

UNDERSTANDING PARTICIPATION OF RACIAL AND ETHNIC GROUPS IN
MULTIPLE SCLEROSIS CLINICAL TRIALS

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ABSTRACT

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By Angela Fuller

Multiple sclerosis (MS) patients from different racial and ethnic groups are equally likely to participate in clinical trials despite the significant risk that experimental drugs pose to their health. This is in contrast to existing literature which points to minority group distrust of medical research as a reason for low clinical trial participation rates. Given this disparity, the purpose of this thesis is to understand the complexities surrounding MS clinical trial participation. A mixed methods approach was utilized, including: 1) review of archival data for racial and ethnic group clinical trial participation rates; 2) an electronic survey to capture MS patient exposure to and knowledge of clinical trials; and 3) semi-structured interviews to elucidate perceptions of clinical trial participation. Despite the predicted influence of distrust on clinical trial participation rates, this study identified no differences in motivations to participate among racial or ethnic groups. Focusing only on minority distrust as a reason for low clinical trial participation may overlook true patient motivations which are mediated, not by arbitrary categories of race and ethnicity, but by balancing the complicated interactions of distrust, risk perception and risk acceptance, with the perceived benefits of clinical trial participation. These motivations are situated within the context of structural barriers that can prevent clinical trial participation, such as health care access and clinician bias.

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Chapter 1 - Introduction

An Introduction to the Unknown

I was at home with my legs paralyzed. That's how bad it got. I couldn't even move these legs. It got really, really bad and I didn't even know if I was having a flare up or not. I was just accepting my condition. And so, I mean, I would say, it's just sheer survival. I think we all have it, whether you're Mexican, Black or whatever race you're in. That might be the common answer. People want to survive. That's what motivated me. It's just plain survival. I was willing to risk my life even if it was to kill me because I really felt like I didn't have anything to live for anymore. [Isabelle Carbajal]

This sentiment was shared with me by one of my clinical trial patients, Isabelle,¹ during our semi-structured interview for this project. Even though I had known her for four years as a participant in a multiple sclerosis (MS) clinical trial, it was still a surprise to hear the dire circumstances she found herself in before she decided to enter the clinical trial she is still participating in today. Because I was working as a clinical research coordinator (CRC) for a San Francisco Bay Area medical center (referred to throughout this document as Bay Area Medical Center or BAMC),² I was able to get to know Isabelle, as well as all the other MS patients who were participating in various MS clinical trials at BAMC. Many of the other MS patients had also been participating in their respective clinical trials for at least four years, and some of the newest patients I had already known for at least a year and a half. What always struck me about these patients was the courage and strength it took to not only face a chronic, debilitating, neurologic

¹ All names have been changed to protect the identities of the study participants.

² Name of medical center has been changed to further protect the identities of the study participants and medical center staff.

disease, but to also jump head first into a clinical trial in which there were so many unknowns. As she candidly explained, Isabelle was willing to participate in a clinical trial, even if it was going to kill her. “I felt like I was almost using [BAMC] to end things for me if I wasn’t going to get any better. I was willing to just give my life for that” (Isabelle Carbajal).

Clinical Trials 101

MS is a complex disease with unknown etiology, equivocal incidence and prevalence rates, unpredictable symptoms and symptom severity, and mildly effective treatments. There is currently no cure for MS. Given all of these unknowns, what motivates patients to participate in clinical trials? On the surface, clinical trials would not seem to provide the bastion of stability MS patients might pursue. Clinical trials are prospective biomedical or behavioral human research studies designed to answer questions about a proposed intervention, medication or therapy. The central focus is to understand whether a new medication is safe and effective. If data from a clinical trial can show that a medication is both safe and effective as it progresses through the requisite three phases of clinical trials, not including the fourth after-market phase (see Table 1), then the US Food and Drug Administration (FDA), after significant review, can approve the medication for use in a larger population (National Institutes of Health 2014a). Conducting a clinical trial is not possible until initial review and approval by an Institutional Review Board (IRB) which is tasked with protection of human subjects in research per Title 21 Code of Federal Regulations (CFR) Part

Table 1. Four Phases of Clinical Trials

Phase	Description	MS Example
Phase 1	First-in-human trials that are usually conducted with a small group (20-80) of healthy volunteers and emphasize safety. The goal is to find out what the drug's most frequent and serious adverse events are and, often, how the drug is metabolized and excreted.	MS Phase 1 trials are usually done with MS patients because the medications are considered to harmful to give healthy volunteers. Because a drug's side effects could be subtle, long term, or happen in a few people, Phase 1 trials are not expected to identify all side effects.
Phase 2	Trials with a larger group of people (100-300) to see if the drug is effective and to further evaluate its safety.	MS Phase 2 trials can be conducted with one group of patients receiving the study drug and another group of patients receiving an inactive substance, or placebo, for comparison. The larger group of people allows for the identification of more side effects.
Phase 3	Final confirmation trials conducted with very large groups of people (1,000-3,000) to gather more information about safety and efficacy. Drug safety profile is finalized in preparation for FDA approval.	MS Phase 3 trials are often done with one group of patients receiving the study drug and another group of patients receiving an FDA-approved platform MS therapy to test superiority to existing MS treatments.
New Drug Application and FDA approval		
Phase 4	Studies conducted after FDA has approved the drug for marketing. These studies gather additional information and a drug's safety, efficacy, or optimal use for the drug's active medical use.	See Chapter 6, Semi-Structured Interviews, Risk, Risk of FDA-Approved MS Medications (page 146) for a discussion of two MS medications that were temporarily removed from the market for safety issues discovered after FDA approval.

Adapted from: National Institutes of Health 2014a.

56 (Food and Drug Administration 2014). This body helps determine whether the benefits of the proposed trial outweigh the risks, and that any potential risks are appropriately mitigated and disclosed.

When assessing the legitimacy of clinical trial data, the gold standard according to the evidence-based medicine movement is the randomized controlled trial. Randomized controlled trials are often employed during Phase 2 and Phase 3 trials, when the efficacy of a drug is tested through comparison to a placebo, an inactive product that looks indistinguishable from the study drug but without its treatment value, or other drug comparator. However, in MS clinical trials, the use of placebos is somewhat limited because of the ethical and safety concerns of MS patients going untreated for extended periods of time. Sometimes MS trials are designed to have a short window of randomization to the study drug or placebo, after which all trial participants, even participants who were in the placebo group, are re-randomized to different doses of the study drug for the remainder of the trial. Randomization ensures that participants are assigned to a treatment group by chance rather than choice, which helps eliminate any treatment bias. Blinding of the treatment assignment prevents the research staff or trial participants from knowing which treatment they have been assigned to so they cannot influence the results. In a single-blind study, only the trial participant lacks knowledge of his or her treatment assignment; in a double-blind study, the trial participant and research staff, including the investigators,

lack knowledge of patient treatment assignments (National Institutes of Health 2014b).

Despite the potential risks of an experimental drug and the unknowns inherent in clinical trial design, the drive for patients to participate in clinical trials, at least from a CRC perspective, is strong. In addition to working on MS clinical trials, I have also had the opportunity to work on clinical trials for stroke, Parkinson's disease, and Alzheimer's disease. For our stroke trial, which was a Phase I clinical trial requiring stereotactic implantation³ of adult stem cells into the brain, I was contacted by hundreds of patients from across the US and abroad for the chance to qualify and participate. Because of the stringent inclusion criteria, a high percentage of patients were ineligible, and much time was spent delivering this news and consoling sobbing patients. For the Parkinson's disease trial, patients were required to undergo stereotactic implantation of a gene therapy product into the area of the brain thought to cause the disease. Because this was a Phase II efficacy trial, a control group was required for comparison; thus, half of patients participating in the trial received the actual surgery, while the other half received a "sham surgery"⁴ and neither patient group could tell which they had received. Again, many patients were interested but few qualified.

The interest in an Alzheimer's disease trial was similar since there are currently

³ A metal frame is secured to the patient's skull at four points to allow for trajectory planning of stem cell implementation into the brain.

⁴ A sham surgery is part of an ethically contentious trial design that provides a truly blinded control group in a surgical clinical trial. In this case, the sham surgery consisted of completely shaving the patient's head, applying the metal frame to the patient's skull, administering anesthesia, drilling a partial burr hole into the skull, sitting in the operating room for at least 4 hours to simulate the length of time an actual surgery would take, screwing a titanium plate over the partial burr hole, and stitching up the scalp.

no treatments for the disease. Many family members were desperate to try anything to help their loved one who was slowly losing touch with reality.

I was in awe at the courage it took for all of these patients to participate in these clinical trials. For the MS patients I worked with, participation in their respective clinical trials was often a calculated decision based on considerations of the currently available FDA approved MS medications, the experimental medications being offered in clinical trials, and the unpredictability of their disease. I wanted to understand the motivations of these clinical trial participants to see if there were commonalities that existed among trial participants that enticed them to seek out clinical trials. I often wondered, if I were in the same position, would I make the same choice?

Clinical Research Coordinator (CRC) or Ethnographer?

As a CRC, I was officially responsible for coordinating the conduct of clinical drug trials for a variety of neurologic conditions, including MS, but it is through my unofficial role as mediator between doctor and patient, liaison between drug company and patient, disability claim consultant, pharmacy aid, patient counselor, family counselor, and friend, that I became privy to the nuanced experience of the MS patient. For the MS patients I had the privilege of getting to know, I became their personal gateway to the world of medical research. Together, we navigated the rigorous protocol requirements of participating in clinical research, made more difficult by the complexities inherent in managing the unpredictable nature of their medical condition. Many of these

patients came to trust me with their most difficult and complex concerns about what it is like to be a person diagnosed with a chronic, disabling disease like MS. I came to learn intimately how much participating in clinical trials meant to these patients, how much it changed their lives, and how it provided them with the agency to take control of an unpredictable disease in an ever-changing landscape of MS medications and therapies.

Thus, when first thinking about conducting this project, I thought that my position as a CRC with such intimate knowledge of the clinical trial patients and being embedded in the BAMC MS clinic every day, provided me with entry to a world few can access. Being a CRC is like being at the central hub of the entire clinical trial enterprise, where responsibilities include dealing with a wide array of social actors including pharmaceutical companies, contract research organizations, IRBs, hospital administrators, research personnel (including neurologists, neuroradiologists, neuro-ophthalmologists, psychiatrists, pharmacists, physical and occupational therapists, nurses, medical assistants, laboratory technicians, etc.), patients, and patients' families. I was part of the team that helped identify potential clinical trial patients and worked to retain those patients in our trials for the length of the study. My experience as a CRC provided an insider's perspective on how clinical trials are conducted and provide access to the MS patients who chose to participate in a clinical trial. As an ethnographer, the benefits of this kind of access could be extremely valuable in developing a nuanced understanding of clinical research at BAMC.

However, because of my role as a CRC, I was afraid that being part of the clinical research team in charge of conducting the clinical trials would hinder my ability to find patients willing to speak openly with me about their experience participating in a clinical trial. There was a possibility that my role as a researcher would place me in a position of power relative to the trial participants, and that it would be a significant barrier to discovering true motivations for participating in clinical trials. Participants might have felt coerced to participate because I was part of the research team, thus affecting “voluntary consent.” Fortunately, I felt that the potential power differential between myself and the patient was minimized as I was considered one of the front line staff instead of a higher level researcher. I was the one helping the MS patient navigate the complexities of the clinical trial on a daily basis and the first one they called with any questions they had, big or small. In fact, all of them had access to my cell phone number in case anything came up at any time.

Although it is unclear whether my role as a researcher affected the responses of the MS patients, I did my best to make each patient feel as comfortable as possible by ensuring confidentiality and assurance that their responses would not affect their normal medical or research care. Offering to do the interviews away from BAMC was an important part of this attempt to separate my formal relationship with patients when interacting inside BAMC from the informal relationship I hoped to foster away from BAMC. Removing myself from this environment was an attempt to alleviate any notion that a patient could not

be honest with me. Interestingly, I think that some patients enjoyed my dual role as researcher and ethnographer. They were all familiar and comfortable with my role as a researcher, but when I was an ethnographer, it allowed the patients to step back and consider what trial participation meant to them on a personal level. Many admitted during the interviews that they had never thought about some of the questions I was asking and that it was nice to stop and reflect. For myself, my role as a researcher was enhanced by my role as an ethnographer. As a researcher, one can get bogged down with regulations and data and paperwork. Conducting this project and connecting with my MS clinical trial patients was an extremely enlightening, unique, and personally rewarding experience.

Objectives

Given my professional and personal connection to MS clinical trial patients at BAMC, I set out to explore the reasons MS patients chose to participate in clinical trials. When I started this research, there were no studies investigating MS patients' reasons for participating in research. However, there was an abundance of studies looking at why other types of patients (e.g., cancer, cardiac, HIV/AIDS, asthma, diabetes and pain disorder) participated in clinical research. Unexpectedly, most of these studies revolved around understanding underrepresentation of racial and ethnic minorities in clinical trials. Results indicated that the biggest contributing factor was systematically identified as distrust of research. I wondered if this was the case for MS patients. Thinking about Isabelle who self identifies as a Latina, it was highly unlikely that she had

distrust of research if she was willing to risk her life over her participation in a clinical trial. Perhaps her desperation to find some kind of treatment to alleviate or halt the progression of MS outweighed her fear and distrust. The biggest factor for her seemed to be a medical need that outweighed any potential risks presented by the clinical trial and perhaps even the risk of not participating in a clinical trial. If her race and ethnicity and distrust of research were not factors in her clinical trial participation, what helped her justify doing something so risky to help meet her medical need?

This thesis set out to answer the following questions regarding participation in MS clinical trials:

1. Is there underrepresentation of racial and ethnic minority groups in MS clinical trials? If so, why?
2. In what ways do preconceptions about medical research, altruistic motivations, and daily experience with disease contribute to MS patients' participation in clinical trials?
3. What are the salient MS patient attitudes towards clinical trials?

If underrepresentation is a factor in MS clinical trials, it would be detrimental to developing a comprehensive understanding of MS treatments that respond to the disease course variety seen in different individuals. It is important to note that underrepresentation in this thesis will focus on minority racial and ethnic groups and not other underrepresented groups, such as older adults, rural populations, and those of low socioeconomic status. Underrepresentation of

racial and ethnic groups leads to clinical trial results that are not generalizable to the public. For trial results to be meaningful to the general public, clinical research participants should approximate the variety of individuals that exist in a given population. Otherwise, a trial conducted with mostly Caucasian, middle-aged men would have results that may not be applicable to other populations, such as women, younger or older adults, and non-Caucasian racial and ethnic groups. MS is already a difficult disease to study given the unpredictability of natural history and patient prognosis. Underrepresentation of racial and minority groups in MS clinical trials would only make the search for an effective treatment more elusive.

Independent of finding underrepresentation of racial and ethnic minorities in MS trials, it is also important to understand whether there are additional factors that determine whether an MS patient decides to participate in a clinical trial. Distrust is often cited as the main barrier to minority group participation in clinical trials for cancer, cardiac, HIV/AIDS, asthma, diabetes and pain disorder. Given that MS patients of different racial and ethnic groups may be equally likely to participate in clinical trials, distrust may not be the most applicable reason for a finding of low participation rates in clinical trials for MS. Instead, other factors like preconceptions about medical research, altruistic motivations, and daily experience with disease may contribute to MS patients' participation in clinical trials. This thesis attempts to elucidate these other factors to determine whether distrust has the biggest influence on participation rates, or some other factor.

Also, illuminating salient MS patient attitudes towards clinical trials will aid in identifying any unknown factors that may contribute to participation rates.

Thus far, much of the anthropological research on minority group underrepresentation in medical research focuses on international ethical concerns, improper informed consent, and misunderstandings of the Western model of medicine and research, which are often incompatible with non-Western environments (Adams, et al. 2007; Petryna 2005; Petryna 2007; Van der Geest, et al. 1996). In the US, there is a great opportunity for anthropologists to contribute to the medical community's understanding of underrepresentation of minority groups in clinical trials. Because anthropologists utilize methods such as participant observation, patient narratives, and analysis of political economic structures, contributions to safer clinical trial design, more culturally competent care, and increased protection and participation of research participants can be made (Azevedo and Payne 2006; Barnett 1985). Ethnographic research methods can be used in this case to elucidate local understandings of clinical research for MS patients and to evaluate patient motivations for participating in clinical trials.

Chapter 2 – The Discourse of Multiple Sclerosis

Multiple Sclerosis as Medical Diagnosis

Multiple Sclerosis (MS) is an autoimmune, inflammatory disease in which the body's own immune cells attack the nerves in the central nervous system (CNS), which is made up of the brain, spinal cord and optic nerve (Vollmer 2007). Inflammation, which is triggered by the immune response, causes damage to myelin, the protective covering surrounding nerve cells. Myelin is like the rubber insulation on a wire: if the rubber on the wire is missing or damaged, electrical conduction is slowed down or obstructed. The same occurs with a patient diagnosed with MS: if the myelin is missing or damaged due to the body's own immune response, nerve impulses to various parts of the body are slowed down or stopped. In 1868, the French neurologist, Jean Martin Charcot, first clarified the clinical and pathological features of MS as being distinct from other neurologic diseases. He named the disease "sclérose en plaques" which described the damage (lesions or plaques) in the brain, spinal cord, and optic nerves characteristic of MS. The name multiple sclerosis describes the "sclerosed" or hardened plaques of tissue lesions located at "multiple" sites throughout the CNS (Holland, et al. 2007). Symptoms for MS patients are extremely variable because they depend on the location and severity of each inflammation attack. Symptoms can include, but are not limited to, numbness, pain, tingling, loss of balance, difficulty walking, vision loss, bowel and bladder

incontinence, decreased attention span and memory loss, slurred speech, fatigue, and depression.

There is no one laboratory test or physical exam finding that can determine whether or not an individual has MS. In order to make a diagnosis, a physician must 1) find evidence of damage or lesions in at least two separate locations in the CNS, 2) find evidence that the damage or lesions occurred at least one month apart, and 3) rule out all other possible diagnoses. These long-established criteria are based on the principle of finding CNS lesions disseminated in both space and time; however, there have been several revisions to the criteria which account for advancements in medical technology and diagnostic thresholds (Milo and Miller 2014). The Schumacher and Poser criteria allow diagnosis with demonstration of two separate MS attacks, or relapses, which involve at least two different areas of the CNS. The 2001 McDonald Criteria, and the 2005 and 2010 Revised McDonald Criteria, allowed for earlier diagnosis and to account for evidence provided to physicians by magnetic resonance imaging (MRI) of the brain and spinal cord.

The natural history of MS is widely variable and largely unpredictable on an individual basis, thus rendering any predication for patient outcome or prognosis tenuous at best. The disease can lie dormant for any brief or extended amount of time with periodic relapses of MS symptoms. Relapses are also called attacks or flares. Alternately, the disease can present as progressive worsening over time without any recognizable relapses or attacks of MS symptoms. With

such variability, physicians have found it helpful to classify the disease under four distinct categories to assist with medical care, rehabilitation, and treatment options. Relapsing-remitting MS is characterized as having unpredictable attacks followed by periods of symptom remissions lasting months or even years. Secondary-progressive MS is characterized as the stage of continuous and progressive neurologic decline which follows the initial stage of relapsing-remitting MS; thus the term “secondary” is used to denote the progressive phase as secondary to the initial relapsing phase. Primary-progressive MS is characterized by continuous and progressive neurologic decline from the outset of the disease without any identifiable relapses or attacks; thus, the term “primary” is used to denote the progressive phase as being the first phase of the disease. Finally, progressive-relapsing MS is characterized by a continuous and progressive neurologic decline from the outset but with relapses and attacks in addition to slow progression (Vollmer 2007). Figure 1 shows the four different disease patterns comparing increasing disability over time.

