying research timeframes may necessitate additional dialogue about the richness of the translational process in the stem cell arena. Findings about heterogeneous patient estimations of timeframes and their appetite to learn more about the research process correspond well with clinician recommendations for further dialogue about clinical translation. As per clinician recommendations, conversations may include clarification about diverse stem cell sources and clinical trial phases and their goals. Clinician recommendations to approach

conversations about the pace of research through a posture of epistemic humility may serve to nurture the physician-patient relationship (Benjaminy & Traboulsee, 2017) and to promote trust in local health care providers and resources (Crooks et al., 2015; Petersen et al., 2017; Petersen, Wilkinson, Petersen, Tanner, & Munsie, 2015; Snyder et al., 2014). In addition to these recommendations, clinical communication may also address the various routes to access stem cell interventions outside of clinical trials (e.g., stem cell tourism). Conversations may include clarification about the level of evidence and regulation associated with routes of administration outside of clinical trials to contextualize premature and illegitimate forms of stem cell application that detract from the translational process of stem cell biotechnologies, prey on patient urgency to access a therapy, and reframe the rigorous and utilitarian process of scientific evaluation as an access hurdle.

5.6 Limitations

As standard in qualitative inquiry, this study has a limited sample size and represents the views of participants in a snapshot in time. It does not aim to be generalizable. While this study explores the perspectives of patients with MS, study findings may not be transferable to neurologic disease characterized by a stationary prognosis as is evident by the differences in the views of patients with spinal cord injury. Recruitment strategies generated a study sample that may be impacted by self-selection bias and the inherent biases of the research team.

5.7 Conclusion

Regenerative medicine has been a focus of hope in the MS community for nearly three decades. While patients eagerly anticipate the therapeutic applications of stem cell research, information

about the timeframes associated with the translation of research into clinically applicable treatments is less accessible. This study characterizes patients' receptivity to stem cell interventions and desire to learn more about the process and pace of research and development. Clinicians address patient inquiries about stem cell research with a clinical communications approach. Results build on ISCCR recommendations for scientist-society engagement about stem cell research, and highlight opportunities to promote transparency in clinical discourse that aims to clarify translational timeframes and promote informed hope.

Chapter 6: Conclusion

In this dissertation, I explore the perspectives of patients and clinicians, and views represented in the news media about the translation of novel biotechnologies for neurodegenerative diseases. I focus on regenerative medicine, an area of inquiry and hope that has also been widely visible in the public eye. Results expand on existing scholarship on: (1) the central tension between demand for rapid access to experimental interventions and the lengthy evaluation process of clinical translation; and, (2) the role of hope in biotechnology development. Here, I explore these topics, deliberate on strategies to address challenges in translation based on emerging data in the dissertation, reflect on the limitations of this body of work, and suggest future directions for research.

6.1 At the Crossroads of Access and Evaluation: Balancing the Duties of Social Responsiveness and Scientific Responsibility

The tension between access to experimental interventions and evaluation through rigorous and time-intensive research are central in this dissertation and a motif that has followed technology development for many decades (Rettig & Jacobson, 2007). Patients in the study described in Chapter 3 deliberate about CCSVI research that was mobilized more by advocacy than by science (Chafe et al., 2011). Research participants in Chapter 5 reflect on and inquire about stem cell tourism, a phenomenon of premature access to unregulated and unapproved regenerative medicine interventions. The impetus for access to developing biotechnologies is fueled by clinical need, particularly in the context of progressive and debilitating neurological disease. Indeed, in a qualitative study of individuals with MS who received CCSVI interventions through

unregulated routes abroad, participant narratives revealed a sense of urgency to access a therapy and a desire to actively pursue a treatment as a means of coping (Snyder et al., 2014).

Public appetite for access to experimental biotechnologies is not only demonstrated by these examples, but also by numerous mechanisms in the translational landscape that promote rapid application of developing biotechnologies. These include regulated application of experimental interventions outside of clinical trials through compassionate access programs (Buhles, 2011; Caplan & Bateman-House, 2015; Jarow, Lurie, Ikenberry, & Lemery, 2017; Ross, 2009) and the use of *bona fide* therapeutics for unapproved medical indications through off-label use (Hyun, 2010). An appetite for accelerated access can be seen in Japanese reforms in adaptive licensing that grant novel regenerative medicine products conditional approval for market use following phase I clinical trials pending a seven-year period to establish efficacy post-licensure (McCabe & Sipp, 2016; Sipp, 2015). Additionally, a movement that calls for deregulation (Yusuf, 2010) has materialized in off-shoring clinical research from jurisdictions with rigid regulatory mechanisms to ones with more relaxed oversight (Caulfield et al., 2009; Garrafa, Solbakk, Vidal, & Lorenzo, 2010; Petryna, 2007).

In a complex translational landscape where an impetus and clinical need for rapid access to developing biotechnologies is implemented through diverse mechanisms with varying degrees of regulation and patient protections, translational researchers and policymakers face conflicting ethical duties. These stakeholders have a duty of social responsiveness. Public engagement in science and policy reinforces the values of accountability and transparency in research (Burgess et al., 2009). Additionally, civic participation in science also promotes public trust in technology

translation (Sclove, 1999; Secko et al., 2008). Research is commonly funded through the public purse, and citizens often bear the risks of biotechnology development. It is therefore the responsibility of translational scientists and policymakers to interface with the public about contemporary research, provide citizens an opportunity to be informed and involved in research applications, and respond to public priorities and concerns about developing research (Illes et al., 2005). At the same time, translational researchers and policymakers have a scientific responsibility and a fiduciary duty to ensure the social value of research and the rigorous evaluation of developing biotechnologies (Emanuel et al., 2000; London et al., 2010). Indeed, regulatory mechanisms ensure the safety of research participants, the efficacy of clinically available interventions, the competitiveness of market-approved therapies in the global market, and promote public trust and continuous support in research enterprises (Canadian Institutes of Health Research et al., 2014; Emanuel et al., 2000; International Society for Stem Cell Research, 2016; Kimmelman & London, 2015).

The tension between access and evaluation may be addressed through creative mechanisms that promote both efficient translation and an opportunity to serve societal interests by advancing knowledge. For instance, several reforms in clinical trial design have been implemented to promote rapid access to novel biotechnologies. These include placebo-controlled crossover and adaptive clinical trials. In placebo-controlled crossover trials research participants receive both the experimental intervention and a placebo, at different sequences, thus allowing all research participants to access to the active agent regardless of randomization outcomes (Mills et al., 2009). Such study designs have been particularly attractive to participants who have progressive illness (Daugherty, Ratain, Emanuel, Farrell, & Schilsky, 2008; Miller & Joffe, 2011). Adaptive

trial design, unlike traditional clinical trial approaches, allows for dynamic revision of study parameters based on interim analyses, with the goals of maximizing efficiencies and yielding more nuanced understanding about treatment effect (Coffey et al., 2012; Food and Drug Administration, 2010). Common adaptive designs in clinical trials include addition or elimination of study arms; combination of multiple phases into single trials (e.g., phase I/II); change of sample sizes; adjustment of power; and change of randomization ratios (Berry, 2011). To promote access to developing biomedicines and ensure recruitment goals are met, clinical research methodology will be likely to incorporate additional reforms in clinical trial design in the coming years.

With the aim of promoting social responsiveness and compassionate care for patients, while at the same time maintaining scientific responsibility, a knowledge generation approach may be helpful (Walker, Rogers, & Entwistle, 2014). Indeed, collecting data from patients who have accessed unproven biotechnologies through medical tourism or compassionate use platforms would provide an opportunity to capture important data that might otherwise be lost. While the number of experimental interventions supplied to patients outside of clinical research is not known, estimates suggest that in some cases these numbers exceed enrolment rates in early-phase clinical trials (American Society of Clinical Oncology, the Association of American Medical Colleges & National Coalition for Cancer Survivorship, 2007). As such, collecting data about the use of developing biotechnologies outside of clinical trials may serve as a valuable resource and an important opportunity to accumulate new knowledge that may inform further clinical research about side effects or efficacy of investigational interventions (Walker et al., 2014).

Scholars have produced new knowledge about decision-making (Crooks et al., 2015; Petersen, Seear, & Munsie, 2014; Snyder et al., 2014) and medical outcomes in the context of medical tourism (Amariglio et al., 2009; Dobkin et al., 2006). Patient communities have also championed a similar knowledge generation approach. For example, in 2008, a group of individuals with amyotrophic lateral sclerosis (ALS) in collaboration with PatientsLikeMe—an online patient network that aims to connect patients, improve outcomes, and promote research—initiated a platform for patients who had obtained off-label lithium carbonate treatment for ALS to submit data about their use and outcomes. Data probes included dosage, weight, and outcomes measures on the ALS functional rating scale. Data from 149 treated ALS patients were matched with historical controls in an observational study that challenged clinical equipoise about the potential efficacy of the intervention (Fornai et al., 2008; Paul Wicks, Vaughan, Massagli, & Heywood, 2011). This patient-lead research endeavor contributed to the early termination of clinical trials due to futility considerations, and spared the ALS community significant divestment of funds from promising areas of inquiry and opportunity costs for patients (Wicks & Heywood, 2014). In addition to serving as an important opportunity to further knowledge, data gathered outside of clinical trials may give patients the opportunity to benefit from the aspirational (e.g., helping advance societal interests) and collateral (e.g., increased access to surveillance and medical attention) outcomes of research participation (King, 2000). Contribution to scientific knowledge may also improve patient care in the future and may be a source of empowerment for patients (Ross, 2009).