Although these four categories help with identifying the nature and pattern of MS symptoms, a large proportion, approximately 85%, of MS patients initially present with the relapsing-remitting MS form of the disease. A relapse, particularly for use in clinical trials, has been defined by Schumacher et al. (1965) as: a focal disturbance of function affecting a white matter⁵ tract; two or more

⁵ White matter is the part of the CNS that contains the myelinated portion of nerve cells. It appears white in color because of the myelin coating which assists in conducting electronic nerve impulses. Grey matter is part of the CNS that contains the cell bodies of nerve cells.

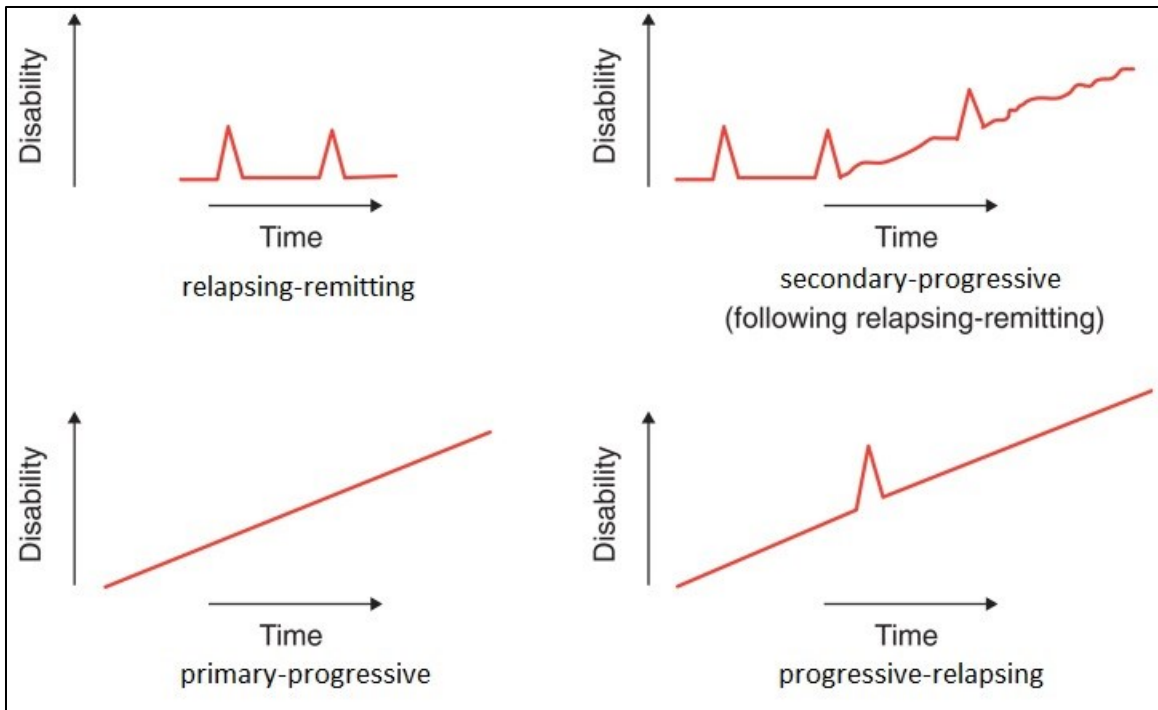


Figure 1. Four Clinical Courses of Multiple Sclerosis

episodes each lasting more than 24 hours that do not have an alternative explanation; and is preceded by more than 30 days of clinical stability. The disturbance of function can include one or more of the following symptoms whether it is new or a worsening from previous levels: numbness, pain, tingling, loss of balance, difficulty walking, vision loss, bowel and bladder incontinence, decreased attention span and memory loss, slurred speech, fatigue, and depression. Typically the MS symptoms which constitute the relapse at any given time can last for a week to a month or more (Vollmer 2007). MS relapses are often treated with a multi-day course of oral or intravenous steroids to speed up the recovery time of the patient. After ten years, about half the people diagnosed with RRMS will gradually develop permanent disability, where

relapses may still occur, but periods in between are characterized by a continued disease progression phase (Pucci, et al. 2011).

Although the treatment of MS has come a long way from the death sentence it used to carry only 20 years ago, there is still much to learn about what causes it, who gets it, how patients and providers can manage it better, or whether finding a cure is possible. Current therapies focus on how to reduce the rate of patient relapses, which slow the progression of permanent neurologic deficiencies, but are not a cure. Annual relapse rate has been used as an outcome in both clinical care and medical research (Coyle and Johnson 2007) and relapse rates currently average 1.1 per year early in the disease course (Vollmer 2007). Despite the overall outlook of disease progression, on an individual level, MS follows unpredictable patterns of disease accumulation and there is still too much variability to predict an individual's disease course (Vollmer 2007).

Multiple Sclerosis as Identity

The manifestation of MS is extremely variable due to the unpredictability of when a patient can expect a relapse and how long and how severe a particular relapse can be. During relapses, in addition to physical changes, cognitive changes can occur and MS patients are often at higher risk for depression. The anticipation and experience of relapses can create feelings of grief, anxiety, anger, and guilt which make it difficult to accept the totality of the diagnosis (Kalb 2007). Upon first diagnosis, the patient, patient's family, and friends may utilize

themes of denial in order to show support that the patient is actually well, that other people with MS are far worse than this, that the doctor made a mistake, or that the patient will be able to beat this. Upon experiencing subsequent relapses, the patient is forced to acknowledge the beginning of his or her life with a chronic illness. This requires a change in self-image, although patients, partners, children, and family may continue to blame the manifestation of the disease on not being strong enough to fight it (Kalb 2007).

Much of the literature on the adjustment period for an MS patient focuses on the transition of self and identity from pre-diagnosis to diagnosis and beyond. The resolution or redefinition of identity occurs slowly over time but is often psychological and spiritual rather than physical. The patient must focus on being successful at fully adapting to his or her diagnosis so that his or her rehabilitation potential and quality of life can be fulfilled (Irvine, et al. 2009). Although fatigue and depression are associated with MS, the correlation of neurologic impairment to fatigue severity disappears when looking at the concept of helplessness (Van der Werf, et al. 2003). Thus, fatigue severity, which is associated with depression, is not directly related to MS severity, but is affected by feelings of helplessness as patients attempt to navigate the unpredictability of MS. Because a patient's understanding and ability to cope with his or her disease can have a direct effect on the physical manifestation of that disease, community groups, even for pediatric MS populations, help foster motivation and self-competency for improved quality of life. Group activities are often designed to help redefine the

assumptions of disability in order to nurture confidence (Block and Rodriguez 2008).

The preservation of self and identity in persons with a chronic illness becomes even more complex with MS because many of the neurologic symptoms of MS, such as fatigue, loss of vision, or numbness, are invisible to others. Unlike those with obvious disabilities, people with MS can often choose whether or not to keep their disabilities hidden. This can be an empowering option, as the possibility of controlling their illness identity is well within reach. However, this often creates a dilemma for the MS patient who may attempt to keep his or her disability hidden from others, at the risk of others assuming that an inability to perform job duties is due to laziness or poor work ethic rather than accumulating physical disabilities. On the other hand, the MS patient may decide to reveal his or her disability, at the risk of assuming the socially created stigma of what it means to be chronically ill or disabled (Fitzgerald and Paterson 1995).

Acceptance of the diagnosis of MS is a long and difficult process that involves redefinition of self, building confidence in identifying with a chronic illness, and understanding how to relate to a world that does not immediately comprehend the needs or accommodations a person with MS may require. Much of the focus for those with MS is on how the individual can cope with the diagnosis and rise above the difficulty in transitioning from a healthy individual to one with chronic illness. The transition can be made psychologically or spiritually. Support groups and counseling available to those with MS offer an

empowering way for each individual to control his or her own disease through self-education, self-advocacy, and self-determination. Mastery and personal control over the unpredictable course of MS involve, “ordering and sequencing the myriad range of phenomena in everyday life which may or may not be perceived as related to health and illness” (Robinson 1990: 1185). It is perhaps this illusion of control that draws MS patients towards clinical trials as a way to exert power and deny the feeling of powerlessness.

An Epidemiological Story

MS is considered the leading cause of neurologic disability in young adults. Onset of the disease typically occurs between the ages of 20 to 50, with 30 the mean age of onset. However, the disease can develop in childhood and after age 60. MS is 2.5 times more common in women than in men (Multiple Sclerosis International Federation 2013; Noonan, et al. 2002). In 2008, the median global prevalence of MS was 30 per 100,000 persons (World Health Organization and Multiple Sclerosis International Federation 2008). By 2013, the median global prevalence of MS increased to 33 per 100,000 persons (Multiple Sclerosis International Federation 2013). It is difficult to ascertain whether this increase was due to a true increase in the number of people who have MS globally, or if it was due to better diagnosis and reporting. While it is clear that MS can be found in all regions of the world, MS prevalence has great variability across the globe. North American, European, East Asian, and Sub-Saharan African prevalence is 140, 108, 2.2, and 2.1 per 100,000 persons, respectively. It

is important to note, however, that these numbers only tell part of the epidemiological story, since MS prevalence also has variability within a particular region. For example in Europe, the highest prevalence is in Sweden which reports 189 per 100,000 persons while the lowest prevalence is in Albania which reports only 22 per 100,000 persons (Multiple Sclerosis International Federation 2013).

Additional indicators of potential MS treatment progress and resource availability may mask continued disparities between countries. From the same period of 2008 to 2013, there was a 30% increase in the number of neurologists in the world. A majority of these were attributed to increases in reporting in the Americas and the West Pacific regions, in addition to a proportionally higher increase in low-income countries than middle- and high-income countries. The increase in the global number of neurologists from 1.01 to 1.32 per 100,000 seems like a positive improvement for patients who did not previously have access to a neurologist. However, the comparison of neurologists between high-income countries and low-income countries reveal the chronic inequalities that remain for patients seeking specialized neurological medical care. High-income countries report 3.6 neurologists per 100,000 while low-income countries report only 0.03 per 100,000 persons, which is approximately 100 times fewer neurologists per person than high-income countries (Multiple Sclerosis International Federation 2013).

Similarly, the number of MRI machines available is indicative of a region's ability to diagnose MS earlier using the most recent McDonald Criteria. Although the number of MRI machines has doubled in the same five year period, high-income countries report 1.474 MRI machines per 100,000 persons while low-income countries report 0.012 MRI machines per 100,000 persons. Because low-income countries do not have the same access to MRI machines as high-income countries, low-income countries were more likely to use older diagnostic criteria to diagnosis MS since the older criteria do not rely on the availability of MRI. Thus diagnosis rates in these countries may not be consistent with the methods used in high-income countries. The availability of disease-modifying therapies which are fully or partially funded by a country's government also follow the pattern of high medication availability in high-income countries, to no availability in low-income countries (Multiple Sclerosis International Federation 2013). When looking at other pieces of the story, such as access to neurologists, clinical technology like MRI machines, and MS treatments, global inequalities are revealed.

In the US, recent estimates of MS prevalence by race and ethnicity suggest a higher prevalence among Caucasian men and women as compared with African Americans and all other racial and ethnic categories. The increased prevalence in women versus men is consistent among all racial and ethnic groups (Noonan, et al. 2002; Noonan, et al. 2010). Table 2 presents the estimated prevalence rates of MS in the US by race and ethnicity. Caucasians

have about double the prevalence risk compared with African Americans and all other races and ethnicities. However, when separating out the individual prevalence risk by sex, the totals hide the increased risk burden carried by women versus men by providing only an average of MS risk. For example, the total prevalence risk for Caucasians is 96 ± 5 persons per 100,000. When looking at the separate risk for men and women, the risk for men is significantly lower at 54 ± 4 persons while the risk for women is significantly higher at 137 ± 8 persons per 100,000. The totals average and mask the actual risk by gender.

Table 2. Estimated Prevalence Rates of MS in the United States by Race and Ethnicity

Race/Ethnicity	Men	Women	Total
Caucasian	$54 \pm 4^*$	137 ± 8	96 ± 5
African American	25 ± 8	68 ± 15	48 ± 9
All other races and ethnicities	19 ± 10	67 ± 19	43 ± 11
*Per 100,000 persons Adapted from: Noonan, et al. 2010.			

In addition to the increased MS risk among women, there is also a suggestion of increasing MS risk among non-Caucasian populations. In a large study of US Veterans, it appears that MS risk has changed in the US over a single generation, and although the risk for developing MS among Caucasian women has increased in comparison to Caucasian men, all women regardless of race and ethnicity now have a significantly higher risk of MS than Caucasian males (Wallin, et al. 2004). These data point to other causes of MS susceptibility

besides race and ethnicity, such a migration history and environmental risk. In addition, Langer-Gould (2013) found that the incidence of MS was actually higher in African Americans, and lower in Latinos and Asians than Caucasians. African American women have a higher risk of MS, while African American men had the same risk compared to Caucasians. These studies challenge the assertion that non-Caucasian groups have a lower risk of MS than Caucasians, and that there may be significant and rapid effects on MS prevalence which have not been noted previously. At the very least, these studies suggest that race and ethnicity and geographic location may have a decreasing influence on MS prevalence, while a yet unknown environmental factor may play an increasing role in MS prevalence.

In addition to different MS prevalence rates in different racial and ethnic groups, there are physical differences in the manifestation of the disease between racial and ethnic groups. Studies have identified what is called a “Western type” of MS versus an “Asian type” of MS, the Asian type MS being characterized by a higher age at onset, selective involvement of the optic nerve and/or spinal cord (versus widespread demyelination of the brain in the Western type), a higher number of lesions on spinal cord MRI, and a lower number of lesions seen on brain MRI (Kira, et al. 1996). Studies in other countries attempt to compare their population’s clinical course to either the Western or Asian type of MS. Arab (Benamer, et al. 2009; Wasay, et al. 2006), Argentinian (Melcon, et al. 2008), and Southeast Asian studies (Wasay, et al. 2006) have identified

similarities between their populations and the Western type of MS rather than the Asian type of MS. Asian type MS seems to affect mostly East Asian populations, such as in Japan, China, Hong Kong, Taiwan, Singapore, Thailand, Korea, and Malaysia (Chan, et al. 2011; Tsai, et al. 2004; Wasay, et al. 2006). Recent radiographic studies on MS are revealing different disease progression profiles in those of Indian and African descent, again highlighting the potential for divergent clinical presentations of MS (Cree and Waubant 2010).

It is important to note that prevalence studies, like the ones discussed above, and even a global meta-analysis of prevalence studies, can only provide a snapshot of what MS looks like at any given time point. Weaknesses include merging together different formats of information from prevalence studies conducted in different areas at different times using a variety of population sizes, ages, ethnic origins, and migratory histories. In addition, the ascertainment of MS cases is dependent on access to medical care, local medical expertise, number of neurologists, accessibility of diagnostic procedures like MRI, and the degree of public awareness of MS (Rosati 2001). Further, local practices may inflate any perceived differences in prevalence rates due to a failure to distinguish between clinical and MRI features of MS and other recurrent inflammatory demyelinating diseases of the CNS, inclusion of cases with MS onset prior to arrival in the study area, and the consideration of neuromyelitis optica as a variant of MS. Thus any differences in race or ethnicity may also be due to variability in diagnosis. Interestingly, in a clinical questionnaire survey that

was sent to 108 neurologists around the world, only two thirds of the 30 cases presented to them were diagnosed correctly, meaning that on average, the neurologists incorrectly diagnosed one third of the patients. Experience, country of training, and specialization in MS made no difference in the error rate (Poser and Brinar 2007).

The Causation Hypotheses

In an attempt to make sense of the epidemiological data and combine them into a unified theory, the following hypotheses have been proposed to explain the observed patterns and exceptions. For example, the latitude hypothesis seeks to explain the greater prevalence of MS in higher latitudes, such as in the northern portions of North America and Europe and in the southernmost areas of Australia and New Zealand, and lower rate in populations located closer to the equator. Many studies have demonstrated the increased incidence, prevalence, and mortalities related to MS as degree of latitude increases on either side of the equator (Noonan, et al. 2002; Risco, et al. 2011; Simpson, et al. 2011). However, additional evidence points to a more nuanced explanation than the latitude hypothesis, since many studies have shown that either the latitude gradient of MS incidence is decreasing over time or that this pattern does not actually hold true in certain areas of the world (Alonso and Hernan 2008; Koch-Henriksen and Sorensen 2011; Melcon, et al. 2008; Wallin, et al. 2004). The epidemiology of MS globally seems to indicate an increase in prevalence of MS in all areas of the world independent of latitude due to

increased survival times, an increase in incidence of MS in women, and an apparent lack of a latitudinal gradient in the northern hemisphere. Interestingly, the north-south latitude gradient in the southern hemisphere seems to be preserved, although at similar latitudes equidistant from the equator where you would expect to see similar prevalence rates, Latin American prevalence is 21.5 per 100,000 persons while the US prevalence is close to 100 per 100,000 persons (Risco, et al. 2011). These exceptions and caveats counter the traditional latitude hypothesis, but may point to a still related phenomenon, namely, Vitamin D production.

A corollary of the latitude hypothesis is that exposure to ultraviolet radiation, which aids in the synthesis and increased absorption of Vitamin D, has been found to have immune system supportive properties, potentially preventing the immune system from attacking its own nerve cells as is the case in MS. Thus, greater exposure to ultraviolet radiation has neuroprotective effects on these individuals, making it less likely that they would develop MS (Cristiano, et al. 2008; Simpson, et al. 2011). For example, in France MS prevalence was correlated with the geographic distribution of ultraviolet radiation (Orton, et al. 2011). Similarly, in Bulgaria an association was found with regional annual sunshine hours rather than latitude (Kalafatova 1987). In Norway, summer outdoor activities in childhood were associated with reduced risk of MS even north of the Arctic Circle (Kampman, et al. 2007). Even if the latitude hypothesis and north-south MS gradient may not hold true, there might be some connection

to ultraviolet radiation exposure which may then be mediated by genetic disposition, additional environmental factors, and migratory patterns. Scientists are still left with the question about whether genes provide susceptibility to particular environmental triggers for MS or whether the environment influences gene expression or a combination of both.

The hygiene hypothesis points to epidemiological studies that find immunological and autoimmune disorders to be less common in developing countries and more common in developed countries. The theory is that people living in developing countries are able to build up stronger immunity due to higher exposure to infectious agents when compared to developed countries. This pattern was recognized as early as the mid-19th century when chronic inflammatory disorders like allergies, inflammatory bowel diseases, Type 1 diabetes, and multiple sclerosis were on the rise (Rook 2012). Since those in developed countries became less and less exposed to infectious agents through modern urban development, they also became more susceptible to being infected by viruses thought to provoke the development of MS, such as the Epstein-Barr virus and the John Cunningham virus among others (Rook 2012).

It seems that a wide range of explanations exist for the variety of incidence and prevalence rates of MS around the world, while the etiology of MS remains unknown. Immunological, environmental, infectious, and genetic factors have all been shown to increase the risk of developing the disease in varying degrees and combinations. Most scientists speculate that certain people are

born with a genetic predisposition that can react to some environmental or infectious agent that, upon exposure, triggers an autoimmune response.