In response to current demand for access to experimental biotechnologies, educational initiatives may be needed to address public evaluation of diverse forms of evidence and regulatory protections. These may be particularly important in light of the powerful and readily accessible calls for access to developing biotechnologies and anecdotal evidence on online fora (Chafe et al., 2011). Education about evidence should be a bidirectional effort. Scientists and clinicians may reciprocally consider that the contemporary focus on evidence-based medicine sometimes overlooks a wide body of knowledge that has been gleaned from medicine-based evidence approaches. Indeed, over the last 50 years 80-90% of innovations in surgical care have been developed on the basis of clinical experience rather than through a traditional research approach (Cosgrove, 2008). An educational initiative alone, however, assumes that an information deficit underlies public demand for access to developing biotechnologies (Marteau, Snowden, & Armstrong, 2002). Indeed, educational approaches do not adequately account for affective factors, such as hope, that extend beyond a deficit of understanding and have a substantial influence in the decision-making process (Brown, 2009).

6.2 Promoting Informed Hope in Biotechnology Development

The development of biotechnologies, including stem cell research, has generated public interest and involvement, and is embedded within a complex landscape of hope. Hope is a force that ubiquitously surrounds developing biotechnologies: it inspires researchers, generates public interest, and mobilizes funding (Hedgecoe, 2004; van Lente, Spitters, & Peine, 2013). At the same time, exaggerated forms of hope may have adverse implications on technology translation and may threaten the sustainability of the research enterprise (Caulfield, 2004; Holtzman, 1999; Kimmelman, 2010; Ogbogu, 2006; Petersen, 2009).

As discussed in Chapter 3, a large volume of scholarship has focused on the theoretical implications of hype across a variety of technology types (Condit, 2007; Downey & Geransar, 2008; Evans, Meslin, Marteau, & Caulfield, 2011). Research to date, however, has not empirically characterized these implications. Results from Chapter 3 demonstrate that at least in the acute case of CCSVI, exaggerated hopes resulted in disappointment and critical opinions in the MS community about the divestment of funds from other areas of research. The CCSVI experience offers an opportunity to reflect on the translational landscape in an effort to promote social responsibility in the development of future biotechnologies.

One lesson that can be drawn from the CCSVI experience is that exaggerated hope and subsequent disappointment present a costly burden in translation. While results demonstrate that disappointment in the context of the CCSVI experience did not cause disillusionment or loss of trust in the research enterprise, many scholars worry that continuous cycles of hype may cause such impact (Downey & Geransar, 2008; Ogbogu, 2006; Petersen, 2009). Therefore, in an effort to promote the sustainable translation of novel biotechnologies, I suggest that mitigating the cycle of hype is key. As demonstrated by the Gartner Hype Curve (Figure 6.1 A), a rise in expectations followed by disillusionment form a well-characterized pattern in technological development (Gartner Inc., 2017; O'Leary, 2008). One approach to promote sustainable and socially conscientious biotechnology development is to address this pattern. The underlying assumption that informs this strategy is that when hopes are informed rather than inflated, disappointment should also be mitigated. As already characterized by the Gartner Hype Curve (Figure 6.1 A) the trajectory of expectations in sustainable biotechnology development (Figure

6.1 B) also begins with an innovation trigger, such as a novel scientific discovery. This trigger is followed by a rise of informed hope. This form of hope serves a valuable social purpose and generates public interest and support in technology development. Informed hope is stimulated by the promise of contemporary research efforts and grounded in the associated caveats. This form of hope is also anchored in realistic communications that clarify timeframes and discrete steps in the process of research and development. As a natural consequence to the rise of informed hope, public expectations follow a downward trajectory of mitigated disappointment. Since hope is informed rather than inflated, the amplitude between hope and disappointment is reduced compared with that seen in the Gartner Hype Curve (6.1 A). The shallow trough that results represents the reduced social impact of unmet expectations in the process of innovation, and promotes sustainable technology development.

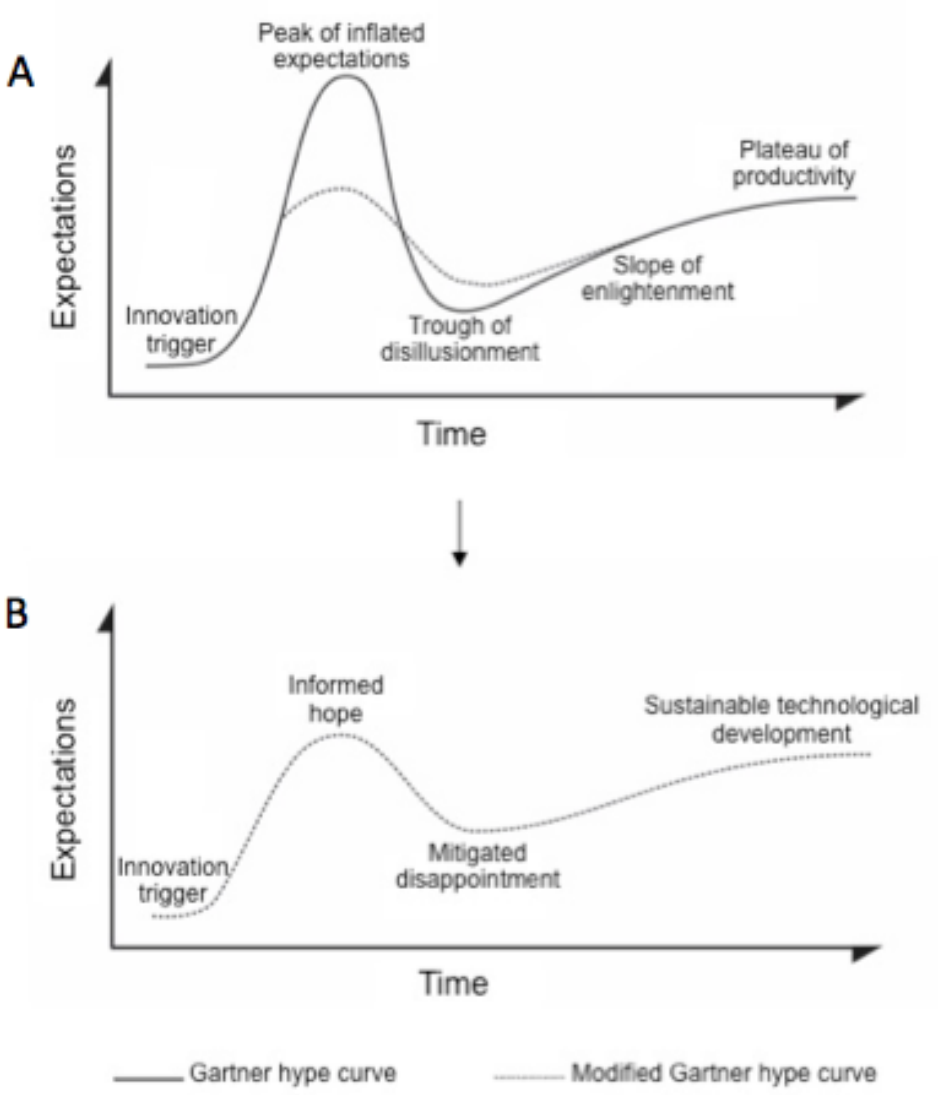

Figure 6.1 Trajectory of expectations in sustainable technology development

Adapted from (Gartner Inc., 2017).

Building on Figure 6.1, I integrate results into two approaches to promote informed hope: (1) news media communication strategies; and, (2) clinical communication strategies.

6.2.1 Media Communication Strategies

Results from Chapter 4 inform strategies to contextualize portrayals of the promise of stem cell research with descriptions of the pace of clinical translation in the news media. These strategies focus on the collective responsibility of reporters, scientists, and clinicians who communicate through the media to describe the steps in the process of research and development. These include descriptions of clinical trial phases and their goals, regulatory mechanisms such as ethics approval, Health Canada approval, health technology assessment, and market approval. In keeping with Figure 6.1 and the goal of promoting informed hope, it may be helpful to describe traditional timeframes associated with technology translation. For example, descriptions of the 10-14 year timeframe historically associated with pharmaceutical translation from novel drug target to market approval may provide additional transparency about the translational pace (Glassman & Sun, 2004). Clarification about the additional time associated with the development of novel biologics, such as stem cell products, which presently require additional oversight and regulatory review, and the challenges of health technology assessment and integration into health care systems and health insurance regimes may also provide important context (Caulfield et al., 2015; Greely, 2013).

While the news media play an important role in directing public attention to particular topics in biomedicine, addressing communications in the news media alone would likely be insufficient. Indeed, as suggested in Chapter 3, initiatives to better resource patient communities to contribute

to public debates, particularly through social media platforms may well be needed. Community engagement in the development of biotechnologies should be reciprocally complemented by responsible scientific citizenship. Indeed, translational scientists and clinicians should be encouraged to interface with citizens about the uncertainties, caveats, as well as the promise of novel biotechnologies (Barfoot, Doherty, & Blackburn, 2017). These stakeholders should be incentivized to interface with the public through social media platforms, where many advocacy campaigns mobilize science (Mazanderani, O'Neill & Powell 2013; Robillard & Wright, 2017).

6.2.2 Clinical Communication Strategies

Results from Chapter 5 confirm the assertion of other scholars that the clinician-patient conversation about hope is best approached with epistemic (knowledge-based) humility: a stance that acknowledges the uncertainty associated with decision-making in medical care, and one that also honours the lived experience that lends credibility to the expertise of patients (Schwab, 2012). Conversations through a posture of epistemic humility that privilege openness and understanding could also strengthen relationships of trust between patients and clinicians (Ho, 2009). The uncertainty that naturally follows biotechnology development lends itself well to approaching clinical conversations through this posture. Indeed, developing biotechnologies are associated not only with variable translational timeframes, but also with high attrition rates in clinical trials (Hay, Thomas, Craighead, Economides, & Rosenthal, 2014). In the case of progressive illness, it may be particularly important to convey uncertainty about whether interventions will be available within limited therapeutic windows.

Hope can serve as an adaptive mechanism for managing daily living with serious illness

(Groopman, 2005). Honouring patient hope for therapeutic development while grounding practical advice in current clinical realities may strengthen collaboration between patients and clinicians and support shared decision-making through an emphasis on informed hope (Benjaminy et al., 2015; Reimer, Borgelt, & Illes, 2010). This includes conversations about contemporary research efforts that are anchored in discussion of clinically available interventions such as pharmaceuticals, physical or occupational therapy, as well as community supports through patient groups or other available resources.

Results from Chapter 5 illustrate a gap in patient understanding of the process of translation, and consequent confusion about translational timeframes. Along with this knowledge gap, findings reveal the desire of patients to learn more about the translational process. To this end, clinicians recommended that conversations with patients explore the phases of research and their goals, the regulatory steps in the translational process, and historical timeframes associated with research and development. In the conversation, current research efforts should be contextualized along the translational continuum to provide clarity on the steps that have been completed and those still necessary to facilitate the uptake of developing biotechnologies into the clinic.

6.3 Limitations

In this dissertation, I explore the perspectives of a select group of stakeholders about developing biotechnologies, with an emphasis on stem cell applications. Other voices such as those of patient advocacy organizations, translational scientists, and policy makers are absent, and present both a limitation and an opportunity for future inquiry.

The perspectives of patient and clinician participants in this dissertation may be biased by recruitment methods. For example, patients and clinicians who enroll in stem cell research are likely to be more interested in it than those who do not. In particular, participants recruited through patient advocacy websites may be more actively engaged in information seeking about experimental interventions or about MS than those who are recruited through other avenues.

A common limitation of qualitative research is the generalizability of the findings. I utilized descriptive qualitative inquiry methods in Chapter 3 and Chapter 5. Qualitative descriptive studies generally have fewer research participants than quantitative analyses, and focus on depth of narrative analysis rather than breadth in sampling (Guest et al., 2006). Small sample sizes are aligned with the goal of maintaining close association with research participants (Crouch & McKenzie, 2006). The data therefore do not provide a representative account of experiences in the MS community. Instead they provide a snapshot of the experiences of specific participants at a point in time.

In Chapter 4 I characterize the landscape of news media representations about developing stem cell research. The analysis, however, does not capture representations in other forms of media, including television and social media that play an increasingly prominent role in disseminating information and influencing public dialogue about developing biotechnologies (Robillard & Wright, 2017). In addition, I did not compare news media representations to content in academic publications. Therefore, the study does not capture errors of commission, or inaccuracies in media content but focuses, instead, on errors of omission, a more common occurrence in media reporting (Bubela & Caulfield, 2004).

6.4 Future Directions

6.4.1 Promoting Strategic Reciprocity Between Science and Society

In this dissertation, I explore the ethical imperative of democratizing science. With growth in Web 2.0 platforms such as Twitter, wikis, blogs, Facebook, and YouTube science communication has increasingly become a bidirectional enterprise that incorporates the voices of citizens. Future inquiry is needed to explore the perspectives of members of the public who contribute to science debates through online fora about their roles in disseminating information about developing biotechnologies and about social responsibility in science communication. Such inquiry will identify public values about science communication and may also uncover informational needs or gaps that can be addressed through tools to help members of the public engage in scientific debates conscientiously and effectively.

6.4.2 Exploring Perspectives in a Multi-Track Translational Landscape

The impetus for access to novel biotechnologies has reformed the previously linear model of translation into a multi-track translational domain that incorporates regulated pathways for access to experimental biotechnologies outside of clinical trials. While research has been dedicated to patient decision-making in the context of clinical trials, and medical tourism, patient perspectives in the context of innovative therapy remain relatively unexplored. Additional research and public engagement about approaches to promote access to regulated developing biotechnologies will fill this gap. Future patient-oriented research that investigates perspectives and values about access in platforms such as compassionate access, off-label, and adaptive licensing will detract from unregulated and dubious medical tourism applications. As new

International Society for Stem Cell Research Guidelines assert the importance of accountability over innovative therapies and call for increased patient contribution in the translational process, an analysis of patient perspectives about regulated access routes outside of clinical trials in the stem cell context is especially timely.

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Appendices

Appendix A Recruitment Materials

A.1 Patient Recruitment Website Advertisement

Invitation to Participate in Interviews

We are seeking English-speaking adults over 19 years of age with Multiple Sclerosis or Parkinson's disease to participate in a 45 minute interview over the telephone, in person, or by Skype as part of a research project.

The purpose of this interview is to explore the perspectives of patients with neurodegenerative diseases about the risks, benefits, and time frames associated with stem cell clinical trials. To participate in or learn more about this study, please contact Shelly Benjaminy, National Core for Neuroethics, at shelly.benjaminy@ubc.ca or 604-827-3690.

Study Investigators:

Principal Investigator: Judy Illes, PhD, Canada Research Chair in Neuroethics, Professor, Division of Neurology, University of British Columbia

Co-Investigator: Anthony Traboulsee, MD, Director of MS Clinic at UBC Hospital, Vancouver Coastal Health, Associate Professor, University of British Columbia

Co-Investigator: Silke Cresswell, MD, Professor, Pacific Parkinson's Research Institute, University of British Columbia

Study contact and lead for informed consent process: Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690

Sponsor: Stem Cell Network

A.2 Patient Invitation Letter


NATIONAL CORE FOR NEUROETHICS
LA NEUROÉTHIQUE

Dear Patient,

Subject: Invitation to Participate in Interviews

We are seeking English-speaking persons who have Multiple Sclerosis to participate in a 45-minute interview as part of a research project. The interview study is designed to explore the perspectives of patients with neurodegenerative diseases about the risks, benefits, and time frames associated with stem cell clinical trials. The results of this research will be used to construct clinical communication tools that will help counsel patients about stem cell research. The interview may be conducted in-person, over the phone, or over Skype to accommodate your preferences. To participate in or learn more about this study, please contact Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690.

Sincerely,

Dr. Anthony Traboulsee

Study Investigators:

Principal Investigator: Judy Illes, PhD, Canada Research Chair in Neuroethics, Professor, Division of Neurology, University of British Columbia, Phone: 604-822-0746

Co-Investigator: Anthony Traboulsee, MD, Director of MS Clinic at UBC Hospital, Vancouver Coastal Health, Assistant Professor, University of British Columbia.

Co-Investigator: Silke Cresswell, MD, Professor, Pacific Parkinson's Research Institute, University of British Columbia

Study contact and lead for informed consent process: Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690

Sponsor: Stem Cell Network

A.3 Clinician Recruitment Poster

NATIONAL CORE FOR NEUROETHICS
LA NEUROÉTHIQUE

Vancouver CoastalHealth
Promoting wellness. Ensuring care.

Evidence-Informed Strategies for Communicating about Time Frames in Stem Cell Clinical Trials

Have your patients asked you about stem cell research for multiple sclerosis?

Researchers at the University of British Columbia are interested in your views about the pace of research and development for stem cell interventions for neurodegenerative diseases. Our goal is to learn about the perspectives and priorities of physicians who care for patients with multiple sclerosis and Parkinson disease, and to develop clinical discourse strategies that promote informed hope in patient communities.

You may be eligible to participate in this study if you are a physician who cares for patients that have multiple sclerosis or Parkinson disease.

Your participation will involve a short interview. The interview will be scheduled at your convenience and can take place in person, over the telephone, or over Skype.

If you would like more information about this study, please contact Shelly Benjaminy at 604-827-3630 or shelly.benjaminy@ubc.ca

YOUR PARTICIPATION WILL PROMOTE THE SUCCESS OF THIS WORK.

THANK YOU.

A.4 Clinician Invitation Letter


NATIONAL CORE FOR NEUROETHICS
LA NEUROÉTHIQUE

Dear [insert clinician name],

Subject: Invitation to Participate in Interviews

We are seeking clinicians who care for patients with Multiple Sclerosis to participate in a 45-minute interview as part of a research project. The interview study is designed to explore the perspectives of clinicians who care for patients with neurodegenerative diseases about the risks, benefits, and time frames associated with stem cell clinical trials. The results of this research will be used to construct clinical communication tools that will help counsel patients about stem cell research.