Missing Pages of the Epidemiological Story

Much of the epidemiological story of MS seems to focus on a difference in both prevalence rates and clinical presentation between racial and ethnic groups. The uncertainty surrounding the cause and prevalence of MS is further complicated by the fact that most of the data collected on individuals with the disease represent primarily Caucasians. For example, in the North American Research Committee on Multiple Sclerosis Registry, one of the largest patient databases specific to MS with about 35,000 registered participants, 93% are Caucasian, 2.5% are Latinos, and 4.5% are African American (Buchanan, et al. 2010). The paucity of information about MS patients who are not of Caucasian descent makes it difficult to narrow down the potential causes of MS and identifying who may be more susceptible to developing MS. In addition, registries like this may, by its design, underrepresent less disabled, rural, southern, and lower income persons with MS (Minden, et al. 2006). Upon further inspection, among Latinos, African Americans, and Caucasians participating in the North American Research Committee on Multiple Sclerosis Registry, significant differences are observed between these groups on several factors, including demographics, disease characteristics, and treatments. Caucasians are typically older when experiencing their first MS symptoms and diagnosis. Latinos report more mobility and bowel and bladder issues than Caucasians.

Latinos and African Americans report more depression than their Caucasian counterparts. More Latinos have never had mental health or rehabilitation care and more African Americans have never seen an MS neurologist (Buchanan, et al. 2010).

In addition to the lack of racial and ethnic representation, differences in prevalence rates and clinical presentations could be due to racial and ethnic differences, which most medical researchers equate with biological and genetic differences, but they could also be due to health disparities between Caucasian and non-Caucasian populations. For example, the presence of comorbidities, which are common in the general population, is associated with worse health outcomes. In the MS population, 37% of patients report at least one comorbidity, with high cholesterol, high blood pressure, and arthritis being the most common. The risk of comorbidity was higher for males, older patients (over age 60), African Americans, and those of lower socioeconomic status. Lower socioeconomic status is associated with decreased access to medical care, lower quality of care, adoption of poor health behaviors, increased psychosocial stress, lower health literacy, and lack of social support (Marrie, et al. 2008; Shabas and Heffner 2005). Because physical and mental comorbidities can affect disease, clinical phenotype, diagnostic delay between onset and diagnosis, disability progression, and quality of life, comorbidities may confound the appearance that non-Caucasians have worse MS presentation than Caucasians (Marrie and Horwitz 2010).

What much of the data seems to indicate is that racial and ethnic differences do have some kind of influence on the prevalence of MS, but that this genetic difference does not operate in a vacuum and is most likely mediated by exposure to the environment, which in turn, is determined by human behavior, migratory patterns, sociocultural norms, access to modern technology, political structure, and economic forces. Researchers should be cautioned against the use of race and ethnic categories to predict a more or less severe disease course or to decide on a treatment regimen since race is difficult to define, even biologically (Cree and Waubant 2010). As seen with heart disease, cancer, diabetes, and a host of other diseases, health disparities that exist between racial and ethnic groups act as a confounding factor.

In addition, some anthropologists argue that attacking a problem as complex as how MS affects the entire life of an individual using the “objective” lens through which medicine and science view disease may be entirely missing important insight due to the structure of rigorous scientific methodologies (Cassell 2002). Modern epidemiology has evolved into an increasingly method-driven science that limits research problems to those that are strictly quantifiable. Despite continued integration of epidemiology and anthropology, epidemiology often translates the concept of culture to a “belief,” which fits within the natural epistemology of Western medicine. This has the detrimental effect of turning culture into “difference” which in turn increases the gap between patients and providers (DiGiacomo 1999).

All of these competing, or more likely overlapping, hypotheses of MS cause and prevalence point to a far more complex interaction of population genetics, geographically determined environmental factors such as ultraviolet radiation exposure and viral agents, cultural habits and behaviors, socio-economic demographics, and access to medical care. Given the number of unknowns about the causes and natural history of MS, the underrepresentation of racial and ethnic minority groups in clinical research has been detrimental to developing a comprehensive understanding of MS treatments that respond to the disease course variety seen in different individuals.

Chapter 3 – Underrepresentation in Clinical Trials

Reporting Rates of Clinical Trial Participants by Race and Ethnicity

In 1993, the National Institutes of Health (NIH) passed the Revitalization Act in an effort to increase women and minority participation in research. It contained Public Law 103-43, which states that women and minorities must be included in all clinical research studies, that cost is not an acceptable reason for their exclusion, and that the NIH will support efforts to recruit women and minorities in clinical research studies (National Institutes of Health 2001). The intent of this mandate was to balance the burdens and benefits of research, thereby improving the ethical principal of justice in clinical research originally stipulated in the 1979 Belmont Report. The Belmont Report resulted from the unethical treatment of African American men in the Tuskegee Syphilis Study (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1979). Despite this mandate, underrepresentation of racial and ethnic minority groups remains pervasive in medical research across all medical specialties.

The North American Research Committee on Multiple Sclerosis Registry for MS patients indicates that disparities exist, not only in the participation of racial and ethnic minorities, but in the demographic and clinical characteristics of the racial and ethnic minorities who do participate in the registry. If underrepresentation of racial and ethnic minorities groups in MS clinical trials exists, then the MS community is at a significant disadvantage to attempt to

answer all of its questions about etiology, prevalence rates, natural history, and finding more effective treatments, perhaps even a cure.

Surprisingly, the issue of underrepresentation in MS clinical trials is not well characterized or described in the medical literature. No studies could be identified that looked at whether underrepresentation in MS clinical studies exists, let alone reasons for the underrepresentation. Aside from the North American Research Committee on Multiple Sclerosis Registry, which reported the proportion of its registry participants by race and ethnic group, little information is available to help understand this deficit. What was readily available in the medical literature were studies about underrepresentation of racial and ethnic minority groups in many other different types of clinical trials, namely cancer, cardiac, HIV/AIDS, asthma, diabetes and pain disorder trials. The first step in understanding the underrepresentation is to review the reporting rates of trial participants by race and ethnicity as required by the 1993 NIH mandate. For example, in a comprehensive review of 156 randomized controlled cardiac trials, race and ethnicity were only reported in 35% of the industry funded trials. NIH funded trials reported at a higher rate of 67% but a significant gap in reporting still exists despite the NIH mandate (Berger, et al. 2009). In a similar review of 47 panic disorder trials, less than half reported racial and ethnic data on their participants. But for those trials that did report this data, underrepresentation of racial and ethnic minorities were revealed. Approximately

82.7% of participants were Caucasian, 4.9% were African American, 3.4% were Latino, 1.1% were Asian, and 1.4% identified as Other (Mendoza, et al. 2012).

When looking at the reporting rates for 87 asthma trials, only 26% reported the race and ethnicity of the participants. Of those trials that did report race and ethnicity, none explained how the racial and ethnic group was determined (whether by participant self-report or by researcher classification), and none did an analysis of the race and ethnicity data (Frampton, et al. 2009). Likewise, an even larger review of 253 diabetes, cardiac, HIV/AIDS, and cancer trials were examined for race and ethnicity reporting, specifically targeted because these are diseases with known racial and ethnic health disparities. This review found that 59% of these trials reported race, but of these, 46% reported only one or two racial categories. Surprisingly, in 43% of the trials that reported race, the participant numbers did not add up properly. Data analysis by race and ethnicity was reported in 2 trials out of the 253 total trials (Corbie-Smith, et al. 2003). Unfortunately, even in diseases with known health disparities, many do not report race and ethnicity, and almost none conduct data analyses by race and ethnicity.

Despite extensive recommendations in the literature and the 1993 NIH mandate, reporting and analysis of demographic data is extremely inconsistent and vague. Identifying underrepresentation and correcting this disparity is only the first step along the path to improving clinical trial design and impact. Analysis by demographics is the next step necessary to determine whether there are any

therapeutic differences by race or ethnicity to be identified and reported; otherwise, the generalizability of the findings are thrown into question without a truly representative sample of participants.

Are There Differences By Race and Ethnicity?

In addition to reporting the racial and ethnic breakdown of trial participants and the participation disparities that exist, studies have looked at reasons for these disparities and posited that underrepresentation is usually due to minority distrust of research or the medical community in general. Much of this research has focused on differences between Caucasians and African Americans. For example, the effect of race and place of residence on cancer clinical trial participation was assessed by comparing clinical trial accrual rate to cancer case ratios. Both race and place were significant predictors of participation in both therapeutic and non-therapeutic clinical trials alike. Caucasian, female, non-Baltimore City catchment area persons of the wealthiest counties had the highest participation rate. African American persons living in Baltimore City or the non-catchment area had the lowest participation rate. Poverty level was not significant but was retained as a confounder (Kanarek, et al. 2010).

Several phone surveys have been conducted with Caucasian and African American individuals not associated with a medical center or particular disease to understand if there are differences in willingness to participate in a clinical trial. African Americans often display lower willingness to participate in trials than Caucasians, even after adjusting for age, sex, and socioeconomic status.

African Americans also report higher distrust of research than Caucasians (Braunstein, et al. 2008; Byrd, et al. 2011; Shavers, et al. 2002).

The impact that knowledge of the Tuskegee Syphilis Study⁶ has on clinical trial participation has also been studied among African American and Caucasian individuals. Using phone surveys, a significantly larger proportion of African Americans (81%) had knowledge of Tuskegee than Caucasians (28%). Knowledge of Tuskegee resulted in less trust of researchers for a greater proportion of African Americans (51%) than Caucasians (17%). Approximately 46% of African Americans and 35% of Caucasian participants said this knowledge would affect their future research decisions. Of these, 49% African Americans versus 17% Caucasians would not be willing to participate in future research at all (Shavers, et al. 2000).

Perhaps because distrust seems to be a recurring theme in understanding why underrepresentation of minority groups exist, a 7-item index of distrust was created by Corbie-Smith, et al. (2002) to measure different levels of distrust in medical research. A phone survey revealed that African Americans are more likely than Caucasians to not trust that their own doctor would fully explain research participation and to say that their own doctor exposed them to unnecessary risk. African Americans also had a significantly higher mean

⁶ The Tuskegee Study of Untreated Syphilis in the Negro Male was conducted by the United States government under the Public Health Service and lasted approximately 40 years from 1932 to 1972. This study was conducted on 399 African American men from Macon County, Alabama who were deliberately denied effective treatment for syphilis in order to document the natural history of the disease, even after penicillin was discovered and proven to be an effective treatment in the 1940s (Brandon 2005).

distrust index score than Caucasians even after controlling for socio-demographic variables, indicating that race and ethnicity on their own yield differences in trust.

To further deconstruct different types of distrust, the 7-item index of distrust was altered to differentiate between societal and interpersonal distrust among Caucasians and African Americans. African Americans were found to have higher societal distrust than Caucasians, but there was no difference between the two groups on interpersonal distrust. Further analysis could not explain the relationship between societal distrust and African Americans using any of the following factors: trust in one's doctor, experience of previous discrimination, or awareness of Tuskegee (Durant, et al. 2011). A parent-report survey on the likelihood that parents would let their children participate in research found that minority parents reported more fear of allowing their children to participate in research, but were just as likely as everyone else to consent their child's participation if asked by their own doctor. All parents, regardless of race and ethnicity, were afraid of their child being a guinea pig. Specifically, Latinos had the highest fear score compared with Caucasian parents, while Asians were the mostly likely group to participate in research. Low education level and public health insurance were associated with higher likelihood of allowing their child to participate in research (Svensson, et al. 2012).

Notably, these results seem to provide direct evidence contrary to the previous studies' results. While distrust seems to be a huge contributor to lower

clinical trial participation rates among African Americans and other racial and ethnic minorities, there may be other contributing factors that trust may be masking. When the notion of trust is divided into different types (societal and interpersonal) and analyzed, the influence that distrust has on clinical trial participation rates becomes murky. One could speculate that distrust could be further divided into institutional distrust, governmental distrust, historical distrust, or present distrust. The issue that causes low representation of minority groups in clinical trials may be distrust, or it may be that the categorization of “distrust” is a proxy for other yet unexplored issues contributing to this representation disparity. Additionally, the connection between knowledge of Tuskegee and lower willingness to participate does not seem consistent across studies, and minority groups other than African Americans may have differing views on clinical trial participation.

Several studies seem to provide more definitive evidence that the proposed connection between minority groups and distrust is tenuous, or at least, more nuanced than researchers previously thought. More phone surveys done with African Americans and Caucasians did not reveal any differences by race in knowledge of or about Tuskegee, and any knowledge of Tuskegee was not a predictor of distrust in medical research (Brandon, et al. 2005). Additionally, African American men of all ages were willing to participate in several different types of studies and their decision to participate was motivated by civic duty,

monetary compensation, and a connection to the disease under study. Higher participation was related to higher education level (Byrd, et al. 2011).

The willingness of racial and ethnic minorities to participate in clinical trials could also be seen in reviews of actual participation data. A review of 20 health research studies accounting for 70,000 patient participants found that African Americans had a lower, non-significant consent rate than Caucasians while Latinos had a higher, non-significant consent rate than Caucasians. For the clinical intervention studies, African Americans had a higher, non-significant consent rate than Caucasians and Latinos had a higher, significant consent rate versus Caucasians. For surgical trials which reported minorities as one group, minorities had a higher, non-significant consent rate than Caucasians (Wendler, et al. 2006). Underrepresentation of minority groups in clinical trials is further challenged when trial participation rates are reviewed by trial phase. There is evidence that minority groups actually participate in Phase I clinical trials as healthy volunteers more than Caucasians (Fisher and Kalbaugh 2011). Most of the literature focuses exclusively on Phase III therapeutic trials, so these studies may mask other important issues regarding minority participation in clinical trials.

Barriers to Clinical Trial Participation

While the degree of underrepresentation of racial and ethnic minorities is yet understudied, many scholars have investigated potential barriers to minority participation. Barriers to participation could be organized into three different themes: patient barriers, structural barriers, and provider barriers (Calderon, et

al. 2006; Colon-Otero, et al. 2008; Corbie-Smith, et al. 1999; Eggly, et al. 2013; Howerton, et al. 2007; Hussain-Gambles, et al. 2004; Joseph and Dohan 2009; Penberthy, et al. 2012; Schmotzer 2012; Sheikh, et al. 2009; van Ryn and Burke 2000). Patient barriers often related to fear of experimentation or harm, mistrust of medical community, transportation issues, lack of financial resources, work and family time conflicts, lack of childcare, language, burden of number of visits required, and when community outreach is involved, poorly developed ideas from community leaders on research aims and characteristics (Calderon, et al. 2006; Hussain-Gambles, et al. 2004; Schmotzer 2012; Sheikh, et al. 2009). Mistrust of doctors, scientists and government were consistently reported and concerns of ethical conduct of clinicians were identified, often with examples of exploitation, like Tuskegee, although participants were misinformed about facts of study. Many also incorrectly assumed that the informed consent form relinquished their autonomy and gave clinicians legal protection. Despite many of these fears, most were still in favor of medical research, but did not want to be a guinea pig (Corbie-Smith, et al. 1999).

Structural barriers are related to clinical trial design that may inadvertently exclude particular groups of people, such as racial and ethnic minorities. In a unique trial design by Penberthy, et al. (2012), clinical trial eligibility and invitations to patients were observed prospectively. Interestingly, African Americans were more likely than Caucasians to be ineligible for the cancer clinical trial being observed, but African Americans were more likely to be

ineligible due to mental status or perceived noncompliance, while Caucasians were more likely to be ineligible due to study-specific or cancer characteristics. However, if African Americans were eligible to participate in the trial, they were more likely to refuse participation than their Caucasian counterparts, even after adjusting for age, gender, study phase, and cancer type. Reasons for refusal were slightly different between the two groups. African American refusal was often because they were not interested in clinical trials, they experienced family pressure, or they felt overwhelmed. Caucasians more likely refused due to the extra burden of trial participation, concerns with randomization and toxicity, or they have a specific treatment preference outside of the study (Penberthy, et al. 2012). Lack of insurance or underinsurance and lack of medical facility access to trials, funding, and investigators also seem to be structural barriers to clinical trial participation (Colon-Otero, et al. 2008).

Provider-related factors may also have a strong influence on recruitment of underrepresented groups to clinical trials. Oftentimes, provider attitudes and assumptions about potential trial participants can affect participation levels of racial and ethnic minority groups. Clinicians, who are often responsible for identifying and recruiting participants to trials, are affected by their own biases and make judgments about how well they think a patient will be able to adhere to a protocol, whether a patient is meticulous, proactive, compliant, a good communicator, and embedded in strong social support networks, all for the purpose of completing the trial in a timely and efficient manner (Howerton, et al.

2007; Schmotzer 2012). Clinicians have admitted to subjectively identifying such “good study patients” to target their recruitment efforts (Joseph and Dohan 2009).

Research suggests that physician perspectives may also be influenced by race and ethnicity and assumed socioeconomic status, even when controlling for patient age, sex, disease status, depression, mastery, social assertiveness, and physician characteristics. African Americans and low and middle socioeconomic groups were perceived negatively by physicians, while Caucasians and upper socioeconomic groups were perceived positively. Patient race was also associated with physician assessment of patient intelligence, feelings of affiliation toward the patient, beliefs about patient risk behavior, and medical adherence. Patient socioeconomic status was associated with physician perception of patient personality, abilities, behavioral tendencies, and role demands (Van Ryn and Burke 2000).

These differences in physician perspectives may also be played out in the actual invitations extended to potential clinical trial participants. Another study video recorded oncology visits with 11 African Americans and 11 Caucasians being invited to participate in a clinical trial. Analysis revealed that visits with African Americans compared to Caucasians were shorter overall and included fewer mentions of and less discussion of clinical trials. Also, visits with African Americans included less discussion of the purpose and risks of trials offered, but more discussion of voluntary participation (Eggle, et al. 2013). Additional provider barriers include provider stereotypes and prejudices about difficulties

engaging with minority populations, deficient provider communication methods (lack of compassion and respect, rushed discussion, defensive and patronizing responses), misgivings about the scientific importance of a study questions, and complete lack of provider awareness of clinical trials (Howerton, et al. 2007; Sheikh, et al. 2009).

Facilitators to Clinical Trial Participation

Importantly, work has also been done to understand what motivates racial and ethnic minorities to participate in clinical trials, what facilitators help influence them, and what strategies have been identified to help further improve racial and ethnic minority group participation. African Americans and Latinos shared several motivators to trial participation including: having a disease without cure, helping a family member who has the disease, wanting to find a cure for the disease, staff being from same racial and ethnic group, providing childcare and transportation, and the trial having a limited number of visits (Calderon, et al. 2006). Physician enthusiasm, good communication, clear and concise clinical trial information, good provider-patient relationship, and caring and understanding trial staff all seem to facilitate participation of racial and ethnic minorities. A common motivation across racial and ethnic groups was appealing to participants' altruistic nature, willingness to help others, and want to contribute to furthering medical knowledge. However, "conditional altruism" appears to be the more accurate term since it is their willingness to help others that initially inclines them to participate in a trial, but it is the perceived personal benefit that

actually informs the decision. Potential clinical trial participants would be less likely to participate if they had willingness to help others but without the personal benefit (Hussain-Gambles 2004; McCann, et al. 2010; Schmotzer 2012).