The interview may be conducted in-person, over the phone, or over Skype to accommodate your preferences. To participate in or learn more about this study, please contact Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690.

Sincerely,

Dr. Anthony Traboulsee

Study Investigators:

Principal Investigator: Judy Illes, PhD, Canada Research Chair in Neuroethics, Professor, Division of Neurology, University of British Columbia, Phone: 604-822-0746

Co-Investigator: Anthony Traboulsee, MD, Director of MS Clinic at UBC Hospital, Vancouver Coastal Health, Assistant Professor, University of British Columbia.

Co-Investigator: Silke Cresswell, MD, Professor, Pacific Parkinson's Research Institute, University of British Columbia

Study contact and lead for informed consent process: Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690

Sponsor: Stem Cell Network

Appendix B Consent Forms

B.1 Patient Consent Form

NATIONAL CORE FOR NEUROETHICS
LA NEUROÉTHIQUE

Consent Form for Interviews with Patients

Evidence-Informed Strategies for Communicating about Time Frames in Stem Cell Clinical Trials

Principal Investigator: Judy Illes, PhD, Canada Research Chair in Neuroethics, Professor, Division of Neurology, University of British Columbia, Phone: 604-822-0746

Co-Investigator: Anthony Traboulsee, MD, Director of MS Clinic at UBC Hospital, Vancouver Coastal Health, Assistant Professor, University of British Columbia.

Co-Investigator: Silke Cresswell, MD, Professor, Pacific Parkinson's Research Institute, University of British Columbia

Study contact and lead for informed consent process: Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3630
Sponsor: Stem Cell Network

PURPOSE
You are being invited to participate in an interview study designed to explore the perspectives of patients with neurodegenerative diseases about the risks, benefits, and time frames associated with stem cell clinical trials. The results of this research will be used to construct clinical communication tools that will help counsel patients about stem cell research.

WHO IS CONDUCTING THE STUDY?
The National Core for Neuroethics at the University of British Columbia (UBC) is conducting this study in collaboration with researchers at the Pacific Parkinson's Research Institute and MS Clinic, University of British Columbia Hospital.

WHO CAN PARTICIPATE IN THIS STUDY?
You can participate in this study if you have been diagnosed with Parkinson's Disease or Multiple Sclerosis, are over the age of 19, and are able to speak English.

WHAT DOES THE STUDY INVOLVE?
If you consent to participate and return the signed consent form, Shelly Benjaminy, or her designate, will contact you to schedule a 45-minute telephone interview about:

- The perceived risks and benefits of stem cell clinical trials.

- Your understanding of the stages and aims of stem cell clinical trials.
- Hopes for your prognosis in light of research efforts.

The interview will be audio recorded. All measures will be taken to assure confidentiality of the interview, as set out below.

WHAT ARE THE POSSIBLE HARMS AND BENEFITS OF PARTICIPATING?
You may find that speaking about some of these issues during the interview is distressing. If you would like to speak with the principle investigator about any distressing matters please contact:
Dr. Judy Illes (604-822-0746)

WILL I RECEIVE ANY REMUNERATION?
There is no remuneration for participating in the interview. Results of the study will be accessible on the National Core for Neuroethics website (http://neuroethicscanada.ca).

What are my rights as a participant?
Your participation is entirely voluntary. If you participate in the study, you may refuse to answer any question that you don't want to answer. You can also agree to participate now, and then change your mind at any time without having to give a reason for your decision and your data will be removed from the study. If you chose to not take part, this will involve no penalty or loss of benefits. Choosing not to participate in this study will not affect your medical care. Study participation does not promote access to clinical trial enrollment.

Your confidentiality will be respected.

None of this information will be released or published without your specific consent to the disclosure. However, research records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of the UBC Research Ethics Boards, or study sponsor such as the Stem Cell Network for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

Signing this consent form in no way limits your legal rights against the investigators or anyone else.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
Your confidentiality will be respected. A unique study number will be used to identify study participants. The audio recordings will be converted into written form for analysis. No names will appear on typed transcripts. Both the recordings and the transcripts will be kept on a password-protected computer or in locked filing cabinets in secured offices at the National Core for Neuroethics at UBC. The recordings and transcriptions will be kept at UBC for 5 years from the time of publication of the results of the study. After this period, the paper forms will be shredded and any electronic records with raw data destroyed. No names will be used in any published and written findings resulting from the study.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?
If you have any concerns or questions about this study, you may contact the investigators, Dr. Illes at 604-822-0746 or Shelly Benjaminy at 604-827-3630.
If you have any concerns or questions regarding your treatment or rights as a research subject, you may contact the Research Subject Information Line in the UBC Office of Research Services at 604-822-8598 or at RSIL@ors.ubc.ca. or the toll free line at 1-877-822-8598.

SUBJECT CONSENT TO PARTICIPATE

I have been fully informed as to the procedures to be followed and have been given a description of the discomforts, risks, and benefits to be expected. In signing this consent form, I agree to have the interview digitally recorded and I understand that I am free to withdraw at any time, without giving a reason.

My signature indicates that I have read and understood the above information, that I have discussed this project with the study investigator and his/her staff, and that I have decided to participate, based on the information provided.

Check List

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific purposes.
- I understand that my participation in this project is voluntary and that I am completely free to refuse to participate or withdraw from this study at any time without changing in any way the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this project will provide any benefits to me.
- I have read this form and I freely consent to my participation in this study.
- I have been told that I will receive a dated and signed copy of this form.

Can we contact you to ask follow up questions or to participate in a follow up focus group? Yes / No
Would you like to be notified of the study results? Yes / No
Please provide your contact information if you answered yes to the previous two questions.

_____

_____

_____

Name of Participant *(Please Print)*	Signature of Participant	Date
Name of Principal Investigator or Designate obtaining consent *(Please Print)*	Signature of Principal Investigator or Designate obtaining consent	Date

Copy: Participant, Investigator's File

B.2 Clinician Consent Form


NATIONAL CORE FOR NEUROETHICS
LA NEUROÉTHIQUE

Consent Form for Interviews with Clinicians

Evidence-Informed Strategies for Communicating about Time Frames in Stem Cell Clinical Trials

Principal Investigator: Judy Illes, PhD, Canada Research Chair in Neuroethics, Professor, Division of Neurology, University of British Columbia, Phone: 604-822-0746

Co-Investigator: Anthony Traboulsee, MD, Director of MS Clinic at UBC Hospital, Vancouver Coastal Health, Assistant Professor, University of British Columbia.

Co-Investigator: Silke Cresswell, MD, Professor, Pacific Parkinson's Research Institute, University of British Columbia

Study contact and lead for informed consent process: Shelly Benjaminy, PhD student, Project Lead, National Core for Neuroethics, University of British Columbia, Phone: 604-827-3690
Sponsor: Stem Cell Network

PURPOSE
You are being asked to participate in an interview study designed to explore the perspectives of clinicians who care for patients with neurodegenerative diseases about the risks, benefits, and time frames associated with stem cell clinical trials. The results of this research will be used to construct clinical communication tools that will help counsel patients about stem cell research.

WHO IS CONDUCTING THE STUDY?
The National Core for Neuroethics at the University of British Columbia (UBC) is conducting this study in collaboration with researchers at the Pacific Parkinson's Research Institute and MS Clinic, University of British Columbia Hospital

WHO CAN PARTICIPATE IN THIS STUDY?
You can participate in this study if you are a physician who cares for patients with Parkinson's Disease or Multiple Sclerosis, and are able to speak English.

WHAT DOES THE STUDY INVOLVE?
If you consent to participate and return the signed consent form, Shelly Benjaminy, or her designate, will contact you to schedule a 45-minute telephone interview about:

- The perceived risks and benefits of stem cell clinical trials.
- Your patients' understanding of the stages and aims of stem cell clinical trials.

- Hopes for your patients' prognosis in light of research efforts.

The interview will be audio recorded. All measures will be taken to assure confidentiality of the interview, as set out below.

WHAT ARE THE POSSIBLE HARMS AND BENEFITS OF PARTICIPATING?
We are not aware of any risks, other the investment of your time, associated with participating in this study.

WILL I RECEIVE ANY REMUNERATION?
There is no remuneration for participating in the interview. Results of the study will be accessible on the National Core for Neuroethics website (http://neuroethicscanada.ca) and also on the websites of collaborating advocacy groups.

What are my rights as a participant?
Your participation is entirely voluntary. If you participate in the study, you may refuse to answer any question that you don't want to answer. You can also agree to participate now, and then change your mind at any time without having to give a reason for your decision and your data will be removed from the study. If you chose to not take part, this will involve no penalty or loss of benefits.

Your confidentiality will be respected.

None of this information will be released or published without your specific consent to the disclosure. However, research records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of the UBC Research Ethics Boards, or study sponsor such as the Stem Cell Network for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

Signing this consent form in no way limits your legal rights against the investigators or anyone else.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?
Your confidentiality will be respected. A unique study number will be used to identify study participants. The audio recordings will be converted into written form for analysis. No names will appear on typed transcripts. Both the recordings and the transcripts will be kept on a password-protected computer or in locked filing cabinets in secured offices at the National Core for Neuroethics at UBC. The recordings and transcriptions will be kept at UBC for 5 years from the time of publication of the results of the study. After this period, the paper forms will be shredded and any electronic records with raw data destroyed. No names will be used in any published and written findings resulting from the study.

WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?
If you have any concerns or questions about this study, you may contact the investigators, Dr. Illes at 604-822-0746 or Shelly Benjaminy at 604-82-3690.

If you have any concerns or questions regarding your treatment or rights as a research subject, you may contact the Research Subject Information Line in the UBC Office of Research Services at 604-822-8598 or at RSIL@ors.ubc.ca. or the toll free line at 1-877-822-8598.

SUBJECT CONSENT TO PARTICIPATE

I have been fully informed as to the procedures to be followed and have been given a description of the discomforts, risks, and benefits to be expected. In signing this consent form, I agree to have the interview digitally recorded and I understand that I am free to withdraw at any time, without giving a reason.

My signature indicates that I have read and understood the above information, that I have discussed this project with the study investigator and his/her staff, and that I have decided to participate, based on the information provided.

Check List

- I have read and understood the subject information and consent form.
- I have had sufficient time to consider the information provided and to ask for advice if necessary.
- I have had the opportunity to ask questions and have had satisfactory responses to my questions.
- I understand that all of the information collected will be kept confidential and that the results will only be used for scientific purposes.
- I understand that my participation in this project is voluntary and that I am completely free to refuse to participate or withdraw from this study at any time without changing in any way the quality of care that I receive.
- I understand that I am not waiving any of my legal rights as a result of signing this consent form.
- I understand that there is no guarantee that this project will provide any benefits to me.
- I have read this form and I freely consent to my participation in this study.
- I have been told that I will receive a dated and signed copy of this form.

Would you like to be notified of the study results? Yes / No
Please provide your contact information if you answered yes to the previous question.

_____

_____

_____

Name of Participant *(Please Print)*	Signature of Participant	Date
Name of Principal Investigator or Designate obtaining consent *(Please Print)*	Signature of Principal Investigator or Designate obtaining consent	Date

Copy: Participant, Investigator's File

Appendix C Interview Guides

C.1 Interview Guide[1] for Patients

Preamble

I would like to thank you very much for taking the time to talk to me about your experiences. They will assist us in helping clinicians communicate about stem cell research.

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

I am going to ask you questions about your experiences with MS and stem cell research. Your experiences will later be analyzed to help us develop clinical communication strategies about stem cell research.

General info

1. Tell me about your history with MS

2. Can you tell me about your emotional responses from learning the news to living with MS?

3. What current care are you receiving for MS?

4. What hopes do you have for the future?

Stem Cell Research Knowledge

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

5. What have you heard about research efforts to treat MS?

6. What do you know about stem cell clinical trials for MS? [Prompt on research vs. treatment distinction]

7. Where do you hear/learn about stem cell clinical trials for MS? Do you trust these sources of information?

8. Describe your knowledge of the clinical trial process [prompt on phases]

9. What is the goal of stem cell clinical trials for MS [prompt on safety vs. efficacy]?

Stem Cell Research Personal Perspectives

10. Have you considered participating in stem cell clinical trials?

11. If you were given the chance to participate in a stem cell clinical trial, what might be some advantages? [If aware of clinical trial phases, prompt question in phase-specific context]

12. If you were given the chance to participate in a stem cell clinical trial, what might be some of your worries? [If aware of clinical trial phases, prompt question in phase-specific context]

13. Have you considered traveling abroad to participate in stem cell clinical trials?

14. Do you believe that stem cell therapies will be available in time to provide you with medical benefits?

15. What would you want your doctor to tell you about stem cell clinical trials?

Conclusion

I would like to thank you for taking the time to speak with me today and for bravely sharing your experiences and perspectives with me. I have asked you many questions today, and I am wondering if you have any questions to ask me?

C.2 Interview Guide[2] for Clinicians

I would like to thank you very much for taking the time to talk to me about your experiences. They will assist us in helping clinicians communicate about stem cell research.

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

I am going to ask you questions about your experiences with MS and stem cell research. Your experiences will later be analyzed to help us develop clinical communication strategies about stem cell research.

General

1. Tell me a little bit about your research/practice

Opinion about Stem Cell Research

2. What is your opinion of the current state of stem cell research efforts to treat MS?

3. What are your expectations for stem cell research efforts to treat MS in the future?

Patient Concerns

4. Do your patients ask you questions about stem cell research for MS? If so, what do they ask?

5. Do your patients inquire about participating in stem cell clinical trials?

6. Do your patients ask about the risks and the benefits of participating in stem cell clinical trials?

---

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

7. Do your patients ask you questions about how long it will take before stem cell interventions will be accessible to them?
    (a) In the form of clinical trials?
    (b) As standard-of-care therapeutics?
    (c) How do you respond to these questions?

8. Do your patients ask you questions about how stem cell clinical trials will affect their prognoses? If so, what do they ask? How do your respond? [Prompt to explore if clinician believes that stem cell clinical trials may or may not affect their patients' prognoses]

Knowledge Translation

9. How do you explain to your patients about stem cell clinical trials for MS?

10. Do you think that your patients have an understanding of the phases of clinical trials and the goals associated with each phase? [Prompt on safety vs. efficacy]

11. How do you think it is best to explain to patients about the phases associated with stem cell clinical trials?

12. How do you think it is best to explain to patients about the time frames associated with the development of stem cell clinical trials into real world treatments?

13. In your opinion, how should clinicians communicate about stem cell research in response to the hopes of patients?

Stem Cell Tourism

14. Do you have patients who have traveled abroad or inquired about traveling abroad to participate in stem cell clinical trials? If so,
    (a) What clinical trials?
    (b) How do you respond to these patients' concerns?
    (c) What motivates patients to enroll in these clinical trials?

Conclusion

I would like to thank you for taking the time to speak with me today. I have asked you many questions today, and I am wondering if you have any questions to ask me?

Appendix D Member Checking Summaries

D.1 Patient Member Checking Summary 1

Fallen off the Bandwagon? Stem Cell Research in the Post-CCSVI Era

Thank you for participating in our research. The contribution of your perspectives has made it possible for us to conduct a series of interviews about hopes for stem cell research for multiple sclerosis (MS) after the chronic cerebrospinal venous insufficiency (CCSVI) research experience. Below is a summary of some of our study findings. We will follow up with additional findings in the future. We would like to make sure that the analysis of your perspectives authentically represents your views, and we welcome your feedback and questions about our work. To ask questions about this study or to share your comments, please contact:

Shelly Benjaminy
E-mail: shelly.benjaminy@ubc.ca
Phone: 604-822-0748
Please accept our sincere gratitude for taking the time to participate in this study and for sharing your perspectives with us.

Kind regards,
Dr. Anthony Traboulsee
Prof. Judy Illes
Dr. Andrew Schepmyer
Ms. Shelly Benjaminy

The Study

Stem cell research has been an area of hope for multiple sclerosis (MS) since early clinical research began in the 1990s. It was not until 2009, when CCSVI research came out that hope in the MS community shifted. Recently, CCSVI has come under a lot of scientific scrutiny. Studies demonstrated flaws in the CCSVI hypothesis, and many serious side effects were reported. At the same time, stem cell research has shown early successes with a bone marrow transplantation approach.

We explored the perspectives of MS patients about how the chronic cerebrospinal venous insufficiency research influences their views on stem cell research. We interviewed 20 MS patients and analysed transcriptions of audio recorded interviews to capture recurring themes.

The Findings

Out of the 20 participants that we interviewed, our interpretation is that 17 were generally critical about CCSVI research and 3 were neutral. Here, we describe the 6 major themes in the study. Themes are followed by example quotes that we chose to give you a sense of participant narratives.

Grasping onto Hope

Participants described the sense of hope and desperation in the community at the time that CCSVI came out. They described how hope enticed some patients to seek access to CCSVI interventions prior to testing.

> *There were a lot of people grasping on to hope... Desperation definitely played a part in it…A lot of people [were] willing to have the procedure [CCSVI] done prior to having North American testing done. And there was a lot of anger directed at Canadian healthcare professionals who wanted to see evidence based research.*
>
> —Participant 8

Costs of CCSVI

Participants described the disappointment that was felt in the MS community and the costs of the CCSVI research trajectory. They explained that CCSVI did not have a lasting effect, and described the procedure as a temporary fix. They explained that those who experienced a temporary sense of wellness after CCSVI procedures felt the most disappointment.

> *I think people go for [CCSVI] and probably the most disappointment [is felt by] the people who have it and six months later they're right back to where they were.*
>
> –Participant 17

Participants also described side effects endured by some patients who have had the CCSVI procedures.

> *I know the people [who] spent a fortune and nothing, and… they're much worse now than they were*. –Participant 7

Some participants were critical about the financial investment in CCSVI research. These participants explained that money that could have been put towards stem cell research was spent on CCSVI research, even though scientific evidence brought the CCSVI hypothesis into question.

> *It's just wasted money, especially when it's a disproved theory, when that money could have gone to better use to support research for the stem cell area.*
>
> –Participant 20

Some participants explained that the time spent on CCSVI research would have been better spent on other areas of research.