Suggested strategies to help increase participation of racial and ethnic minority groups in clinical trials include solutions on a spectrum from the macro-scale to the micro-scale. The following macro-scale solutions have been identified: reforming the health care system for better health care access, provide regulatory incentives for industry to enroll diverse populations, provide better training for researchers to understand disparities and engage communities in planning, enrollment, and dissemination stages of research, prioritize and fund research through government agencies that address diseases affecting underserved populations (which are less likely to be funded by industry), develop programs to increase minority physicians, implement navigator programs to help potential trial participants address the logistic barriers of trial participation, and partner with nonprofits, local health departments, and private practices to increase trial visibility (Colon-Otero, et al. 2008; Gross 2008). Providing better education in school on the importance and purpose of research may also help dispel any fears or misunderstandings (Corbie-Smith, et al. 1999).

Mid-level strategies might include institutional actions to try and increase racial and ethnic minority participation. Successful strategies include implementation of structural changes to induce and sustain minority accrual to therapeutic cancer clinical trials via 1) leadership support, 2) center-wide policy

change, 3) infrastructural process control, data analysis, and reporting, and 4) follow up with investigators (Anwuri, et al. 2013). Community-based recruitment strategies have also been successful in recruiting more minority populations to clinical trials by targeting faith-based institutions, health fairs, senior centers, university employees, and physicians serving African Americans and Latinos or other minority populations. Building a relationship with community leaders, community advisory panels, or utilizing community-based participatory research methods help with visibility and trust. Approaching community members as partners and not subjects is essential (Cabral, et al. 2003; Coakley, et al. 2012; Corbie-Smith, et al. 2007; De las Nueces, et al. 2012).

Micro-scale strategies highlight the importance of interpersonal relationships in recruiting for clinical trials. Honest and respectful communication, sharing full knowledge of the risks and benefits of research in different formats, having appropriate time to consider with family and friends, and having the study physician available for questions at any time for the duration of the study are all vital components of building a strong provider-patient relationship (Coakley, et al. 2012; Corbie-Smith, et al. 1999; Corbie-Smith, et al. 2007). Specific tailoring of these strategies is likely required depending on the local context of the health care facility, local population, and regulatory requirements. For example, African Americans and Latinos in South Carolina were asked to assess solutions to commonly cited barriers to clinical trial participation. Common responses between the two groups included addressing

trial costs to the participant, recruiting in community contexts, providing community and individual education on trials, and sharing patient safety information. African American specific solutions included diversification of the research staff, recognition of past research abuses, and increasing community trust. Latino specific solutions included provision of low-literacy materials, provision of Spanish-speaking doctors and advocates, and clarification that immigration status does not get documented or prevent trial participation (Ford, et al. 2013; Symonds, et al. 2012).

Finally, issues with informed consent are often cited as barriers to recruitment so strategies focusing on how to tailor consent forms to the local racial and ethnic minority population should be considered, as well as alternatives to the traditional written informed consent for those from cultures with no previous experience with clinical research or human subject's protection. Written translations of informed consent forms are often of limited value if patients have limited or no knowledge of English. Tape recorded audio consent should be considered acceptable rather than written consent and considerations for familial consent rather than individual consent may also be required to accommodate differences in decision-making practices among racial and ethnic minority groups (Adams, et al. 2007; Ryan, et al. 2008; Sankar 2004).

Precautions

The existence of underrepresentation of racial and ethnic groups in clinical trials can be seen in a number of disease indications including cancer, cardiac,

HIV/AIDS, asthma, diabetes and pain disorder trials. There are indications from the North American Research Committee on Multiple Sclerosis Registry that underrepresentation may also exist for MS clinical trials, but there are no studies to date that have been completed. Barriers to clinical trial participation for minorities are plentiful, but the majority seems to center around issues of patient distrust, provider bias, and structural obstacles including access to health care, and transportation, financial, childcare, and time constraints. The selection of a representative sample from the larger population to participate in a clinical trial is critical for the results of the trial to be valid and for those results to be generalizable to the larger population. The consequences of not having a representative sample for a clinical trial can result in incorrect conclusions about a drug's safety or efficacy for the general population, or overlooked safety and efficacy differences between particular subgroups.

For example, during a statin drug trial to reduce cardiovascular disease, only 16.3% of trial participants were women, while women make up 45% of the general population with statin needs. Those aged 65 and older made up two-thirds of the statin needs population while the same group made up only one fifth of the trial sample. Although no severe consequences have been reported, association of side effects with socio-demographic factors was only revealed in follow up data analysis after drug approval, and not during the clinical trials (Bartlett, et al. 2005). Similar to sex and age underrepresentation, if race and ethnicity are not appropriately represented in a trial, evidence can be skewed to

show drug effectiveness and safety when it might not exist or it could exist at a different effectiveness and risk level for particular socio-demographic groups.

Underrepresentation can bias any effectiveness or safety estimates.

Alternatively, underrepresentation of a particular group can also prevent a helpful medication from reaching an audience who could benefit from its use. This was the case with an improper subgroup analysis by gender, which resulted in aspirin treatment being withheld from women in the prevention of stroke for 20 years until an appropriately designed trial showed that aspirin therapy is also beneficial to women for the prevention of stroke (Kreatsoulas and Anand 2009; Ridker, et al. 2005).

Although the risks, remedies, and consequences of underrepresentation of racial and ethnic minorities in clinical trials have been well documented, the numerous causes of participation disparities offer conflicting evidence of what might be driving this phenomenon. Some studies have pointed to distrust of research, particularly in the African American community, which leads to unwillingness to participate, while others have found that levels of distrust, even knowledge of Tuskegee, does not influence minority willingness to participate. In fact, there is evidence that minority groups are just as willing as their Caucasian counterparts to participate in medical research, but either 1) provider bias results in inequitable trial discussions, 2) minority groups are not asked to participate in the first place, and/or 3) minority groups are less likely than Caucasians to have

health insurance which often provides access to medical facilities and the clinical trials conducted within (Fisher and Kalbaugh 2011; Hasnain-Wynia, et al. 2007).

The equitable inclusion of all racial and ethnic groups in clinical trials is a noble and ethically necessary goal, but explicit consideration of race and ethnicity as a prerequisite for trial participation does raise some concerns worth exploring. What is still unclear in many studies thus far is the process by which the low participation rates of minority groups are determined. The proportions of racial and ethnic groups should be a reflection of a variety of contextual factors, namely geographic variations in demographics, differences between urban and rural populations, differences in prevalence rates depending on the disease in question, and differences in which groups have access to the medical centers conducting the trials. The question of underrepresentation may need to be revisited depending on the particular context the underrepresentation is taking place. What exactly constitutes the “right” prevalence of racial and ethnic groups in a clinical trial? The racial and ethnic make-up of participants in a clinical trial could be designed to match that of the general population. It could be designed to match that of the disease under examination. If designed to match the disease under examination, researchers could look at prevalence, incidence, burden of disease, or outcomes. Once a proper prevalence rate is chosen, proper analysis of racial and ethnic subgroups in clinical trials needs to be considered. In order to assess the consistency of study findings across different groups, oversampling of racial and ethnic minorities would be required. If the

real intent of clinical trials is to produce results that consider differences in safety and efficacy by racial and ethnic group, then these considerations need to be incorporated into the trial's initial design. The consequences of attempting to include racial and ethnic minorities in research without properly considering trial design can result in inaccurate conclusions of racial variations in therapeutic efficacy when none exists, or vice versa (Rathore and Krumholz 2003).

Another consideration for explicitly including racial and ethnic minorities in clinical trials is determining whether or not race and ethnicity categories constitute biological differences that have real effects on trial outcomes. There are considerable dangers to assuming race and ethnicity are biological constructs rather than social constructs. More likely, race and ethnicity are proxies for a mix of genetic, disease, social, behavioral, and clinical characteristics that vary and overlap by group. Using race and ethnicity rather than the specific factor causing the difference, results in pseudoscientific rationalizations of categorization. Also, the fact that race and ethnicity are determined either by the physician based on a subjective assessment on what he thinks the patient looks like, or by patient's perceived or self-reported race and ethnicity, may not capture the supposed difference between groups (Acquaviva and Mintz 2010; Rathore and Krumholz 2003; Schwartz 2001). Thus, race and ethnicity should not be considered equivalent to genetic or biological differences, nor should they be considered equivalent to socioeconomic status.

Chapter 4 – The Anthropology of Clinical Trials

The Inclusion-and-Difference Paradigm

The 1993 NIH Revitalization Act changed the face of clinical research through its requirement that researchers actively recruit previously underrepresented groups such as women, children, the elderly, and minority groups. Although underrepresentation of racial and ethnic groups is still rampant in the medical literature, a lot of attention is being paid and resources allocated to remedying this gap. Interestingly, the NIH mandate encompasses two seemingly opposing goals: 1) to include members of groups who have been previously underrepresented as subjects in clinical trials, and 2) to analyze the differences that exist between these groups related to treatment effect, disease programs, or other biological processes. The slow but powerful adoption of this “inclusion-and-difference paradigm” was promoted by biomedical reformers, including policy makers, scientists, clinical providers, and patients, who argued for greater inclusiveness in clinical trials.

These reformers framed their arguments in five distinct ways. First and foremost was the focus on underrepresentation of minority groups in research, which helped make the case for inequity by focusing attention on inclusion statistics. Secondly, well-intentioned regulations were critiqued as misguided protectionism resulting in paternalistic systems that only served to neglect specific populations. Not only were the risks of research being removed from these “vulnerable populations,” so were the benefits. The AIDS activist

movement served as a fulcrum to push for the right of patients to choose to serve as guinea pigs, to access experimental drugs, and to consider access to experimental trials a social good (Epstein 2007). Third, false universalism has extended the experience of Caucasian males, as the dominant group in society, to represent the general population and universal experience. Finally, both health disparities and biological differences point to the negative consequences of inadequate inclusion of underrepresented groups in clinical research (Epstein 2007).

Although reformers rejected the idea of the universal human, they failed to advocate for clinical research to produce individualized therapy. Instead of focusing on the medical uniqueness of each individual, reformers proposed the standardization of medical therapy, not for one type of person, but for specified human groupings: women, children, and racial and ethnic groups. Even in medicine itself, the language of individualism is used even though the policies developed are aimed at social groups. For example, according to an article in *Science*, “Since the early 1980s, the FDA has been interested in the individualization of therapy, that is, determining whether and how treatment should be modified for various demographic groups within the population” (Epstein 2007: 139). Using the terms individual and group interchangeably is a common feature of the inclusion-and-difference paradigm. This flexibility provides the paradigm with legitimacy through the association with individualism, an ever-present value upheld by American culture. On the other hand, the

grouping of individuals into demographic groups may reflect the reality that medical science and technology is not yet able to tailor medications and treatments to individuals, and instead merges tenuous categories of individuals together with little evidence that significant differences actually exist between them.

Ultimately, though, the reformers did not simply presume the biological significance of categories; they reinforced this perception. The irony of the inclusion-and-difference paradigm is that while health inequalities by race and ethnicity are a very real and overwhelming social problem deserving significant attention, the focus on race and ethnicity as a proxy for biologically based differences is not the way to address them. The focus on biology is misplaced because there is an assumption that the categories created to include specific groups of people by scientific and government entities are in fact based in a biological reality that can be clearly delineated. While seeking to reduce inequalities between groups, the inclusion-and-difference paradigm only serves to reshape how we think about sex, gender, race, and ethnicity in that it encourages and reinforces these ways of differing as attributable to strictly our biological makeup.

Biopolitical Citizenship and the Illusion of Race

Citizenship can be understood as the different ways individuals or groups are fully or partially incorporated into the national polity which is mediated by the notion of member rights and responsibilities. Biology has become grounds for

social membership in a group and the basis for staking citizenship claims (Petryna 2002). Other forms of group classification have been created which also provide a basis for affiliation and include all those who share a disease, a treatment, a genetic risk factor, an exposure, gender, or racial and ethnic group (Rabinow 1996). Because of increased attention on the effect classification has on social actors, many concepts have been offered to understand this phenomenon including, “biological citizenship,” “genetic citizenship,” “therapeutic citizenship,” and “sanitary citizenship” (Briggs 2005; Briggs and Mantini-Briggs 2003; Epstein 2007). For Epstein (2007), all of these concepts can be combined into the concept of “biopolitical citizenship” because those promoting inclusion of underrepresented groups in clinical trials were looking for more than just representation in a quantifiable sense; they were looking for inclusion into society for political representation. This biopolitical citizenship points to the political nature of making claims to these groupings and being able to control their meaning. The ability of individuals or groups to lay claims to the full rights and responsibilities of this citizenship is dependent on the influence that the biomedical industry has on creating and transforming these categories into tools of social stratification and exclusion.

It is helpful to conceptualize the clinical encounter as an interaction between patient, as potential clinical trial participant, and provider, as gatekeeper to the clinical trial. This singular encounter, which occurs within a particular place at a particular time, is the result of the regulatory, political, medical, institutional,

social, cultural, and personal forces intersecting and influencing their actions. When this encounter is influenced by meanings of biological difference and the status of socially subordinated groups, new and generally accepted ways of categorizing patients and bodies are created. These classification systems reflect prevailing hierarchies of power (Farmer 2006) and help shape social and moral order where benefits are distributed on the basis of categorical membership. Briggs (Briggs 2005; Briggs and Mantini-Briggs 2003) refers to the way that social actors seek to control the production, circulation, and reception of public discourses about difference as the politics of “communicability.”

The idea that every citizen is shaped through the everyday acts of creating hierarchies of communicability is powerful in explaining the evolving and dynamic relationships that exist between medical researcher and the community. Communicability is the central dimension of self-regulation and self-control, in which individuals find themselves disseminators, receivers, or not in the loop at all. In the clinical trial industry, communicability connects medicalization and racialization to explain how theories about medical causation constitute ways of thinking about the world and acting on it. Narratives about underrepresentation of racial and ethnic minorities in clinical trials seem natural when explained by the medical community as a result of minority distrust. These racialized populations are then deprived of any agency, and become either passive victims (who lack of knowledge and resources), or targets of blame. As a result, medical profiling of patients can occur where clinicians assume that members of certain communities

are less likely to be capable and cooperative patients. Those who can demonstrate the subjectively determined characteristics of a compliant and proactive clinical trial participant are acknowledged as “sanitary citizens,” while those who are deemed to be incapable of adopting these characteristics become “unsanitary citizens” (Briggs 2005).

This medical and racial profiling is used on a large scale when attempting to ameliorate the underrepresentation of minority groups in clinical trials. The remedy to underrepresentation is to increase representation of minority groups, without true consideration of what their inclusion means. Many researchers openly defend race as a legitimate framework for analyzing genetic difference in disease risk (Gravlee and Sweet 2008). Models in health research treat race as a “black box” and fail to explore how race actually impacts health. As a result of the assumption that race is a legitimate and meaningful classification, its continued use seems rational, logical, and incontestable (Hunt, et al. 2013). In fact, race and ethnicity are the most commonly used variables in health research and the use of these variables is on the rise. Despite their pervasive use, the concepts of race and ethnicity are rarely defined (Gravlee and Sweet 2008). However, over the past two decades, more health researchers, as well as anthropologists, have become increasingly critical of using race and ethnicity as a biological construct.

Genetic studies actually show the recency of our common ancestry and continuous gene flow exchange which results in less genetic variation among

human populations than many other non-human mammals (American Anthropological Association 1998; Jablonski 2004; Kuzawa and Sweet 2009; Race Ethnicity and Genetics Working Group 2005). In fact, genetic data show that no matter how racial groups are defined, two people from the same racial group are as different from each other as two people from two different racial groups (American Anthropological Association 1998). In addition, skin pigmentation, often used as a subjective determinate of race, is a recent human adaptation and its evolution has been influenced by environmental conditions rather than genetic differentiation. Thus light or dark skin only provides evidence of past environments, and is not a unique marker for a particular race (Jablonski 2004).

Even if one assumes that racial and ethnic categories are a proper genetic representation of unique human groupings, our current understanding of genetics remains problematic. For example, Marks (2002) argues that the recent discovery that human and chimpanzees share 98% of their DNA structure is flawed. Depending on the techniques used and DNA segments that are compared, the rate of similarity can be widely varied. In addition, genetic expression of a particular DNA segment (or epigenetics) seems to vary depending on the particular individual, which scientists speculate may be due to environmental exposure, diet, exercise, geographic location, or a host of other social and cultural influences. For example, given the same DNA segment between two individuals, the one who is more likely to have a particular vitamin in

his diet may result in 100% gene expression while the one who does not have that vitamin in his diet may only have partial or no gene expression. Thus, even genes by themselves do not determine a specific gene expression. Because of this and because there is similar genetic variation among all humans, identification of discrete genetic groups has been impossible (Marks 2002).

Race and ethnicity are social and cultural constructs that categorize people based on perceived differences in biology or physical appearance. Categorization of groups of people by race has been and continues to be controversial because of the numerous ways these invented categories have served to rationalize mistreatment or justify exclusion. Categories of race have historically been used to achieve political ends (such as during the Holocaust and slavery), without true consideration of biological differences. These perceived differences have their roots in a European taxonomy which was solidified after Columbus sailed to the Americas. It was used as a way to determine the absolute biological, behavioral, and cultural differences between races that not only served to create arbitrary categories of race, but categories which served the basis for ranking the superiority of races.

The fluidity of racial and ethnic categories is appreciated when considering their history and change over time. For example, Irish, Italians, and Jews were all considered to be racial groups in the early 20th century, distinct from the white population. Today, we observe that these same groups are now considered to be part of the majority white racial group (American Anthropological Association

1998). In addition, health research often relies on the racial and ethnic categories developed by the US Census which were not created based on a scientific, biological understanding of race, but on a mixture of criteria, including national origin, language, minority status, and physical characteristics in an attempt to represent true differences between groups of people (Kuzawa and Sweet 2009). Racial and ethnic categories are also conceptualized differently outside of the US, again showing that the construction of racial and ethnic categories is the result of social and cultural preconceptions (American Anthropological Association 2011). An additional incongruence exists between these racial and ethnic categories and the way people choose to self-identify. Individuals of the same “race” may choose to identify themselves differently. Also, an individual’s association with a particular racial group may also be fluid and change over time (American Anthropological Association 1998).

When attempting to identify the reasons for underrepresentation of minorities in clinical trials, racial and ethnic minority group distrust of research and medicine is often invoked as a reason for low participation rates. To the contrary, there is ample evidence suggesting that regardless of feelings about distrust, minority groups are just as willing as their Caucasian counterparts to participate in a clinical trial. Other structural confounders may also explain low participation rates, such as provider bias and access to care. The continuous recycling of distrust as a reason minority groups do not participate in clinical research only serves to “blame” the disparity of participation on a particular

attitude of the minority group in question. When framing these discussions in the context of spheres of communicability, how much of the discourse currently used to try and improve disparities in minority participation only serve to maintain the difference, distrust, and paternalistic relationship between medical researchers and potential clinical trial participants?

Recruitmentology

Despite the concerns raised about medical and racial profiling when recruiting minorities for clinical trials, Epstein (2008) has identified the emergence of a new science that he calls, “recruitmentology,” which seeks to develop an empirical body of evidence evaluating the efficacy of particular social, cultural, psychological, technological, and economic strategies to convince people to participate in research studies. Practitioners attempt to generate and disseminate knowledge about how to successfully recruit and retain participants in clinical trials, particularly those considered to be hard to recruit populations. Many of the current techniques borrow cues from the marketing and advertising worlds. For example, in a new clinical trial studying a novel infusion therapy for MS at BAMC, all study literature and patient information is tagged with the name of the study and its slogan: “OPERA: The sound of a new research opportunity in MS.” Similarly, a non-profit organization called The Center for Information and Study on Clinical Research Participation (CISCRP), attempts to engage and inform the public about clinical research. CISCRP invites those who have participated in a clinical trial to join their “Medical Hero Community” which serves

as a public service campaign to assist the public in thinking differently about clinical research (Center for Information and Study on Clinical Research Participation 2014).

As more and more portions of clinical trial activities are being outsourced to private companies, recruitment is often turned over to for-profit companies who specialize in recruitment of trial participants. This specialization is transforming the art of recruitment into an actual science through establishment of quantitative measures of recruitment effectiveness (i.e., cost-benefit analysis of recruitment efforts and potential subject “yield”). The science of recruitmentology, to its credit, has recognized the need to address the collective memory of racism and research abuses, distrust of research, fear of experimentation and perceived lack of benefit. Additional efforts have focused on highlighting the altruistic side of clinical trial participation. Still others have looked at research positionality and have recognized the relative success of recruitment based on a researcher’s embeddedness and connectedness within community networks. Others have attempted to create a body of evidence for particular cultural groups, such as how confidentiality issues would affect potential participants in rural areas, or how the family orientation of Native Americans may affect researchers’ ability to enroll Native American participants. However, caution must be applied here since these categories are treated by practicing recruitmentologists as static and homogenous groups that are knowable and unchanging (Epstein 2008).

Significant attention is paid to the issue of distrust in recruitmentology. Trust is described in the context of historical abuses of patients by researchers, of which Tuskegee is not the only event to contribute to the collective memory of research abuses and unequal power relations. Additional historical examples cited include the use of slaves for medical experimentation in the pre-Civil War South, the use of black cadavers for dissection in the 19th century, legends about “night doctors” in the post-Civil War period who were hired to kidnap blacks in the South to use in medical experiments, the Tuskegee syphilis patients who were denied treatment even though treatment was available for nearly three decades, the HIV/AIDS epidemic, and the presence of drugs in black neighborhoods which is related to a claim that the CIA deliberately pushed the sale of crack cocaine in black neighborhoods (Epstein 2008). Although Tuskegee is often used and mentioned as a placeholder of the source of mistrust, it only serves to mask a real consideration of the broader set of historical and political issues affecting minority groups and their willingness to participate in clinical research.

Trust-building can be directly related to transforming the imbalance of power that exists in the provider-patient relationship (Grimen 2009). Epstein (2008) recommends that building trust can be accomplished using a variety of methods such as participatory action research and community-based participatory research. These methods involve a reciprocal relationship with a mutually beneficial exchange of knowledge and resources. “Drive-by” research is discarded for a true, long-term commitment and relationship to the community.

While the inclusion-and-difference paradigm attempts to remedy the underrepresentation of minority groups by promoting the use of race and ethnicity as distinct biological groups, the science of recruitmentology seeks to solve deep, historical issues of trust by scientifically engineering strategies to induce cooperation and participation of these underrepresented groups.

Unfortunately, the use of race as a biological construct may undermine the larger goal of eliminating health disparities which are mostly due to sociopolitical causes rather than biological. In addition, the attempt to better recruit minority groups to clinical research by scientifically engineering recruitment efforts does not serve to change the power dynamic in the provider-patient relationship. In this sense, the problem of minority recruitment remains a problem to be solved or socially engineered by the researcher, rather than a problem of social relationships governed by positionality and embeddedness in arenas of power.

Risk

Remarkably, little attention is paid to the concept of risk in the debate over underrepresentation of racial and ethnic minorities in clinical trials. Much effort is spent trying to understand the causes of underrepresentation by attributing the existing participation disparities to an intrinsic cultural factor, distrust, with variable results. Then potential strategies for correcting this underrepresentation are elucidated. Although this is not a frivolous exercise, a discussion of the causes and solutions to underrepresentation cannot be comprehensive without thorough consideration of risk and risk perception. Perhaps the lack of

discussion is due to the fact that participation in clinical trials carries inherent risks that both researchers and patients are aware of and assume no further attention is required. However, risk may be the most salient issue to consider when trying to understand minority underrepresentation in clinical trials. The use of distrust in minority populations to explain underrepresentation has not yielded consistent findings and this could be because participation is mediated by a related but separate concept, risk perception.

Risk is not an unknown concept to many MS patients. Current MS treatment options carry significant side effects, and oftentimes the choice between treatments is a choice, not of fewer side effects, but acceptable side effects. Much time is spent by the MS medical community to evaluate, monitor, and quantify therapeutic risk. The MS field is at a unique point in its history since there has been an explosion of treatment options in the past decade. This is remarkable considering that the first MS medication was available in 1993, a little over 20 years ago. Since then, different types of therapeutics have been developed, each with their own treatment benefits, modes of administration, and risk profiles. Attempts to generate a general risk algorithm for all MS treatments have been difficult considering this ever-changing therapeutic landscape (Clanet, et al. 2014). Risks related to specific MS medications have also been difficult to understand because comparison of “actual” risk (quantified, statistical risk of a particular side effect) often does not match patient perceived risk. MS patients treated with natalizumab and mixantrone were often willing to accept a higher

risk of side effects than their neurologists (Heesen, et al. 2010; Hofmann, et al. 2013). There may also be a difference between risk perception and risk acceptance. Risk perception is when patients perceive and interpret risk differently from others; risk acceptance is when patients may perceive a risk to be high but determine that it is an acceptable risk to take (Tur, et al. 2013).

This approach to understanding risk, through use of calculated probabilities and epidemiologic statistics, dominates research in the health sciences. In epidemiology, risk is calculated as the probability that something will occur given a specific population and risk factor relative to a reference population (Frankenberg 1993; Launiala and Honkasalo 2010). This approach is often used to assist clinicians and patients make “objective” decisions about a medical intervention. However, it is often the case that even if individuals perceive themselves to be at significant health risk, they do not take the identified measures to reduce that risk. The conception of an “objective” and calculable risk is at odds with local experience and perceptions of identity. Given the same danger, people do not consider themselves equally at risk of harm (Nichter 2001). Risk perceptions are influenced by a process of cultural interpretation, disease identity, and personal meanings of vulnerability, agency, and perhaps trust (Goldade and Nichter 2010).

Anthropologists critique the epidemiological approach to risk as failing to account for the complex sociocultural context within which risk is situated (Frankenberg 1993; Launiala and Honkasalo 2010; Lupton 1999; Trostle 2005).

This critique was first cited in the work of Mary Douglas (1992) on risk and blame, in which she identified the disadvantages to risk analysts' assumptions. In an effort to avoid bias and politicization, risk researchers purposefully chose to omit considerations of culture, politics, and morals in search of objectivity (Douglas 1992). Because of these shortcomings, social scientists have attempted to move beyond the medicalization of risk and the individualistic risk paradigm into risk behaviors that are understood within their respective social and cultural contexts (Frankenberg 1993; Sommerfeld, et al. 2002). Medical anthropologists have taken this approach to risk further by pushing for an examination of the structural forces that exist, such as poverty, inequality, access to health care, and health economics, which contribute to risk perception (Farmer, et al. 2006; Sommerfeld, et al. 2002). Taking these macro level factors into consideration makes it clear that individual risk behavior and perceptions of risk are severely limited and mediated by intersecting agencies of power.

Chapter 5 – Research Design

Research Questions

The intent of this project is to better understand the complexities surrounding MS clinical trial participation, in the context of underrepresentation of minority racial and ethnic groups in clinical trials, the unknowns that exist about MS etiology and prognosis, and the conflicting evidence on whether reasons for participation are related to distrust as the medical literature seems to suggest, or some other unknown factor. In order to explore these issues in more detail, I set out to answer three main research questions:

1. Is there underrepresentation of racial and ethnic minority groups in MS clinical trials? If so, why?
2. In what ways do preconceptions about medical research, altruistic motivations, and daily experience with disease contribute to MS patients' participation in clinical trials?
3. What are the salient MS patient attitudes towards clinical trials?

Research Methods

A mixed-methods approach was utilized to answer the three research questions. First, archival data were reviewed for all MS patients being seen at BAMC to identify whether the racial and ethnic group proportions matched the racial and ethnic group proportions of the general MS population. The racial and ethnic makeup of MS patients who had participated or were currently participating in clinical trials at BAMC were compared to the findings from this

review to determine whether there is underrepresentation of minority groups in BAMC clinical trials. Second, an electronic survey was administered to capture opinions from MS patients regardless of their exposure to or knowledge of clinical trials. Third, semi-structured interviews were conducted with MS patients who have experience participating in a clinical trial to provide depth to the topic and rich context for thematic analysis.

Archival Data

In the original study design, I wanted to understand the proportion of MS patients who had been invited to participate in a clinical trial, the number of that group who had accepted or declined, and whether there were any differences by racial and ethnic group. To do this, a search of BAMC's electronic medical record database was conducted. In theory, the database could be used to search and extract from clinic notes whether or not patients with an MS diagnosis with reported gender, race, and ethnicity were invited to participate in research, whether they accepted or declined, and any other reasons noted for the acceptance or decline. Unfortunately, this database review of MS patients revealed that I would not be able to ascertain which patients had been invited to participate in a clinical trial, nor whether a patient had declined or agreed. There was no formal section of the electronic medical record where a clinician could document that a patient was participating in a clinical trial. In lieu of this, I attempted a key word search in the text of every clinic note to see if I could find mention of clinical trial invitations during clinical encounters. In an attempt to be

as inclusive as possible, general search terms such as “trial,” “research,” and “study” were used but did not reveal any documented clinical trial discussion. Often these words were used interchangeably in documenting a patient’s regular medical care (i.e., try a different medication for a “trial” period). Thus, it appeared that information about clinical trial invitation, acceptance, or decline was not documented in any official or unofficial way in the patient’s medical chart. Given this constraint, the database review was then used to learn the number of total MS patients served by BAMC’s MS Clinic. Additionally, the racial and ethnic make up of the MS patient population was obtained to reveal if BAMC’s MS patient population matches that of the US and whether underrepresentation of minority groups in clinical trials exists at BAMC.

Because there are no studies to date documenting whether underrepresentation exists in MS clinical trials (except for the North American Research Committee on Multiple Sclerosis Registry), the government website, ClinicalTrials.gov was reviewed to determine participation rates of minority groups in MS clinical trials across the US. ClinicalTrials.gov is a web-based database that is maintained by the National Library of Medicine and the NIH. This website was created as the result of the Food and Drug Administration Modernization Act of 1997. The FDA Modernization Act required the NIH to develop a registry of clinical trials for both federally and privately funded trials conducted under investigational new drug applications. The website was made available for public use in February 2000. Additional requirements were

expanded in the FDA Amendments Act of 2007. The FDA Amendments Act required that more types of trials be registered and additional trial information be submitted. In addition, the law required submission of results for certain trials, which can now be found in the ClinicalTrials.gov results database which contains information about study participants, such as total number of participants, participants by sex, race, ethnicity, and disease status (National Library of Medicine and National Institutes of Health 2014). The demographic data gathered from Clinicaltrials.gov provided information about MS clinical trial participants across the country by race and ethnicity and serves as a comparison to BAMC's MS population.

Electronic Survey

An electronic survey was developed using REDCap, which is a secure, HIPAA⁷ compliant, web application for building and managing online surveys. Because the database search did not reveal any documentation of actual clinical trial invitations or trial acceptance or declines, the survey was created to understand whether MS patients had ever been invited to participate in a clinical trial, what their primary reason would be for accepting or declining participation in a trial, and their general knowledge of and views towards clinical trial participation. Potential reasons for acceptance and declination were adopted from common reasons for trial participation identified in the medical literature.

⁷ HIPAA is the Health Information Portability and Accountability Act which provides federal protection for individually identifiable health information.

The survey had a total of 34 questions including demographic questions at the end.

All BAMC MS patients were eligible to participate. MS patients were chosen from the total list of 1,439 MS patients being seen at BAMC. In May, June, and July 2014, surveys were administered to MS patients in four waves. The first wave of invitations was emailed to 102 MS patients with an email address listed in their electronic medical record regardless of race and ethnicity. The second wave of invitations was emailed to 24 MS patients with an email address listed in their medical chart, specifically targeting non-Caucasian patients. A significantly lower proportion of non-Caucasian patients had an email listed in their medical chart (26%) than Caucasian patients (68%). Because of this, it was exceedingly difficult to target non-Caucasian patients by presence of an email address alone in the electronic medical record. Thus, a third wave of invitations was sent by mail to 68 non-Caucasian MS patients at their listed address, which instructed them to go online and take the electronic survey. Finally, a fourth wave of invitations was emailed to 60 Caucasian patients in an attempt to increase participant numbers. Out of 254 invitations to participate in the survey, only 48 patients responded (19% response rate). Of these, 37 were Caucasian and 11 non-Caucasian (seven Hispanic/Latino, three Asian, and one African American patient). The survey served as a validity check against data gathered during the archival data review and semi-structured interviews. Survey data were analyzed using SPSS (Version 21.0).

A major limitation of the survey is the fact that it was created only as an electronic survey to be administered online. Even when I attempted to remedy the oversampling over Caucasian MS patients by sending the survey invitations in the mail rather than by email, patients were still required to have access to a computer with an internet connection to complete it. Because I designed the survey to be anonymous to protect the confidentiality of MS patients, no link was available for me between survey responses and patient to determine which patient from which invitation wave decided to complete the survey. Thus, I was unable to discern how successful each wave of invitation was at reaching MS patients for survey participation.

Semi-Structured Interviews

The initial intent for the semi-structured interviews was to interview two groups of patients: those who had accepted participation in a clinical trial and those who had declined participation in a clinical trial. The purpose was to do a comparison of willingness or unwillingness to participate in a trial and see if there were any differences based on race and ethnicity or any other factor. However, upon conducting the archival research and completing the BAMC electronic medical record review, documentation by clinicians of their invitations to patients for clinical trials and their subsequent acceptance or rejection were nonexistent in the medical charts. Therefore, it was nearly impossible to identify a patient who had been previously invited to a trial and declined participation in order to interview. In addition, MS trials at BAMC were not currently enrolling, so there

were no prospective declinations available either. Instead of having two groups, the study was altered to interview only MS patients who had been invited to participate in clinical trials and had accepted. Thus, only currently active MS clinical trial patients were available for invitation to the interview. There were 22 MS clinical trial patients in this category, 6 of whom were non-Caucasian. An attempt was made to over sample non-Caucasian patients to explore any potential differences in attitudes toward clinical trials by race and ethnicity. Sixteen patients were invited to participate in the semi-structured interview, 10 Caucasian and 6 non-Caucasian. Only 11 MS patients agreed to participate, 7 Caucasian and 4 non-Caucasian (one African American and three Hispanic/Latino patients).

An interview guide was created for the semi-structured interview to direct the conversations through a natural, but logical progression using open-ended questions (Bernard 2011). Some questions were added and others removed as the utility and relevance of certain topics became clear after conducting the first few interviews.

Interviews were conducted in May, June, and July of 2014 in a location that was most convenient and comfortable for the patient. The first offer for an interview location could be outside of BAMC so that any potential influence from being in the medical center during the interview would be allayed. Despite the offer, two patients preferred to come to BAMC to complete the interview while they were already at BAMC for another medical appointment, six patients

preferred to meet in public locations (coffee shop, café) for the interview, and three preferred to conduct the interview in the comfort of their own homes. The interviews lasted from one to one and a half hours and all were consented in-person and agreed to audio-recording.

The audio recordings of the interviews were transcribed using manual transcription software (oTranscribe.com open source software) and input into Atlas.ti for coding and analysis. A codebook was made based on a review of themes from the first several interviews, and was refined as additional interviews were transcribed and coded. A total of 47 codes were created to capture the themes from all 11 interviews. These codes were analyzed further for relevant sub-themes to identify significant patterns across all interview participants.

Institutional Approvals

Because participants for this project were recruited from BAMC's MS Clinic, institutional approvals from both BAMC and San Jose State University's IRBs were obtained. Approval for the BAMC clinical database, the electronic survey, and the semi-structured interviews were first submitted and approved under the BAMC IRB on March 7, 2014; then these approval documents were submitted to SJSU IRB and approved on April 9, 2014. The SJSU IRB accepted the consent format from BAMC because study participants were being recruited through BAMC which has its own consent requirements for human subjects.

Chapter 6 – Results

Archival Data

To understand whether underrepresentation of racial and ethnic groups exists in MS clinical trials, a review of the national clinical trial database, ClinicalTrials.gov, was completed on all MS trials being currently conducted in the US. In addition, a search of BAMC's patient database was completed to reveal rates of MS clinical trial participation by race and ethnic group compared to the overall population of BAMC MS patients.

National Reporting

Using the ClinicalTrials.gov database, a search was done for all MS clinical trials registered on the website. A total of 1,334 clinical trials for MS patients were registered. Of those, 475 were completed trials (the remaining 859 trials were either newly registered trials still recruiting patients or still actively conducting the trial). A total of 134 MS clinical trials had actually reported results. Some of this low reporting percentage (28%) could be due to the different reporting requirements based on clinical trial type, or for the simple reason that these completed trials failed to report their results. Of the 134 MS clinical trials reporting results, only 22 trials (16.4%) reported on participants' race and ethnicity. The remaining 112 trials only reported participants based on sex and disease status, along with trial results and adverse events, but failed to report participant race and ethnicity data.

As discussed earlier, the MS prevalence rate for females is approximately 2.5 times the prevalence rate for males in the US (Multiple Sclerosis International Federation 2013; Noonan, et al. 2002). Comparing this prevalence rate with the participation rates of males and females in MS clinical trials in Table 3, the proportion of male and female participants in MS clinical trials roughly mirrors the prevalence of MS. In this case the participation rate for females is 2.2 times the participation rate for males (1,241 males and 2,734 females) perhaps indicating a slightly heavier participation of males relative to the general MS population.

Table 3. MS Clinical Trial Participants in the US by Sex

Trial	Male	Female	Total
1	185	332	517
2	159	322	481
3	60	179	239
4	154	248	402
5	129	300	429
6	13	11	24
7	11	20	31
8	100	308	408
9	8	12	20
10	66	111	177
11	16	22	38
12	9	51	60
13	70	144	214
14	1	9	10
15	3	36	39
16	87	182	269
17	46	132	178
18	22	91	113
19	22	126	148
20	2	9	11
21	24	23	47
22	54	66	120
Total	1241	2734	3975
Percent	31.2%	68.8%	
Data from systematic review of ClinicalTrials.gov as of December 2014.			

When looking at the prevalence breakdown of racial and ethnic groups in the US, the prevalence of Caucasians (96 per 100,000 persons) is approximately 2.0 times the prevalence rate of African Americans (48 per 100,000 persons) and 2.0 times the prevalence rate of all other racial and ethnic groups (43 per 100,000 persons) (Noonan 2010). Rates of participation by race (Table 4) and ethnicity (Table 5) show that the proportion of Caucasian MS patients participating in clinical trials far exceeds the proportion of Caucasian MS patients in the general population. For example, the participation rate of Caucasian MS patients is approximately 36 times the participation rate of African American MS patients (Table 4). Similarly, when combining all other racial categories, the participation rate of Caucasian MS patients is almost 57 times the participation of MS patients from all other racial categories (Table 4). Similarly, the participation rate of Non-Hispanic/Latino patients is significantly higher than the participation rate of Hispanic/Latino patients (Table 5).

Of significance, the reporting of race and ethnicity was not consistent across trials. Most trials used the most recent 2010 US Census race categories, but without reporting ethnicity categories. Some trials reported both race and ethnicity categories while other trials only reported ethnicity categories. Some trials added their own racial category of “Hispanic” rather than separating it out as an ethnicity category. One trial even created its own race and ethnicity categories of “White” and “Non-White.”