> *It makes me sad that it [CCSVI research] turned into such a fiasco cause…it'll [stem cell research] take longer and it'll take more proving…We wouldn't have to work so hard to prove [stem cell research] if we hadn't have shot ourselves in the foot with CCSVI first.*
>
> –Participant 14

Cautious Optimism

Despite having experienced disappointment with CCSVI research, participants still articulated hopes that stem cell research would bring a treatment for MS. This time, hopes were guarded and cautious.

> *Five years ago it [CCSVI] came out and a lot of people saw it as a cure, and so everybody jumped on that bandwagon…So I didn't want to put all my cards on that table. And I'm at sort of that point with stem cell. I'm hopeful and eager to see what happens, but I'm not ready to jump into it.*
>
> —Participant 5

Enduring Hopes

Participants explained that hopes for stem cell research, unlike those that supported CCSVI research, are based in trusted science. They explained that this is why they continue to support stem cell research.

> *I think CCSVI was anecdotal…**[stem cell research] has hard science behind it**…they've been researching it for many years in relation to different uses.*
>
> —Participant 1

Forging Onward

Participants explained that they continue to support the development of research that for MS. They explained that there are no guarantees in research, and that scientists must move forward despite setbacks to find new treatment options.

> *It was a disappointment but…I knew it wasn't a guarantee, and so I guess I went into it with open eyes; if it works it works and if it doesn't, well, let's go forward.*
>
> –Participant 6

Lessons Learned

Participants explained that we, as a society, must reflect on the CCSVI experience to learn lessons about how to do research in the future. They suggested that scientists ensure that research is safe before the public accesses it.

> *I would say that before you started treatment on the patient…you should be…sure that it's very safe to try it and the trial goes on and stop the treatment before it goes bad.*
>
> – Participant 12

They also suggested that people who communicate responsibly about the promise of new research to make sure that the community does not experience disappointment or loss of trust in research.

> *…not to jump the gun and say…"we found a new cure for MS…come and try this", and then it doesn't work…because…people get their hopes up, and then…it's just going to damage the [community's] view of [research].*
>
> —Participant 20

Conclusions

CCSVI research illustrates the costs of unrealized hopes in science. It also reveals the resilience of the MS patient community, who remain hopeful for new treatments in the wake of disappointment. The CCSVI story reminds us of challenges we must tackle in research and teaches us many valuable lessons on how to carry out research for multiple sclerosis in the future.

D.2 Patient Member Checking Summary 2

When Will Stem Cells Reach the Clinic for MS?
Patient Perspectives about Timeframes in Stem Cell Research

Thank you for participating in our research. The contribution of your perspectives has made it possible for us to conduct a series of interviews stem cell research for multiple sclerosis (MS). Below is a summary of some of our study findings. We would like to make sure that the analysis of your perspectives authentically represents your views, and we welcome your feedback and questions about our work. To share your comments or ask questions about the results, please contact:

Shelly Benjaminy
E-mail: shelly.benjaminy@ubc.ca
Phone: 604-822-0748

Please accept our sincere gratitude for taking the time to participate in this study and for sharing your perspectives with us.

Kind regards,

Ms. Shelly Benjaminy
Prof. Judy Illes
Dr. Anthony Traboulsee
Mr. Cody Lo
Dr. Andrew Schepmyer

The Study

Stem cell research has been an area of hope for multiple sclerosis (MS) since early clinical research in the 1990s. To date, there are no market approved stem cell therapies for MS and only a handful of clinical trials have been completed. The progressive nature of the disease may lead individuals with MS to wonder: *How long will it take until a stem cell therapy is available in the clinic?* We explored the perspectives of 20 MS patients like you about their views the pace of stem cell research for MS and their understanding of the process of moving research along to the clinic (a process that researchers call "translation").

Study Highlights

- Four major themes came emerged from patient interviews: optimism, receptivity, timeframes, and accelerators and barriers to translation.
    - *Optimism* – Participants expressed hopes that stem cell research would someday produce a treatment option for MS.
    - *Receptivity* – Some participants hoped that they would benefit from stem cell therapies; others believed stem cell interventions would be more appropriate for participants with more severe disease.
    - *Timeframes* – Participants expressed diverse predictions for when a stem cell therapy for MS will be widely available. Similarly, participants had diverse opinions about whether stem cell therapies will likely be available for them within their therapeutic windows.
    - *Accelerators and barriers to translation* funding/costs of the procedure, public awareness of research, competition with pharmaceuticals, ethical dilemmas, scientific hurdles, and access challenges to stem cell therapies.

The Findings

<u>Optimism</u>

Participants expressed optimism that stem cell research would someday produce a treatment option for MS. Many cited other recent advancements in the field of MS to support these views. Some participants drew examples from medical interventions that had successfully made the transition to the clinic after years of research.

> *I have great hopes that it [stem cell interventions] will be a very viable treatment for MS…there's so much research being done… oncology took a long time before they got to the transplant stage.*
>
> — Participant 13

<u>Receptivity</u>

Many participants expressed support of stem cell research and a desire to undergo stem cell interventions.

> *I know about stem cell research and where it goes for these kinds of autoimmune diseases, I absolutely believe in it and I absolutely support it… I'm quite optimistic about success for this in the future…if they [researchers] did a clinical trial I would absolutely participate.*
>
> — Participant 1

While maintaining support for stem cell research, other participants explained that they would not consider undergoing stem cell interventions at this time, because they have stable disease. They explained that their MS is being well controlled with pharmaceutical interventions and that stem cell applications might be risky. Some also explained that while they would not choose to have a stem cell intervention at the present time, they would consider it if they were to experience more progressive disease or increased disability in the future.

> *When I hear you talking about stem cell clinical trials and their relation to MS, the first thing that comes to my mind is patients who are in wheelchairs, or…have permanent disability due to their MS…I imagine that [stem cell interventions] would be most relevant and most effective and most needed…by them.*
>
> — Participant 2

Timeframes

Participants provided diverse estimates about the timeframes necessary for stem cell therapies to become widely available in MS clinics, with predictions ranging from 2 to 30 years. Some participants expressed hopes that stem cell therapies will be widely available in time to provide them with medical benefits. Others explained that by the time stem cell therapies will be available, their disease course would likely be too far progressed to benefit.

> *I would like to think that there will be stem cell therapies available for me in my lifetime… you can never really predict what course your disease is going to take. So, I like to remain hopeful that my disease will stay sort of at the course it's at and stem cell therapies will help me at some point.*
>
> — Participant 5

> *I'm 60 and a cure might not be found in my lifetime, but hopefully it's going to be found for a kid. That's the way I look at it."*
>
> — Participant 12

Many participants explained that they have trouble making informed estimates about when stem cell therapies will be available in the clinic, because they have limited knowledge about the process of moving stem cell research products into the clinic, including an understanding of different stem cell sources and the stages of clinical research and their goals. Participants expressed a desire to learn more about the research process.

> *I don't know how far along they [researchers] are with the research. I don't know what they've done or what the next steps are. I don't know what's involved.*
>
> — Participant 2

Accelerators and Barriers to Translation

Participants discussed a number of accelerators and barriers that may impact the rate at which stem cell research might produce clinically available treatment for MS. The most prominent considerations raised were: funding/costs of the procedure, public awareness of research, competition with pharmaceuticals, ethical dilemmas, scientific hurdles, and access challenges as the intervention would likely only being offered in a limited number of centres.

Funding:
I think it has to be like a priority for government funding agencies, right… so I feel that if the government decided to make MS, curing MS or treating MS, like a national strategy or something, which then increased the amount of money and increased like the focus and the energy.

— Participant 7

Public awareness of stem cell research:
I think there's a lack of knowledge… and if they [people] knew more, they'd have less fear about it [stem cell research], I think.

— Participant 8

Competition with pharmaceuticals:
I think that the first thing [barrier] would be pharmaceutical companies because it's [stem cells] not a drug so they can't produce any kind of medication so they can't make money.

— Participant 20

Ethical dilemmas:
I know there is a lot of the religious opposition to embryonic stem cells.

— Participant 9

Scientific hurdles:
It's always difficult to turn something that works in theory, or works in a lab, into…a treatment for individualized patients…part of the problem of treating MS…is it's such a different disease in everybody…the process that is needed to treat relapsing remitting [MS] is different than the process needed to treat primary progressive [MS].

— Participant 7

Access challenges:
For people, depending on where they live, that [location] will be one barrier... if you were living in Newfoundland and had to go to Ottawa for transplant, that could be quite cost prohibitive because of the length of stay in the hospital.

— Participant 13

Conclusions

Stem cell research remains a source of hope for individuals with MS. While individuals with MS maintain hopes for the development of stem cell therapies, they also remain realistic about the enduring challenges associated with its translation. The variability in participants' timeframe estimates for when stem cell treatments might reach the clinic coupled with interest to learn more about the process of research could be addressed by a responsive clinical counseling approach. We will couple these findings with data from interviews of MS physicians about to develop a strategy for clinical communications that promote informed hopes about the pace of stem cell research for MS.