Table 4. MS Clinical Trial Participants in the US by Race

Trial	White	Black	Asian	American Indian / Alaskan Native	Other	More than 1 Race	Unknown /Not Reported	Total
1	516	1	0	NR*	0	NR	NR	517
2	462	2	3	NR	9	NR	NR	476
3	221	15	NR	1	NR	NR	NR	237
4	401	1	NR	NR	NR	NR	NR	402
5	NR	NR	NR	NR	NR	NR	NR	0
6	21	1	1	0	0	0	1	24
7	29	1	1	0	0	0	0	31
8	350	28	1	NR	10	NR	NR	389
9	18	1	0	1	NR	0	0	20
10	171	2	0	0	NR	4	0	177
11	38	NR	NR	NR	NR	NR	NR	38
12	53	5	1	1	NR	NR	NR	60
13	201	8	0	1	NR	0	4	214
14	8	1	0	0	NR	1	0	10
15	39	0	0	0	NR	0	0	39
16	251	11	3	0	NR	3	1	269
17	176	2	0	0	NR	0	0	178
18	91	8	1	NR	1	NR	NR	101
19	141	3	NR	NR	4	NR	NR	148
20	11	0	0	0	NR	0	0	11
21	44	3	0	0	NR	0	0	47
22	114	NR	NR	NR	6**	NR	NR	120
Total	3356	93	11	4	30	8	6	3508
Percent	95.7%	2.7%	0.3%	0.1%	0.9%	0.2%	0.2%	
Note: There were no Native Hawaiian/Alaskan Native participants reported for any MS clinical trial. *NR = Not Reported **6 “Non-White” participants Data from systematic review of ClinicalTrials.gov as of December 2014.								

BAMC Reporting

The BAMC MS Clinic is part of a private teaching hospital in the San Francisco Bay Area. Because the San Francisco Bay Area has its own unique racial and ethnic makeup, the prevalence rates reported at the clinic will likely not

Table 5. MS Clinical Trial Participants in the US by Ethnicity

Trial	Non-Hispanic/ Latino	Hispanic/ Latino	Total
1	NR	NR	0
2	476	5	481
3	237	2	239
4	NR	NR	0
5	409	20	429
6	NR	NR	0
7	NR	NR	0
8	389	19	408
9	NR	NR	0
10	NR	NR	0
11	NR	NR	0
12	59	1	60
13	NR	NR	0
14	9	1	10
15	NR	NR	0
16	NR	NR	0
17	178	0	178
18	101	12	113
19	144	4	148
20	11	0	11
21	47	0	47
22	NR	NR	0
Total	2060	64	2124
Percent	97.0%	3.0%	
Data from systematic review of ClinicalTrials.gov as of Dec 2014.			

translate directly to the national rates, although they do serve as an approximate guide. The BAMC database was searched to obtain the most recent census of MS patients served by the BAMC MS Clinic. The ICD-9 code for MS (340.0) was used in the search to identify all patients with a documented MS diagnosis. Table 6 shows the demographic characteristics of the MS patients currently served at the BAMC MS Clinic as reported in the electronic medical record.

Table 6. Demographics of MS Patients Served by BAMC MS Clinic

Demographic	Count	Percent
Sex		
Male	379	26.3
Female	1,060	73.7
Total	1,439	100.0
Race/Ethnicity		
Caucasian	1,149	79.8
African American	83	5.8
Asian	73	5.1
Other	5	0.3
Native American	4	0.3
Unknown	1	0.1
Hispanic	124	8.6
Total	1,439	100.0
Data from systematic review of BAMC database as of May 2014.		

The BAMC MS Clinic serves a slightly higher proportion of women than men compared to the national average of 2.5 women to every one man (Table 6). Women are served by BAMC MS Clinic approximately 2.8 times the rate of men (1,060 females to 379 males). Almost 80% of the BAMC MS Clinic patients are Caucasian, while the remainder of the racial and ethnic categories total to approximately 20% of the BAMC MS patient population (Table 6). While this is still a far cry from the nationally reported proportions of race and ethnicity, this may be a reflection of the local region, as well as the ability of patients to access the medical care offered by the BAMC MS clinic. When exploring these numbers to determine whether there is underrepresentation of minority groups in MS clinical trials, it is important to note that the participation rates by race and ethnicity in BAMC MS clinical trials should be compared to the makeup of the BAMC MS patient population since these actual numbers reflect the reality and

constraints of local demographics, socioeconomic, and health care access issues.

As discussed previously, initial attempts to pull clinical trial participation rates from past patients were unsuccessful because the BAMC database did not contain any documentation of clinical trial participation, clinical trial invitations, nor subsequent acceptance or declination of the clinical trial. In addition, an attempt was made to access participation rates from the BAMC IRB since they are required by federal regulation to collect information about participants' race and ethnicity. However, the IRB was unable to disclose this information, as it is only collected to monitor equitable access of clinical trials to all patients. Thus, only information on current MS patients participating in clinical trials was collected. Table 7 shows demographic information about MS patients currently participating in clinical trials at the BAMC MS Clinic. The proportion of males and females participating in clinic trials at BAMC roughly approximates the proportion seen in the larger BAMC MS patient population, with only a slight increase in male representation in clinical trials (total male BAMC MS patient population 26.3% versus male BAMC MS clinical trial population 29.5%). Interestingly, the proportion of non-Caucasian clinical trial participants is higher than in the total BAMC MS patient population (approximately 40% non-Caucasian BAMC clinical trial participants versus 20% in the total BAMC MS patient population). Although this is also significantly higher than the proportions of non-Caucasian patients participating in clinical trials nationally, this rate still does not match the national

prevalence rates by race and ethnicity. For example, the prevalence rate reported by Noonan et al (2010) for Caucasians, African Americans, and the remaining racial and ethnic categories is a 2 to 1 to 1 ratio. For BAMC that ratio is approximately 13 to 1 to 7.

Table 7. Demographics of MS Patients Participating in Clinical Trials at BAMC MS Clinic

Demographic	Count	Percent
Sex		
Male	13	29.5
Female	31	70.5
Total	44	100.0
Race/Ethnicity		
Caucasian	27	61.4
African American	2	4.5
Asian	2	4.5
Other	6	13.6
Native American	0	0.0
Unknown	2	4.5
Hispanic	5	11.4
Total	44	100.0
Data from systematic review of currently active and recently completed BAMC MS clinical trial participants as of July 2014		

Electronic Survey

An electronic survey was created in order to capture the opinions of the larger BAMC MS patient population regarding participation in clinical trials. Since participation of patients in the in-depth semi-structured interviews would be limited, an electronic survey would be able to reach more patients, require significantly less time for the patient, and could be completed in a convenient location and time. Although 254 email and letter invitations were sent to BAMC

MS patients, only 48 responded. Table 8 shows demographic information reported by the survey respondents.

Table 8. Demographics of Electronic Survey Respondents

Demographic	Count	Percent
Sex		
Male	9	19.1
Female	38	80.9
Age		
Minimum	21 yo	N/A
Maximum	69 yo	N/A
Mean	48 yo	N/A
Race/Ethnicity		
Caucasian	37	77.1
African American	1	2.1
Asian	3	6.3
Other	0	0.0
Native American	0	0.0
Unknown	0	0.0
Hispanic	7	14.6
Annual Income*		
\$49,999 or less	8	17.0
\$50,000-\$99,999	11	23.4
\$100,000-\$149,999	8	17.0
\$150,000 or more	20	42.6
Education		
Less than Bachelor's	18	37.5
Bachelor's	11	22.9
Master's	10	20.8
Professional or Doctorate	9	18.8
Insurance		
Private	38	79.2
Medicare	8	16.7
Other	2	4.2
Total	48	100.0
*Total Annual Household Income		

As shown in Table 8, the population of MS patients surveyed for this study includes individuals from a wide variety of backgrounds. However, the

population's demographic characteristics are skewed and do not meet the requirements for a normally distributed population. In fact skewedness and kurtosis were extremely variable for all demographic variables and the only potentially normally distributed variable is age (Kolmogorov-Smirnov = 0.089, df = 48, p = 0.200). All other demographic variables failed this test of normality. Thus for this analysis, non-parametric statistics were used to account for the underlying population distribution, the small sample size, and measurement of categorical variables. Chi-square tests for independence were used for categorical responses, while Mann-Whitney U tests were also done to test for differences between two independent groups on a continuous variable (e.g., four-point scale from "No Influence" to "Strongly Influence"). Kruskal-Wallis tests were used to compare scores on a continuous variable for three or more groups. Follow up Mann-Whitney U tests were also done when a statistically significant result was identified from the Kruskal-Wallis test to determine which responses were significantly different from one another.

Patients were asked about their familiarity with and opinion about clinical trials, which were defined in the survey as "research studies that involve patients receiving an experimental drug, treatment, or device to evaluate its safety and efficacy." Patients were also asked whether they would participate in a clinical trial and to rank the reasons why they would or would not choose to participate in a trial. Overall, most respondents (42 out of 48 respondents) said they were either "Very Familiar" or "Fairly Familiar" with the term "clinical trial." However,

fewer respondents had ever seen a print advertisement (18 out of 48 respondents) or a digital advertisement (13 out of 48 respondents) inviting them to participate in a clinical trial. No significant differences were found between racial and ethnic categories.

Exactly half of respondents (24 out of 48 respondents) had discussed participation in a clinical trial with their doctor, nurse, or research personnel. However, a chi square test for independence (with Yates Continuity Correction) indicated a significant association between being Caucasian or non-Caucasian and discussing participation in a clinical trial (χ^2 [1, n = 48] = 4.24, p = 0.039, phi = -0.347). Caucasian MS patients were more likely to have discussed participation in a clinical trial than their non-Caucasian counterparts (Figure 2). Respondents were also asked whether they had ever been invited to participate in a trial, if they have ever agreed to participate in a trial, or if they have ever declined participation in a trial, but chi square tests did not reveal additional significant differences between the responses and racial or ethnic category.

Comparisons between proportions of Caucasian and non-Caucasian patients' stated exposure to clinical trials revealed some interesting differences. Regarding whether a patient had discussed a clinical trial with their doctor, nurse, or research personnel, Caucasian patients were significantly more likely to have discussed a trial than non-Caucasian patients (Z = 2.4039, p = 0.0164). Additionally, although a chi square test did not reveal a significant difference in responses between racial and ethnic groups on invitations to participate in a trial,

Z tests indicated that a significant difference exists in the proportion of Caucasian patients who are invited to participate in clinical trials versus non-Caucasian patients ($Z = 2.0794$, $p = 0.03752$). In other words, Caucasian patients are more likely to be invited to participate in a trial while non-Caucasian patients are less likely to be invited to participate in a trial. These results may point to structural factors (e.g., clinician bias) that influence whether a doctor discusses a clinical trial with a patient or whether a patient is invited to participate in a clinical trial.

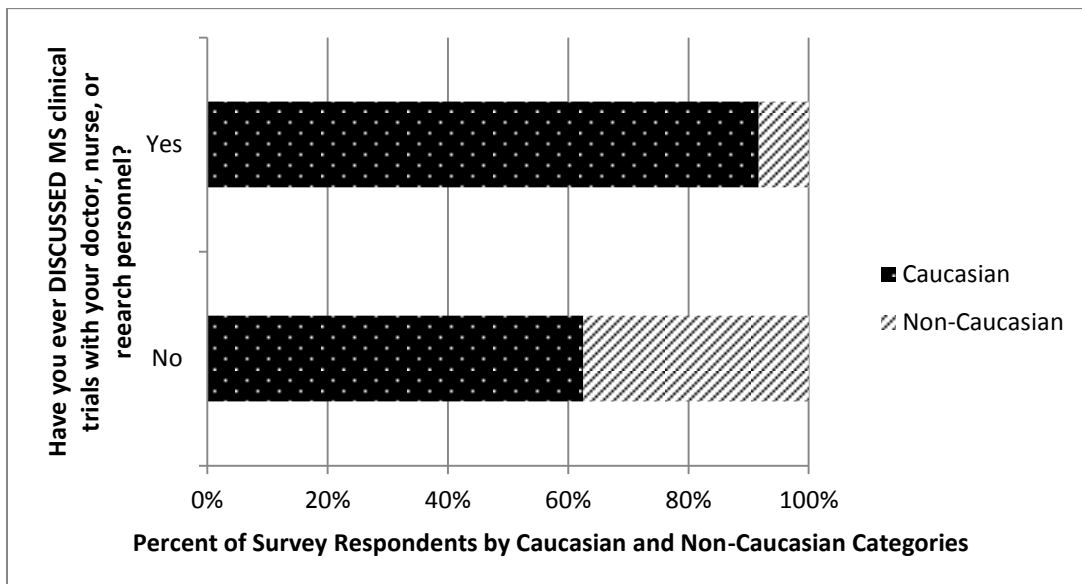


Figure 2. Percentage of Caucasian and Non-Caucasian Respondents who have Discussed Clinical Trial Participation with their Doctor, Nurse, or Research Personnel

Respondents were also asked to choose their primary reason for both participating in a clinical trial and declining participation in a clinical trial. The list of reasons for agreeing to participate and declining to participate was compiled from other studies looking at patients’ willingness to participate in clinical trials. Tables 9 and 10 show the frequencies of responses, with “To advance science

Table 9. Frequency of Survey Respondents' Primary Reasons for Accepting Participation in a Clinical Trial

If you decided to participate in an MS clinical trial, what would be your PRIMARY reason for participating? Please choose only one (1) answer.	Total
To advance science and medicine	23
To receive better medical care for my diagnosis	8
To help others with a similar diagnosis	7
Because current therapies for my diagnosis have failed	5
I would not participate in a clinical trial	3
Because my doctor, nurse, or research personnel recommended it	2
Because my spouse, family, or friends recommended it	0
To earn extra money	0
To receive free medication	0
Other	0
Total	48

Table 10. Frequency of Survey Respondents' Primary Reasons for Declining Participation in a Clinical Trial

If you decided to decline participation in a MS clinical trial, what would be your PRIMARY reason for declining? Please choose only one (1) answer.	Total
The risks are too great	21
I would accept participation in a clinical trial	8
It is too much of a time investment	7
I have a preference for a specific treatment	7
I do not want to feel like a guinea pig	2
I have transportation issues	1
I have other health problems	1
Other	1
I am not interested in the topic	0
I do not trust medical research	0
Total	48

and medicine” being the top reason why most respondents would choose to participate in a clinical trial, and “The risks are too great” being the top reason why most respondents would decline participation in a clinical trial. It is important

to note that there were no significant differences found between responses by race or ethnicity, or by sex, education level, income level or insurance type.

To further tease out how much influence some of these reasons might have on a patient's decision to participation in a clinical trial, respondents were asked to rank the degree of influence each of these reasons for accepting and declining participation would have on their decision-making process.

Respondents ranked the reasons in both Tables 9 and 10 as either "Strongly Influence (Level 4)", "Moderately Influence (Level 3)", "Little Influence (Level 2)", or "No Influence (Level 1)." For all of these reasons, no significant differences were found between the degree of influence for each reason by race or ethnicity (Table 11), sex (Table 12), or income level (Table 13). However, there were a few significant differences found between the degree of influence of particular participation reasons and education level and insurance type which are discussed in more detail below.

For most influences that would affect participation in a clinical trial, there were no significant differences found by education level except for the following two reasons patients said they would accept participation in a clinical trial: "To receive free medication" and "Because current therapies for my diagnosis have failed." A Kruskal-Wallis test revealed a statistically significant difference in the influence of receiving free medication on participation in a clinical trial across four different education levels (Less than Bachelor's Degree, n = 18; Bachelor's Degree, n = 11; Master's Degree, n = 10, Professional or Doctorate Degree, n =

Table 11. Degree of Influence on Participation in a Clinical Trial by Race or Ethnicity

Reason to Participate	U	z	p-value
To advance science and medicine	186.5	-0.473	0.636
To receive better medical care for my diagnosis	171.0	-0.872	0.383
To help others with a similar diagnosis	186.5	-0.467	0.640
Because current therapies have failed	182.5	-0.538	0.591
Because my doctor recommended it	177.5	-0.561	0.575
Because my family recommended it	201.0	-0.066	0.947
To earn extra money	202.0	-0.041	0.967
To receive free medication	188.0	-0.409	0.682
Reason to Not Participate	U	z	p-value
The risks are too great	158.5	-1.203	0.229
It is too much of a time investment	162.5	-1.071	0.284
I have a preference for a specific treatment	169.0	-0.881	0.378
I do not want to feel like a guinea pig	149.0	-1.485	0.138
I have transportation issues	170.0	-0.859	0.390
I have other health problems	140.0	-1.734	0.083
I am not interested in the topic	143.0	-1.656	0.098
I do not trust medical research	150.5	-1.473	0.141
Note: Race and Ethnicity categories combined into Caucasian versus Non-Caucasian categories due to small sample size. Mann-Whitney U test used to test differences between two independent groups (Caucasian and Non-Caucasian) on a continuous measure (Level 1 to Level 4 influence).			

9), χ^2 (3, n = 48) = 8.212, p = 0.042. The Bachelor's Degree and Professional or Doctorate Degree education level groups recorded a higher median score (Md = 2) than the other two education levels which had median values of one. To understand which groups were statistically significant from one another, Mann-Whitney U tests between pairs of groups were completed. Using the Bonferroni adjustment to take into account the number of comparisons done (three comparisons to analyze Bachelor's Degree versus all other education levels), a Mann-Whitney U test revealed a statistically significant difference in the influence receiving free medication has on participating in a clinical trial between patients

Table 12. Degree of Influence on Participation in a Clinical Trial by Sex

Reason to Participate	U	z	p-value
To advance science and medicine	153.5	-0.539	0.590
To receive better medical care for my diagnosis	170.5	-0.015	0.988
To help others with a similar diagnosis	136.5	-1.047	0.357
Because current therapies have failed	171.0	0.000	1.000
Because my doctor recommended it	130.0	-1.096	0.273
Because my family recommended it	139.0	-0.934	0.351
To earn extra money	151.0	-0.611	0.541
To receive free medication	149.5	-0.629	0.530
Reason to Not Participate	U	z	p-value
The risks are too great	135.0	-1.056	0.291
It is too much of a time investment	139.5	-0.904	0.366
I have a preference for a specific treatment	120.0	-1.439	0.150
I do not want to feel like a guinea pig	135.0	-1.088	0.276
I have transportation issues	142.5	-0.807	0.420
I have other health problems	147.0	-0.728	0.467
I am not interested in the topic	170.5	-0.015	0.988
I do not trust medical research	155.5	-0.479	0.632

Note: Mann-Whitney U test used to test differences between two independent groups (Male and Female) on a continuous measure (Level 1 to Level 4 influence).