D.3 Clinician Member Checking Summary

When Will Stem Cells Reach the Clinic for MS?
Clinician Perspectives about Timeframes in Stem Cell Research

Thank you for participating in our research. The contribution of your perspectives has made it possible for us to conduct a series of interviews with clinicians like you about timeframes associated with stem cell research and development for multiple sclerosis (MS). Below is a summary of some of our study findings. We would like to make sure that the analysis of your perspectives authentically represents your views, and welcome your feedback and questions about our work. To share your comments or ask questions about the results, please contact:

Shelly Benjaminy
E-mail: shelly.benjaminy@ubc.ca
Phone: 604-822-0748

Please accept our sincere gratitude for taking the time to participate in this study and for sharing your perspectives with us.

Kind regards,

Ms. Shelly Benjaminy
Prof. Judy Illes
Dr. Anthony Traboulsee
Mr. Cody Lo
Dr. Andrew Schepmyer

The Study

Stem cell research has been an area of hope for multiple sclerosis (MS) since early clinical research in the 1990s. To date, there are no market-approved stem cell therapies for MS and only a handful of clinical trials have been completed. The progressive nature of the disease may lead individuals with MS to wonder: *How long will it take until a stem cell therapy is available in the clinic?* We explored the perspectives of 15 MS clinicians about their views on the timeframes associated with the translation of stem cell research.

Executive Summary

- Four major themes emerged from the analysis: receptivity, timeframes, accelerators and barriers to translation, and clinical discourse strategies.
    - *Receptivity*: Patients are receptive to stem cell interventions and some feel a sense of urgency to access
    - *Timeframes*: Urgency motivates patients to ask questions about when stem cell interventions will be available in the clinic. Clinicians explained the challenges of responding to such patient inquiries, given the uncertainties associated with research and development in the stem cell arena.
    - *Accelerators and barriers to translation*: Clinicians articulated accelerators and barriers to the clinical implementation of stem cell interventions. These included competition with pharmaceuticals, safety, efficacy, financial considerations, personnel and facility shortages, scientific hurdles, and ethical considerations.
    - *Clinical discourse strategies*: Clinicians suggested clinical communication approaches to address patient inquiries about stem cell research and elucidate the pace of research and development. Strategies focus on two main goals: (1) promoting informed hope; and, (2) clarifying timeframes for the clinical implementation of stem cell research.

Results

<u>Receptivity</u>

Many clinicians noted that patients who are receptive to learning about stem cell research often ask about developments in the field. The majority of inquiries focus on the most recent advancements in research and the potential therapeutic benefits of stem cell interventions. Clinicians explained that their patients often express a sense of urgency to access stem cell interventions, particularly in light of the progressive nature of MS.

> *I think many of them [MS patients] feel a sense of urgency to do something about their disease… So I think that patients…know that time is brain and they want to get on board [with stem cell interventions] as fast as they can.*
>
> — Clinician 5

<u>Timeframes</u>

Clinicians explained that urgency often motivates their patients to ask questions about the pace of stem cell research, particularly with respect to their therapeutic windows. Clinicians also explained that the stem cell tourism phenomenon compels many patients to inquire about the timeframes for clinical application of stem cell interventions locally.

The problem is, is that they're [patients] fully aware that there are people around the world that are willing to inject…stem cells into them and they're actually coming wanting a kind of an honest answer as to is this technology at the point where they can trust it enough to consider having something like this done to them? Or is this a money making process? And that's really what they want. They want to know is it available right now? Should they go off and get this right now?

— Clinician 2

Clinicians expressed difficulty responding to questions from their patients given the uncertainties associated with the research and development process.

I think when I tell them [patients]…that it's [stem cell interventions] experimental and they ask me…when do you expect it to come on the market or when is it going to be kind of standard treatment? But I myself don't know the answer.

— Clinician 1

Some clinicians provided estimates for when stem cell interventions will be clinically available as standard of care therapies. Estimates ranged from 5 to 25 years. Clinicians were most optimistic about the pace for clinical application for autologous hematopoietic stem cell approaches. Some noted referring their patients to centers that provide the intervention through a special access programme following phase II clinical trials that demonstrated indexes of safety and efficacy. Clinicians indicated that additional research would promote the translation of this stem cell approach to a market-approved standard of care procedure for the treatment of MS. Clinicians provided more uncertain and distant timeframes for the clinical application of both mesenchymal and neural stem cell approaches for treating MS.

With the mesenchymal [approach]…we have to follow up with the study and see if there's…early data that suggests it's helpful. And then the restorative stuff [neural stem cell approach]…I think that we're twenty years out from…finding a process that works…But if there's strong proof of concept, it'll probably be another five years until you find something for all patients.

— Clinician 5

<u>Accelerators and Barriers to Translation</u>

Clinicians described a number of accelerators and barriers to the clinical translation of stem cell interventions for multiple sclerosis. These included competition with pharmaceuticals, safety, efficacy, financial considerations, personnel and facility shortages, scientific hurdles, and ethical considerations.

Clinicians explained that while regenerative medicine is often regarded as a curative approach, limited efficacy has been demonstrated in the MS area. While hematopoietic stem cell transplantation has been the most studied regenerative medicine approach for MS, it demonstrated potential to halt the course of MS, but will be unlikely to provide a cure.

…the evidence that has come out is it [autologous hematopoietic stem cell transplantation] seems to have an effect on reducing relapses. But it doesn't seem necessarily to stop the progress of the disease.

— Clinician 5

Clinicians expressed concern about the safety profile of stem cell interventions, indicating that research will need to explore opportunities to promote the safety of patients. They also commented on the landscape of pharmaceutical therapies that may present a reduced niche for stem cell interventions in the current market. To this end, clinicians explained that the

risk/benefit profile of stem cell interventions will need to be weighed against that of pharmaceutical therapies.

> *...hematopoietic stem cell transplant is…a promising type of treatment but there is a lot of risk to it…it involves chemotherapy…and that puts the patient at risk for infections, haemorrhage, and death even. So, with that type of risk/benefit ratio we have a lot of effective medications that are coming down the pipeline that are much less risky, and I would be more inclined to offer that to a patient as opposed to the hematopoietic stem cells.*
>
> — Clinician 11

One of the main challenges discussed was the need for more robust infrastructure, including personnel and specialized centres, to support stem cell transplantation approaches for MS. Clinicians were concerned given this investment stem cell interventions may not withstand a cost-effectiveness analysis when compared with existing less costly pharmaceuticals.

> *...you have to remember that even if something becomes available, they might make it third or fourth line [therapy]…Do you know how much it costs to get a stem cell transplant?...it's like a quarter of a million dollars to do it… so cost will become a problem.*
>
> — Clinician 5

Finally, clinicians remarked on lingering ethical considerations that arise with the use of stem cells, particularly when concerned with neural stem cell approaches that have been historically derived from fetal tissue.

<u>Clinical Discourse Strategies</u>

Given patient urgency to access an intervention within their limited therapeutic windows, clinicians suggested clinical communication approaches to address patient inquiries about stem cell research and elucidate the pace of research and development. Strategies focus on two main goals: (1) promoting informed hope; and, (2) clarifying timeframes for the clinical implementation of stem cell research.

(1) Promoting Informed Hope

Clinicians expressed that helping patients establish a sense of informed hope is key. That is, a sense of hope that is grounded in both scientific promise and acknowledges the caveats of research. Clinicians explained that it is important to ensure that patient hope is rooted in realistic expectations, rather than informed by sensationalism in the public sphere. At the same time, clinicians explained that it is important to honour patient hope despite scientific uncertainty.

> *I try not to…create false hopes. I try to be fairly honest. But on the other hand you don't want to take all hope away from individuals. Patients…cling to hope and you want to…[promote] reasonable, realistic hopes. And I think that this is one area [stem cell research] that I personally believe is…eventually going to be helpful to them. So, I don't have a problem giving them that hope.*
>
> – Clinician 2

(2) Clarifying Timeframes

In order to achieve a balance between honoring patient hope and avoiding sensationalism, clinicians suggested that clinicians engage in dialogue with patients to explore their hopes with reference to contemporary research. This strategy aims to help patients ground their hopes in current scientific realities. Clinicians articulated that it is important to acknowledge the uncertainty of research in an honest manner, even if that requires adopting a stance of knowledge-based humility. Indeed, clinicians articulated that clinicians should be upfront with their patients about the scientific uncertainty associated with stem cell research, particularly about whether stem cell therapies will be available within their therapeutic windows.

Although clinicians articulated their uncertainty about the trajectory of stem cell research for MS, they also reinforced the importance of engaging with patients about the process of research and the associated timeframes. Clinicians indicated that patients often are not familiar with the stages of clinical trials. To this end, they suggested that dialogue could explore clinical trial phases, their goals, and the timeframes historically associated with each phase of clinical research.

> *I…explain…you have to have various…studies; you do the…open label early stuff to find out if the intervention's safe at all in the human body. And then you do the phase two study, which generally is shorter and has less patients and is generally supposed to show that there might be some effect…And then they do a larger…phase three studies, where we really get a sense of if the intervention works.*
>
> – Clinician 5

Clinicians indicated that it would be beneficial to highlight the heterogeneity of stem cell sources (e.g., hematopoietic, mesenchymal, neural) used in MS research, and explain that research using different stem cell sources may be at different stages of development. Clinicians also suggested that along with general explanations about the research process and the phases of clinical research, it is important to highlight both the progress achieved in the stem cell arena and the challenges that remain. This includes discussion about the facilitators and barriers noted above and an exploration of completed and ongoing clinical trials.

> *We talk about that study [a phase I/II autologous hematopoietic clinical trial] and how it was published, how it was indicated for a very sort of small percentage of people and why and how it was helpful for that group. And then we talk about other stem cell work going on, and we usually talk about the study in Ottawa with the mesenchymal stem cell and how that works and why they would or wouldn't qualify.*
>
> – Clinician 14

Clinicians explained that it is important to help patients ground hopes not only in contemporary research efforts, but also to anchor expectations in current clinical realities. Clinicians explored strategies for informing patients about the landscape of current therapeutic options, be it pharmaceutical interventions, physical or occupational therapy, and community supports, to help manage their disease while research is underway.

> *…it's…about not taking away their hope…but to explain to them that right now the focus is more on the things that we can do something about, like managing their spasticity, managing their pain, optimizing their functioning. And maintaining their body, ready for*

> *any potential cure that may come out of stem cell, not knowing when that is going to occur, but we need to maintain their bodies as best as possible to receive anything, should it happen.*
>
> – Clinician 4

Finally, clinicians suggested that in addition to a clinical discourse approach, clinicians should direct patients to credible resources that have been reviewed by the scientific community in an effort to offset potentially misleading information about stem cell research in the public sphere.

Conclusions

Clinicians explained that patients have many questions about stem cell research and seek to understand the timeframes associated with its clinical implementation. Clinicians made predictions about the timeframes associated with the clinical implementation of stem cell research and explored diverse facilitators and barriers for its development. To address patient interest in stem cell interventions and help patients ground hopes in research efforts, clinicians suggested clinical discourse strategies that aim to promote informed hope and elucidate the pace of research and development of stem cell interventions for MS.

Appendix E Coding Frames for Analysis of News Articles

E.1 Coding Frame for News Articles with Primary Focus on Neurodegeneration

1. Diseases Discussed

a. Neurodegenerative

(e.g., Parkinson disease, MS)

b. Non-neurodegenerative diseases

(e.g., SCI, Cancer)

2. Basic Information

a. Country

b. The name of the newspaper

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

c. Enter the date of the article

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

3. Attention Structure

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

a. Newspaper section

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

b. Newspaper section number

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

c. Page number

d. Word count for the article

Number of words

e. News Format

Here we are attempting to distinguish between facts and opinion

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

4. Voices

Who/what are the main spokespeople/groups/institutions quoted?

(Can select more than one)

1. Not applicable, unknown
2. Affected individuals
3. Family members of affected
4. Friends of affected
5. Public Sector Researchers
6. Public funding agencies (e.g., NIH, CIHR)
7. Parliament/Congress
8. Ethics committees
9. National patent offices
10. Judicial, legal voice
11. The Public, public opinion (e.g., surveys)
12. The media, published opinion
13. Celebrity (sports, film TV)
14. Scientists in private laboratories
15. Biotechnology Company/Spokesperson
16. CEO or upper management

17. Venture Capital
18. Private Investors
19. Stock Exchange
20. Political parties
21. Religious organizations
22. Patient Groups/Lobbies
23. Professional organizations (medical, legal etc.)
24. Developing countries
25. European Union
26. European Parliament
27. United Nations Organizations
28. Other International Organizations
29. Clinicians
30. Other

5. Human Interest Story

a. Does this article contain a human interest story?

1. Yes
2. No

b. If human interest, what is the main perspective? (choose one)

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

6. Dominant Frame (choose one)

1. Social progress
2. Economic development
3. Morality/ethics
4. Scientific uncertainty
5. Pandora's box/frankenstein's monster
6. Public accountability
7. Middle way/alternative path
8. Conflict/strategy
9. Descriptive
10. Human interest story

7. Tone

a. What is the tone of stem cell research representation in the article?

1. Positive
2. Neutral
3. Negative

b. What is the tone of *projections for the future* of stem cell research?

1. Optimistic
2. Neutral
3. Pessimistic
4. Not mentioned

8. Controversy

Legal issues are controversy

a. Is the article framed as a controversy?

1. Yes
2. No

b. If controversy, how was it presented?

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

9. Funding Sources

Are funding sources discussed?

1. Yes
2. No

10. Conflict of Interest

Are conflicts of interest discussed?

1. Yes
2. No

11. Methods

a. Does the article clearly state whether the stem cell intervention is research or treatment?

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

b. Are sample sizes of research or clinical trial stated?

1. Not applicable
2. Yes
3. No

c. Did the article indicate phase of clinical trial?

1. Not applicable
2. No
3. I
4. I/II
5. II
6. II/III
7. III

d. For clinical trials, did the article explain the immediate goal of the research?
Leave blank if no mention of clinical trials
1. No
2. Yes (safety)
3. Yes (efficacy)
4. Yes (safety and efficacy)

12. Risk/Benefit (for outcomes of research)

a. Number of benefits

b. Number of risks

c. What are the benefits described?

d. What are the risks described?

13. Timeframe Projection

a. Does the article make timeframe projections for the application of stem cell intervention? (ONLY regarding Neurodegenerative diseases)
1. Yes
2. No
3. Clinical trial has begun

*If yes, then continue with b, c, d and e
*If clinical trial has begun, continue with c,e

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

c. If applicable, state year for human clinical implementation

d. If vague time frame projection, state time frame for commencement of human clinical trial

1. Imminently (fast approaching, immediately)
2. Vague soon (soon, in the near future, within a few years, on the horizon)
3. Vague far
4. Never

e. If vague time frame projection, state time frame for commencement of human clinical implementation

1. Immediately
2. Vague soon
3. Vague far
4. Never

f. If time frame projection is made, who made the time frame projection?

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

14. Public Health Claims

Does the article make public health claims about stem cell interventions?
E.g., decreasing burden of disease, treating of multiple diseases
Claim must put into context of why disease impacts the health of overall society
1. Yes
2. No

15. Regulatory Hurdles

Are regulatory hurdles discussed?
1. Yes→ please specify
2. No

16. Availability Abroad

a. Is availability of stem cell interventions abroad described?
1. Yes
2. No
*If yes, continue with the rest of the questions

b. If availability abroad is described, in what form?
1. Clinical trials
2. Treatment
3. Conflation (e.g., sometimes as research and sometimes as treatment)

c. Does the article discuss evidence informing stem cell intervention abroad?
1. No
2. Yes → in vitro studies
3. Yes → animal studies
4. Yes → clinical trials
5. Yes → anecdotal evidence
6. Yes → "clinical" experience

d. Does the article discuss regulatory approvals of stem cell intervention abroad?
1. No
2. Yes → regulatory approval
3. Yes → no regulatory approval

e. What is the tone of the article about stem cell interventions abroad?
1. Supportive
2. Condemnatory
3. Ambivalent (not sure, confused)
4. Neutral

17. Urgency

Does the articles make any statements regarding urgency for application of stem cell interventions?
1. Yes
2. No

E.2 Coding Frame for News Articles with Secondary Focus on Neurodegeneration

1. Diseases Discussed

a. Neurodegenerative diseases
(e.g., Parkinson disease MS)

b. Non-neurodegenerative diseases
(e.g., SCI, Cancer)

2. Basic Information

a. Country

b. The Name of the newspaper
(e.g., Globe and Mail, National Post, Washington Post, The Independent, etc.)

c. Enter the date of the article
(Day-Month-Year e.g., 17-July-2001)

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

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

b. Newspaper section number
(e.g., A, H, F)

c. Page number

d. Word count for the article
Number of words

e. News format
Here we are attempting to distinguish between facts and opinion
1. Article with latest news
2. Investigation, reportage, background
3. Interview (mainly)
4. Column, commentary by regular columnist
5. Editorial (paper's editor)
6. Commentary from other people (e.g., politicians, religious leaders, special interest groups)
7. Letters to the editor

8. Review of books, films etc.
9. Other
10. European Parliament
11. United Nations Organizations
12. Other International Organizations
13. Clinicians
14. Other

4. Tone

What is the tone of *projections for the future* of stem cell research?

1. Optimistic
2. Neutral
3. Pessimistic
4. Not mentioned

5. Time Frame Projection

a. Does the article make time frame projections for the application of stem cell intervention? (ONLY about neurodegenerative diseases)
1. Yes
2. No
3. Clinical trial has begun

*If yes, then continue with b, c, d and e
*If clinical trial has begun, continue with c,e

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

c. If applicable, state year for human clinical implementation

d. If vague time frame projection, state time frame for commencement of human clinical trial

1. Imminently (fast approaching, immediately)
2. Vague soon (soon, in the near future, within a few years, on the horizon)
3. Vague far
4. Never

e. If vague time frame projection, state time frame for commencement of human clinical implementation

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12. The media, published opinion
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15. Biotechnology Company/Spokesperson
16. CEO or upper management
17. Venture Capital
18. Private Investors
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6. Public Health Claims

Does the article make public health claims about stem cell interventions?
E.g., decreasing burden of disease, treating of multiple diseases
Claim must put into context of why disease impacts the health of overall society
1. Yes
2. No

7. Urgency

Does the articles make any statements regarding urgency for application of stem cell interventions?
1. Yes
2. No