Table 13. Degree of Influence on Participation in a Clinical Trial by Income Level

Reason to Participate	χ^2	df	p-value
To advance science and medicine	4.051	3	0.256
To receive better medical care for my diagnosis	1.152	3	0.764
To help others with a similar diagnosis	1.250	3	0.741
Because current therapies have failed	4.524	3	0.210
Because my doctor recommended it	0.541	3	0.910
Because my family recommended it	1.165	3	0.762
To earn extra money	0.943	3	0.815
To receive free medication	5.895	3	0.117
Reason to Not Participate	χ^2	df	p-value
The risks are too great	1.823	3	0.610
It is too much of a time investment	2.722	3	0.437
I have a preference for a specific treatment	2.335	3	0.506
I do not want to feel like a guinea pig	4.463	3	0.216
I have transportation issues	4.007	3	0.261
I have other health problems	3.299	3	0.348
I am not interested in the topic	3.309	3	0.346
I do not trust medical research	3.047	3	0.384

Note: Kruskal-Wallis test used to test differences between four independent groups (\$49,000 or less, \$50,000 to \$99,999, \$100,000 to \$149,999, and \$150,000 or more) on a continuous measure (Level 1 to Level 4 influence).

having a Bachelor's Degree (Md = 2, n = 48) and a Master's Degree (Md = 1, n = 48), $U = 20.0$, $z = -2.621$, $p = 0.009$, $r = 0.38$.⁸

A Kruskal-Wallis test revealed a statistically significant difference in the influence of failing current therapies on participation in a clinical trial across four different education levels (Less than Bachelor's Degree, n = 18; Bachelor's Degree, n = 11; Master's Degree, n = 10, Professional or Doctorate Degree, n = 9), $\chi^2(3, n = 48) = 8.876$, $p = 0.031$. The Master's Degree education level group recorded a higher median score (Md = 4) than the Bachelor's Degree and Professional or Doctorate Degree education levels which both recorded median values of 2, and the Less than Bachelor's Degree education level which recorded a median value of one. To understand which groups were statistically significant from each other, Mann-Whitney U tests between pairs of groups were completed. Using the Bonferroni adjustment to take into account the number of comparisons done (three comparisons to analyze Master's Degree versus all other education levels), a Mann-Whitney U test revealed a statistically significant difference in the influence failing current therapies has on participating in a clinical trial between patients having a Master's Degree (Md = 4, n = 48) and Less than a Bachelor's Degree (Md = 1, n = 48), $U = 32.5$, $z = -2.892$, $p = 0.004$, $r = 0.42$.⁹

For most influences that would affect participation in a clinical trial, there were also no significant differences found by insurance type, except for one

⁸ The guidelines proposed by (Cohen 1988) for interpreting effect size classifies 0.01 as a small effect, 0.06 as a medium effect, and 0.14 as a large effect.

⁹ The guidelines proposed by Cohen (1988) for interpreting effect size classifies 0.01 as a small effect, 0.06 as a medium effect, and 0.14 as a large effect.

reason patients said they would decline participation in a clinical trial: “I do not want to feel like a guinea pig.” A Kruskal-Wallis test revealed a statistically significant difference in the influence of feeling like a guinea pig on participation in a clinical trial across three different insurance types (Private, n = 38; Medicare, n = 8; Other, n = 2), $\chi^2(2, n = 48) = 6.859, p = 0.032$. The Other insurance type group recorded a higher median score (Md = 4) than the Private and Medicare insurance type groups which both recorded median values of one. To understand which groups were statistically significant from each other, follow up Mann-Whitney U tests between pairs of groups were completed. Using the Bonferroni adjustment to take into account the number of comparisons done (two comparisons to analyze Other insurance versus Private and Medicare), a Mann-Whitney U test revealed a statistically significant difference in the influence feeling like a guinea pig has on participating in a clinical trial between patients with Other insurance (Md = 4, n = 48) and patients with Medicare (Md = 1, n = 48), $U = 0.000, z = -2.372, p = 0.018, r = 0.42$.¹⁰

Semi-Structured Interviews

Compared with the electronic surveys, the semi-structured interviews allowed for a more open, unstructured and nuanced exploration of each patient’s opinion of clinical trials. A total of 11 patients from the BAMC MS Clinic who were currently participating or had recently participated in a clinical trial were interviewed for this study. These patients represent a variety of clinical trials

¹⁰ The guidelines proposed by Cohen (1988) for interpreting effect size classifies 0.01 as a small effect, 0.06 as a medium effect, and 0.14 as a large effect.

being conducted at BAMC, and also represent a wide, demographic spectrum. Table 14 shows the demographic information for the 11 interview participants. Most interview participants were female which does match the higher proportion of females who are diagnosed with MS. In addition, most interview participants were Caucasian, although attempts were made at over sampling non-Caucasian patients in order to understand if there are any differences in attitudes towards clinical trials by race and ethnicity. Age of interview participants ranged from 20s to 50s, while length of MS diagnosis ranged from a new diagnosis within the past year to a diagnosis over 11 years ago. Most of these patients have their own private insurance, but the ones who have either Medicare or no insurance at all were all patients who had been referred from the local community hospital, and specifically came to BAMC to participate in a clinical trial in lieu of having medical coverage.

Although it is difficult to quantify the degree of MS disability, these patients ranged from have very mild MS symptoms such that an outside observer would not be able to tell the patient had MS, to severe MS symptoms which require that patients are in a wheelchair with constant caregiver attention. In addition, 4 out of the 11 patients receive California State Disability Insurance. These 11 patients also represent a number of different trials being conducted at the BAMC MS Clinic ranging from a Phase I to a Phase III trial. These trials also range in study duration, experimental treatment type, and the presence or absence of a placebo arm.

Table 14. Demographics of Interview Participants

Demographic	Count	Percent
Sex		
Male	4	36%
Female	7	64%
Race/Ethnicity		
White	7	64%
Black	1	9%
Hispanic	3	27%
Age		
20-29	3	27%
30-39	4	36%
40-49	1	9%
50-59	3	27%
Length of Diagnosis		
1 year	1	9%
2 years	2	18%
5 years	2	18%
6 years	2	18%
7 years	2	18%
11 years	2	18%
Insurance*		
Private	9	82%
Medicare	1	9%
None	2	18%
Disability		
Yes	4	36%
No	7	64%
Study**		
Acorda (Phase I)	2	18%
Actelion (Phase II)	3	27%
Biogen (Phase II)	1	9%
Genzyme (Phase III)	1	9%
Opera (Phase II)	2	18%
Vitamin D	3	27%
*One patient had two types of insurance		
**One patient participated in two trials		

Primary Reasons to Participate in a Clinical Trial

Of key interest to this study was to elucidate the reason or reasons that patients decided to participate in the clinical trial they were currently participating in or had just finished participating in. Patients provided a spectrum of answers that ranged in influence level and that often weaved together with their journey exploring and experiencing their MS Identity. Before diving into specific reasons for participation in a trial and examining the context and details, patients were first asked to come up with a primary reason for participating in a trial before being able to add ancillary reasons. Most patients' primary reasons centered around two major themes, namely for "selfish" reasons and for the bigger picture contribution to science and medicine and other fellow MS patients. Each theme is explored in more detail below.

For "Selfish" Reasons

Interestingly, when asked as an open-ended question, the primary reason for participation in a clinical trial often centered on the admission that the patient participated for a "selfish" reason. Oftentimes the patient would explicitly state that it was a selfish reason, but helping science and medicine and other MS patients were beneficial side effects. For example, to advance science and medicine "...would never be my first reason because I'm entirely too selfish for that...So I really like that reason. It's just that I think most of us who actually...have a condition, it invents this sort of selfishness in you" (Christine Rogers). The "selfish" reason often met an immediate need that the patient had

depending on his or her particular situation. Those selfish reasons were related to the following topics: negative side effects of current MS medications, the desire to receive better medical care, the desire to receive free medication, future health prospects, and finally, pure survival.

A couple of patients decided to participate in their clinical trial because currently approved MS medications had negative side effects which they could no longer tolerate. One patient, Jaime, was on Avonex for almost one year and experienced severe flu-like symptoms every week which were often bad enough to leave him in bed for the 24 hours immediately following the injection. After enduring this medication for a year, his doctor finally recommended switching to a different medication, Rebif, but it too was an injection that could also cause flu-like symptoms and the frequency of the injection would have to increase from once per week to three times per week. The difference was that Rebif was supposed to be a more potent medication to help better prevent the increasing MS symptoms that Jaime was experiencing at the time. This alternative was not ideal to Jaime so there was hesitation to make the switch. His doctor, who was at the local community hospital, then recommended a clinical trial at BAMC to Jaime in case he wanted to consider it. However the risk of the trial was that he could be randomized to one of two groups: 1) taking Rebif, like he was originally considering outside of the study, or 2) the experimental medication which was an IV infusion for a 5-day cycle during Year 1, and a 3-day cycle during Year 2.

Ultimately, Jaime decided to participate in the trial as an alternative to his options outside of trial participation.

Another patient, Christine, was on Copaxone for one year but every injection was extremely painful and left necrotic areas of skin at her injection sites on her legs and stomach. Christine was seeing a neurologist at BAMC for her regular MS medical care at the time, and at the end of the year, her neurologist said she had given the Copaxone a good trial run and agreed that it was not working for her. Similar to Jaime, Christine's only other alternatives were other self-injections which she refused to endure ever again. It was at this point that her neurologist introduced a clinical trial to her that was testing a new oral medication for MS (there were no currently approved oral medications for MS at the time). For her, it was an easy decision to go into the clinical trial because when comparing the approved MS injections to the oral pills, "It's like one was hellacious and seriously impacting my life and the other is like nothing" (Christine Rogers). For both Jaime and Christine, neither the currently approved MS medications that they were on, nor the other medications that were available, were a preferable alternative. After being introduced to their respective clinical trials, both decided that being in the trial provided them with a medication, or in Jaime's case a chance at a medication, that they could better tolerate both physically and mentally.

Another "selfish" reason that some patients claimed was their primary reason for participation in a trial was related to the desire to receive better

medical care for their condition. This was true for Carol who admittedly did not take very good care of her health once she was diagnosed with MS in 2009. At the time, she herself was a caregiver to both her grandmother and her mother, so she did not go on any MS medication for almost two and half years. When MS symptoms bothered her, she would get a several day course of IV steroids to help speed her recovery time, but the frequency and severity of the attacks increased. Finally her neurologist at the local community hospital said she could no longer go without an MS medication because her MRIs showed many new lesions in the brain and spinal cord. “I remember after he had said that to me, it was just the way he looked at me, but I went down to the beach that night by myself and I just lost it. And it was like, okay, the realization that I've been putting it off for so long and now I really need to do something about it and take care of my health” (Carol Heuser). The same neurologist then suggested that she might consider a clinical trial that did not have a placebo arm, and would guarantee her an MS treatment, independent of which treatment arm she might be randomized to. Consequently, she chose to participate in the clinical trial. “I think the first motivator was the fact that I would have a treatment team...I would have protocols to stick to...and just the fact that I wasn't having to be one hundred percent in charge of my own treatment” (Carol Heuser). Because of her past disregard for her own medical care early in her diagnosis, Carol primarily wanted structured care for her MS. The trial provided a treatment team that she felt was watching multiple aspects of her disease and was vigilant for any drug adverse

effects. It also provided a schedule to follow according to the trial protocol so it was clear to her and through continuous staff communication, where she needed to be and when.

Another primary reason some patients cited as their reason for participation was the benefit of receiving free medication through the trial. For Lydia, this was her primary reason, even though she had private insurance that would cover a large portion of the drug costs. Because the trial was two years, that was two years she didn't have to fight with her insurance company about covering the costs, or paying whatever the monthly copay would be. MS medications are a significant financial burden to many MS patients, and even the coverage of insurance plans does little to lessen the financial burden. In addition, the burden of proof for starting a medication is often on the patient and his or her neurologist as many of the MS medications have restrictions on availability. Most MS medications are only approved for the RRMS form of MS, and even if you are a patient with RRMS, you might also need to prove that you failed your previous MS medication before the insurance company can approve you for another MS medication. Oftentimes this "proof" involves months of waiting while MS attacks occur and increased disability progression develops. So for Lydia, when asked what her primary reason for participating in her clinical trial, she replied, "Honestly? The free, not having to pay for my medication. That's the big, that was the selling point pretty much is, okay I'm going to be helping

somebody else, but I don't have to pay for my medication because I don't know if my insurance was going to cover it completely" (Lydia Ochoa).

Still other patients expressed their primary "selfish" reason for participating in a clinical trial being related to their future health prospects. Bruce explained that his primary reason for participating in a clinical trial was to help secure his future with his wife and a family. "I want to have as normal of a life as possible with kids. So I don't want to be the dad in the wheelchair on the sidelines of the soccer game or the ballet recital. I just want to have a normal life. I don't want my wife to have to take care of me" (Bruce Eldridge). So if a positive result can come out of the trial he is currently participating in, that would help contribute to improving the prospects for his health in the future and his participation would be worth the effort. Similarly, Edward participated in his clinical trial because if he is going to deal with MS for the next 50-60 years, then anything he can do now to help in the next 50-60 years will directly benefit him. "It's a little selfish to be that way. But I find it pragmatic and proactive" (Edward Foster). If his participation in the trial can help make an impact on the way treatment is provided for MS patients, then it will have a direct impact to him. Even though both Bruce and Edward have such mild forms of MS that an outside observer would not be able to tell they had MS, both were fully aware of the unpredictable nature of the disease and saw the clinical trial as a way to help improve their future health projections.

Finally, in some of the MS patients who have more severe MS symptoms and disability progression, the main “selfish” reason for participating in a clinical trial was for immediate MS symptom relief and survival. For Faye, who was the most severely affected patient that was interviewed, was in a wheelchair, and required a caregiver, participating in a clinical trial was a potential way for her to try to actually see improvements in her current disease state. When Faye was first referred to BAMC by her neurologist at the local community hospital to participate in a clinical trial, she did not qualify for the trial because there were specific requirements patients had to meet in order to be included. Specifically, she needed to walk unassisted (without a cane, crutch, or human assistance) for a length of 100 feet and she was unable to meet this requirement. Faye kept in touch with me for over a year checking in to see if there were any new clinical trials she could qualify for. Finally, she was able to enroll in a clinical trial and even enrolled in a second clinical trial immediately after the first one ended. When asked if she could identify what her primary reason was for participating in these clinical trials, she said,

The main reason is for me to be able to play with my grandbaby. And be able to take her to the park and be able to help her ride her first bike. I mean, she is what I'm fighting for because that's my baby. And all she's known Nana as being in the [wheel] chair. I want to be able to have my independence back because I have a caregiver now and I just don't like anybody taking care of me. I want to be able to do everything by myself. I've always been an independent lady, always. And right now is just hard to be independent. This is not me at all. [Faye Smith]

Faye has a continued interest in clinical trials because her regular medical care cannot offer her anything except maintenance of her condition. In her opinion, she doesn't see the need to go to a regular doctor anyways. They just bring her in every six months and tell her to keep taking her injections. The clinical trials offered her a way to actually do something about her diagnosis. "I don't want to say I'm to the point where I'm desperate but kinda. Because I just don't like living like this. It's just tough. It's tough. I can't drive anymore. I can't do anything. It's terrible. I have to do something so that's what I did right? I signed up" (Faye Smith).

As we learned in the introduction of this paper, Isabelle expressed her reason for participation in a clinical trial as pure survival. Since her diagnosis in 2008, despite being on Rebif, Isabelle continued to have MS attacks and accumulated more disability at a faster and faster rate. She tried going to occupational therapy to re-train herself to do activities of daily living with appropriate modifications, and tried physical therapy to learn how to use crutches when she was having difficulty walking on her own. Through this physical decline, she was no longer able to work and lost her medical insurance. She also went through a divorce and found herself extremely depressed with no hope. Her physical health continued to decline and she was finally given a prescription by her neurologist to get a wheelchair. She remembers the moment when she wanted to consider a clinical trial. "I had a prescription in my hands to get a wheelchair. But I refused it. I was just too stubborn and that was the

crossing point for me saying okay I'm going to get on some kind of study" (Isabelle Carbajal). She explained that somehow she pulled herself out of the despair and wanted to fight for her survival. She was even willing to risk her life for the clinical trial because she didn't feel like there was anything to live for anymore. Isabelle thought at least the clinical trial was a way for her to try something since she did not have any insurance.

For Science and Medicine and "Fellow MS Sufferers"

Another group of patients stated that their primary reasons for participating in a clinical trial were to advance science and medicine and help others with MS. Some explained that if you have a condition like MS, you have an obligation to try to make a contribution to understanding the disease, making progress in treatment, and finding a cure. Patients also talked about an almost higher-order connection to other MS patients and the need to reduce suffering, lessen the confusion around MS diagnosis, lessen the confusion about medication choices, and diminish the guilt they had about patients with greater disability than themselves. According to the patients, all of this could be accomplished through participation in clinical trials.

Several MS patients talked about the idea of participating in a clinical trial to be somewhat obligatory considering the nature of the disease and the need for better treatments and a cure. Carol discussed her feeling of obligation as being part of a larger community with a responsibility to help where she can. "I think that's really important, especially if you're somebody without any medical

conditions, then you have a different view on things. If you have medical conditions that bug you, you're like, what can we do about it, especially if you're running out of treatment options" (Carol Heuser). Similarly, Bruce saw his role participating in a clinical trial as an obligation to help contribute to pushing the research forward.

I think one of the big factors was, I'm a big believer in data, so if I'm going to be selfish and say no. Like, oh it's too much hassle for me to go every 3 months or whatever, if there's 100 other people like me or just 20 other people like me that also say no and have the same thought process, there's going to be no progress in the industry. So it's like, well, I have to do my part and contribute to the, even if I'm not, even if I'm just a blip out of 100 people, I have to do, I have to do what I think's right. [Bruce Eldridge]

Other MS patients recognized that they had the ability to help fellow MS patients, just like past MS patients had done to help them. If MS patients had not participated in the clinical trials of the past, then the explosion of MS medication options would have never happened and diagnosis would still be extremely slow with high misdiagnosis rates. Mary admitted that previous research and past MS patients helped get her an extremely fast MS diagnosis. Before this breakthrough, doctors would have dismissed her symptoms of tingling fingers for months, perhaps even years, depending on how quickly her MS symptoms developed without treatment. If she could provide someone with the same assistance, then she was willing to participate. Jaime also wanted to provide better medication options for fellow MS patients through his participation in a clinical trial, although at first his motivation was to help get better treatment options for himself. His painful experience with Avonex injections inspired him to

want to help others to not go through what he had to go through. He also spoke of his participation in a trial as a kind of obligation. “It [to advance science and medicine] was basically one of the main reasons because you have to be able to find the cure you know? Regardless you have to be able to help out to find the cure” (Jaime Alarcon).

These sentiments were echoed by all of the MS clinical trial patients. Many wanted to contribute to something bigger than themselves. When asked why she wanted to participate in a clinical trial, Sarah Tomas explained, “Just to do something good. Something good for the cause. Something bigger than myself, you know?” Edward Foster relayed a similar thought:

I think this is probably one of the other really big parts of the reason why I decided, was that it gives me some sort of impact on MS. Like I'm having an impact on it. I don't know how huge or wonderful or great it is. But the decision to participate, I think, the biggest motivator was the feeling that I was having an impact on something that's part of me. [Edward Foster]

For Lydia Ochoa, “You know, if it's going to help somebody else that's even better so they don't have to go through the same thing I went through. And you know, maybe it will help to get them diagnosed a little sooner. Anything. Okay, you know, do it. Yes, you're going to find a better cure? Okay, let's go.” For Faye Smith, “You know...I also want to help others that are suffering, the MS sufferers. If I could do something in research that's going to really work for me that could also help somebody else, then I'm down for that.”

When describing additional reasons for participating in a clinical trial, including advance science and medicine and help others with a similar diagnosis,

oftentimes the explanation bordered on guilt the patient felt for other MS patients who might have more severe symptoms or a lack of opportunities for treatment. Bruce felt that helping others through participating in a clinical trial was necessary considering how many MS patients have more difficult MS symptoms and disability.

That can be a good reason [to help others]. You know especially when you start googling and researching and see how many people have it worse than you. Or you see people in the 1990s when treatment was a lot less prevalent and people didn't know. They don't find out they have MS until they're 75 and by then it's too late you know. They've already had their disability. So yeah, I think if you can be involved to prevent the same type of thing from happening to other folks [Bruce Eldridge]

Likewise, Carol Heuser expressed her concern for other MS patients who have it worse than her: "But since I have the disease and I think it's the people who are very debilitated by it that sort of get me in the gut, in the heart more. Because it, especially if you haven't done something and you've gotten a disease, it's like, kind of unfair."

Jaime also expressed concern about his fellow MS patients experiencing worse MS symptoms and drug side effects than he experienced on Avonex.

I know what it is to go through every week taking a shot and it's really stressful. And then from what I heard, there's people who get even worse symptoms than what I got. So if that was really hard for me to take, just the headache, I could just imagine other people having worse symptoms than that you know? [Jaime Alarcon]

Finally, Isabelle specifically shared her feelings of guilt with me regarding those MS patients who have not been able to experience the kind of turn around she has had participating in her clinical trial.

I can never forget how far along I've come even in some of the hardest days, it's like, you know, the people that I know of who do have MS, I feel guilty when I see them, like the person I was going to refer to you, cuz I know that there is much better stuff out there now that I've been on the study and just thinking about where I've been. [Isabelle Carbajal]

Additional Reasons to Participate in a Clinical Trial

After patients were asked identify their primary reason for participating in a clinical trial, they were asked to discuss any additional reasons that might influence their participation in a trial based on a similar list of reasons offered in the electronic survey (see Table 9). As shown in Table 15, more interview participants said “To help others with a similar diagnosis” would influence them more often when deciding to participate in a clinical trial. For survey participants, “To advance science and medicine” was the most frequent response chosen. Although there seems to be a contradiction in reasons for participating in a trial between survey and interview respondents, the interview participants often spoke about advancing science and medicine and helping others with a similar diagnosis interchangeably. So it could be that these two reasons are two sides of the same coin. All four of the non-Caucasian interview participants said “To receive better medical care for my diagnosis” would not influence their participation in a clinical trial. For the remainder of the reasons below, there were no discernable patterns seen in the responses by race or ethnicity of the patient.

Table 15. Interview Participants' Primary Reasons for Accepting Participation in a Clinical Trial

If you decided to participate in an MS clinical trial, would the following reasons influence your decision?	Yes	Partially	No
To advance science and medicine	4	2	4
To help others with a similar diagnosis	10	0	1
To receive better medical care for my diagnosis	3	0	8
Because my doctor recommended it	3	2	6
To earn extra money	0	0	11
To receive free medication	4	3	4
Because current therapies for my diagnosis have failed	2	2	7

Reasons to Not Participate in a Clinical Trial

Similar to the reasons above for participating in a trial, interview participants were then asked to consider if they did decline participation in a trial, how much some of the reasons listed in the electronic survey (see Table 10) would influence their decision to not participate. As shown in Table 16, more interview participants thought that the reason, “The risks are too great,” would have a substantial influence on their decision to decline trial participation. This matches with the most frequent reason chosen by the survey participants. When looking at responses by race and ethnicity, the influence of time and transportation on clinical trial declination rates did not reveal any differences between Caucasians and non-Caucasians. However, all three interview participants who answered “No” to whether the reason “The risks are too great” would influence their declination were non-Caucasian (the fourth non-Caucasian participant answered “Yes”). In addition, the one interview participant who

answered “Yes” to whether the reason “I do not want to feel like a guinea pig” would influence her decision was Caucasian. Otherwise, a majority of the interview participants, 10 out of 11, said that feeling like a guinea pig would not influence their decision to decline a clinical trial. Similarly, the one interview participant who answered “Yes” to “I do not trust medical research” was also Caucasian. Again, the majority of interview participants said that not trusting medical research would not have an influence on their decision to decline a clinical trial.

Table 16. Interview Participants’ Primary Reasons for Declining Participation in a Clinical Trial

If you decided to decline participation in a MS clinical trial, would the following reasons influence your decision?	Yes	Partially	No
It is too much of a time investment	3	1	7
I have transportation issues	2	1	8
The risks are too great	8	0	3
I do not want to feel like a guinea pig	1	0	10
I do not trust medical research	1	0	10

Attitudes Towards Clinical Research

Most of the interview participants had been participating in their respective clinical trials for at least one year and some had been participating in the same clinical trial for over four years. So most were very well-versed in how a clinical trial protocol works and most felt comfortable with where they were in their current clinical trial. So not surprisingly, since most were still participating in a clinical trial and were comfortable with its progress, most patients expressed overall positive feelings towards research but for slightly different reasons and

their personal experience colored their particular opinions. Many of the patients had actually seen improvements in their health which could have contributed to the positive attitudes. Still others, even when experiencing significant side effects, had a positive opinion about research because the study still offered them a superior treatment to what was currently approved.

For example, Isabelle, who had a prescription for a wheelchair in her hand before she signed up for a clinical trial and can now walk moderate distances without a cane or crutches, is ecstatic about clinical research. She described her experience with a clinical trial to be a life-changer, not only medically speaking, but as a whole person. Because she regained her ability to walk again, her whole life turned around. Before, her confidence was low and she was depressed about her condition. When she had to use her crutches in public places, everyone would ignore her and bump into her. She attributes her improvement to the experimental drug in the clinical trial. Being in the trial allowed her to walk which, in turn, allowed her to do things she hadn't been able to do in years. Over four years into her clinical trial, she is now happily remarried with a supportive husband who comes with her to all of her clinical trial visits, and she runs her own graphic design business which is so successful that she has to turn down work. Regarding her participation in her trial and her positive outcome, "It's like winning the lottery. The difference is night and day. It's not a one hundred percent cure, but oh my God, you get your life back" (Isabelle Carbajal).

For the patient currently in a wheelchair, Faye, participating in both of her clinical trials has given her hope that she hasn't had in a long time. Most people take things for granted like being able to shower by yourself, being able to drive a car, or just being able to walk in a park or through a mall. But she has seen little improvements here and there since her clinical trial participation. She also appreciates when her family and friends notice the improvements. She joked that she didn't know if it was the first clinical trial or her current clinical trial that is making her better, but either way she is extremely happy about it. Her participation in the trials and the small improvements have also helped to improve her mood.

Jaime looked to his clinical trial as a chance to stop his self-injections with horrible flu-like symptoms if he could just get randomized to the experimental study drug. He was extremely excited when he was, in fact, randomized to receive the experimental study drug. This meant that he no longer had to take any self-injections, but did have to endure a 5-day infusion cycle followed by a 3-day infusion cycle one year later. Unfortunately for Jaime, his very first infusion turned out to be very difficult because he had an allergic reaction to one of the pre-medications (which, ironically, is given to the patient prior to the experimental study drug to prevent reactions) with a large body rash. It made him extremely uncomfortable for the first day but it was easily treated with Benadryl. Within two days of starting the infusion cycle, his MS symptoms of vision loss, body numbness, and difficulty walking went away completely. Jaime has since

completed his first 5-day infusion cycle and the 3-day infusion cycle and has not had to take any MS medications since the 3-day infusion cycle, which was approximately three years ago. Jaime has also not experienced any MS attacks since before starting on the experimental study drug. So he is also very impressed with clinical research and has an extremely positive attitude towards it, despite the initial allergic reaction.

Another patient, Christine, has positive feelings towards research despite experiencing a moderate adverse effect from taking the experimental medication. The main mechanism of action of the experimental oral medication she is on, which is similar to most FDA-approved medications for MS, decreases the body's ability to fight infections because it reduces the number of white blood cells available to defend from bacterial or viral intruders. The theory is that by reducing the number of white blood cells, the body is less likely to attack its own nerve cells in the CNS which in turn, reduces the number of MS attacks and CNS lesions a patient might otherwise accumulate. However, it has the added side effect of an increased risk for many infections. Two years into taking her experimental medication, Christine developed vaginal herpes simplex virus-1 (HSV-1). HSV-1 is typically the virus responsible for cold sores but it has been shown to also cause genital herpes. Unfortunately this is something that Christine will have to manage for the rest of her life, in addition to her MS, and it requires her to take another daily medication to prevent outbreaks. Despite this, the study is still worth participating in. For her, being in the trial is bigger than

anything money can provide. “It’s beyond worth it to me. My life changed taking one little pill instead of all those shots” (Christine Rogers).

Other patients had a change in opinion after deciding to participate in their clinical trials. For Sarah, her initial opinion of clinical trials was that they were dangerous and pharmaceutical companies do not have a patient’s best interests in mind. She had also received a negative message about clinical research from media sources. However, now that she has been participating in her clinical trial for over four years, her opinion has changed to a more positive view of research since her personal experience in her clinical trial has been positive. She also feels that the study isn’t as risky or dangerous as she first thought when considering participation. For Edward, he went into his clinical trial with negative connotations from the public feeding his perceptions, although at the same time he didn’t think he was going to be guinea pig. But his experience in his clinical trial for a year and a half has been extremely positive and he did not expect the level of care that he received under the trial. “I’m not saying that I expected it to be bad, I just wasn’t expecting it to be as phenomenal as it’s been to be honest... I did not expect the level of humanity to be involved in the research process” (Edward Foster). He was immediately impressed with the clinical trial team’s concern for him as a person and patient rather than a subject. Everyone started conversations with him almost like they were catching up with a friend and wanted to know what was new in his life and how he was doing instead of going straight to the clinical testing or obtaining data from him.

Other positive attitudes towards research included the benefit of having the clinical research staff stay on top of the scheduling the appointments, sending reminders, and checking that patients remember to take their study drug. The goal of advancing science and helping others with MS also contributed to positive patient outlooks on clinical trials. One patient, Ronald, even expressed his opinion of research as being fun. He said he would participate in clinical trials anytime, all the time.

One out of the 11 interview participants, Mary, expressed an uneasy feeling towards clinical research despite participating in a clinical trial because she was very uncomfortable with the idea of being randomized to a placebo instead of an actual medication. The clinical trial she is participating in provides her with an FDA-approved medication while being randomized to a high or low-dose of Vitamin D. Thus, she was very comfortable participating in her clinical trial since there was no placebo arm. Even so, research in general still made her comfortable because of the uncertainty that comes with potentially being randomized to a placebo arm. She would resent the fact that she participated in a placebo-controlled study if something happened to her while she was on placebo. The unknown element of other trials served to maintain her uneasy attitude towards research even though she admits she has had a positive experience participating in her current clinical trial for the past year and a half.

Comparing Medical Care with Research Care

All interview participants were also asked to compare the medical care they received for their MS with the research care they were experiencing in their respective clinical trials. Only one patient, Sarah, found research care to be more difficult than medical care, mostly because of how many appointments were required of her for the clinical trial she is participating in. Although her visits are once every three months, her visits are two-day ordeals which require a minimum of 10 appointments to be made for her at many different departments throughout the hospital. Sarah walks with a cane so mobility is difficult and oftentimes walking between different departments on different floors or on the opposite side of the building can be a significant challenge. Hospital parking is also a major obstacle. Some of the appointments she has to make are at a satellite campus about 20 minutes away from the main hospital. Even though she knows what to expect from the clinical trial since she has been participating in it for over four years, it is still a pain. When asked whether the all of the inconvenience was worth being in the trial, there was a long pause before she answered, "I think so" (Sarah Tomas). When she first started the trial she would have said yes right away, but now the trial is not new and exciting anymore.

In spite of Sarah's response, a majority of the participants, 10 out of 11, agreed that there were significant differences between their medical care and research care, and most of them attributed those differences to a similar observation. Medical care was described as generally decent, but that there

were limits to what current medical care could offer for an MS patient. The medical care focuses on trying to figure out what the underlying problem is at first, so much of the initial time spent with a neurologist is trying to confirm the diagnosis of MS while ruling out other neurological conditions. Once the diagnosis is confirmed, however, there is not much current medical care can offer except the FDA-approved medications and monitoring of MS symptoms every few months and doing an MRI of the brain and spinal cord every year. For Christine, medical care is like “using already established practices to treat already established diseases, illnesses. Whereas with research there’s the promise that it’s going to be eradicated all together” (Christine Rogers). So despite the fact that with research there is no guarantee of successful outcomes and a chance of unknown side effects, it is that very fact that research is figuring it out as it goes along, so there is more promise that a new breakthrough could be made.

Medical care seemed to do well with providing a diagnosis, deciding which medication to take, and making patients comfortable for the long road of chronic disease maintenance. Research care seemed to offer another level of care that medical care could not provide. By participating in their respective clinical trials, the patients came to see research as being more interested in figuring out exactly what MS is, how a patient gets it, why certain medicines work better with some patients and not others, or trying to find better medications and ways to treat MS. With research there are more eyes watching an individual patient and

the research staff pays more attention and asks more questions to understand how the patient is doing. For Bruce, in medical care no one is watching or double-checking that he takes his medications properly or closely watching all of his minor MS symptoms. With research care, the staff takes care of all the details for the patient so there is little to worry about. Additionally, as a medical patient, you might be one out of hundreds of other patients, whereas as a research patient, you are often only one out of four patients in that clinical trial at that site.

Jaime much preferred his research care to his previous medical care. He often felt that with his medical care, they saw him every three to six months just to check in but they didn't really worry about him until he walked in the clinic door again. With his research care, even though his visits were every three months, he was required to do blood tests and phone calls every month, so he felt that the research staff were keeping a much closer watch over him and his MS symptoms. He also liked that fact that when his research doctor told him he was doing well, he actually believed it since it was based on all of the data they were collecting on him. This is in opposition to his medical care where he felt that his medical doctor didn't have as much data to be able to say how he was doing with any certainty.

Although Edward didn't have much medical care experience for MS outside of his clinical trial, with other specialists he has seen, the focus is more on trying to figure out what the problem is, but not how to solve that problem

once it is identified. In his research experience, Edward felt like the focus was more on him as a person rather than a patient. For him, being in research “feels very self-determinate. I feel like I’m very much in control of my health or my path even though I’m in a clinical trial” (Edward Foster). He explained that despite all of the circumscribed procedures and protocols of the trial, ultimately it was his decision to choose to participate in order to help improve his health and possibly the health of other MS patients. He feels that all of his decisions about his health are his and are completely within his control. Edward explained that he feels like he is planting some seeds and working on a garden, the effects of which cannot be seen right now, but at some point in the future it will be extremely rewarding.

Although most patients had a very positive view of research care and an average opinion of medical care, a couple patients had a positive view of research care combined with a negative view of medical care. For Isabelle, her experience at the local community hospital made her feel like just a number. She also had to meet with so many different doctors, so there was no consistency in her care. “When the doctor would see me for the first time they would show up with this thing [her medical chart] and I knew they didn't read it and didn't know what I was seeing them for” (Isabelle Carbajal). She admitted that her experience was probably due to the fact that it was a large, regional community hospital that was overwhelmed with patients like her. But it still made her feel like a lost number in a sea of thousands of other patients. She felt like her medical care for her MS was not satisfactory, so when she was given the

prescription for her wheelchair, she refused to fill it and wanted to look to clinical trials instead. That's when she told her neurologist that she was going to take things into her own hands and raise money to do an MS stem cell trial abroad. "You have to be your own advocate one hundred percent because you won't get the care you need" (Isabelle Carbajal). It wasn't until she mentioned her intention to her neurologist that he told her about the clinical trial at BAMC, a mere 30 minutes from her house rather than a plane ride away. Isabelle much preferred the research care because she wanted more than just maintenance for her MS diagnosis; she wanted to get better.

Ronald also had a more negative view of medical research. For him, medical research represented the unknown because every time he went in for an appointment, his care or treatment might change, or his neurologist might inform him of a new affliction. He remembers leaving many of his medical care visits in tears because of the adjustments he had to make to accept his disease. The uncertainty, especially immediately after his MS diagnosis was scary. With research care, he always knew what to expect and it was very clearly laid out for him. There were absolutely no surprises and all trial activities were set. Nothing about his research experience was ever upsetting like his medical care visits sometimes were.

Guinea Pig

It is difficult to talk about medical research and clinical trials without talking about the concept of guinea pigs. The idea of being a guinea pig in a clinical trial

is an image that looms large in the public consciousness when it comes to medical research. Oftentimes the term has a negative connotation implying experimentation on unknowing people without their knowledge or consent of what the true risks and consequences of their participation really are.

Interestingly, 5 out of the 11 interview participants independently mentioned the term “guinea pig” before being officially asked about it as part of the semi-structured interview. One additional patient independently referred to a test monkey and used the term in a similar vein as the guinea pig users. Thus, at least half of the interview participants were familiar with and freely associated the term “guinea pig” with their participation in a clinical trial without being prompted. When all interview participants were asked how much the idea of being a guinea pig would influence them to decline participation in a clinical trial, 10 out of 11 patients vehemently responded “No.” Despite most agreeing that this would not influence them in declining a clinical trial, the respondents were split on whether they thought they were guinea pigs or not. About half of the patients said they were not guinea pigs and would not decline a trial, while the other half said they were guinea pigs and still would not decline a trial.

For patients who did not feel like they were guinea pigs, there were a variety of explanations and caveats provided. Patients do not feel like a guinea pig:

- Because you always feel like a person and patient, not a test subject
- Because you do not feel demeaned or dehumanized

- If you chose this and know what your reasons are for participating
- Because study risks are so low
- Even though you are a guinea pig
- But would be if you were in a placebo study

Many interview participants repeated the idea that they did not feel like a guinea pig because they never felt like they were a test subject where the research staff was just collecting data in a standardized, sterile fashion. It always seemed that the research staff genuinely cared about them and their wellbeing as a person. Even when a hand dexterity test or an audio cognitive test needed to be administered, patients never felt dehumanized or demeaned and understood that this data was necessary in order to determine whether the study drug was making any significant clinical improvements for MS patients. “I think the whole term guinea pig or lab rat...is to feel dehumanized, to feel like you're not a person... I've never once not felt like a patient in any aspect” (Edward Foster).

One patient, Carol, explained why she didn't feel like a guinea pig and, in fact, embraces the title in jest when she explains to friends that her treatment for MS involves being a guinea pig at BAMC. The main reason she doesn't feel like a guinea pig is because she chose to participate in the trial and she knows exactly what her reasons are for agreeing to participate in the trial. In a sense, she is taking ownership of her decision to be in the trial and it is that agency that helps her rise above the status of guinea pig. “I feel like it's not a guinea pig kind

of thing. I'm choosing to do this and I know what my reasons are for doing it too. It's not like I'm just going out there and saying, hey go ahead and stick me [draw blood] for the fun of it. There's reasons and objectives behind it" (Carol Heuser).

Some of the patients did not feel like guinea pigs because their risk perception of the clinical trial they were participating in was low. For Bruce, his trial involved taking a currently approved MS medication, Copaxone, which has already been on the market for almost 20 years. In addition to taking the Copaxone, he is being randomized to a high or low-dose of Vitamin D. Although he doesn't know which dose he has been randomized to, Bruce was already taking Vitamin D as a supplement before the trial so this was something that he wanted to continue taking and the chance of having an adverse reaction to Vitamin D is extremely low. Although he didn't speculate, it does raise the question about whether he would feel like a guinea pig if he considered the risk of a clinical trial to be higher than his current experience. This sentiment was explicitly expressed by one of the patients who did feel like a guinea and is described in more detail below.

Echoing Bruce's response, Lydia agreed that she didn't feel like a guinea pig in the clinical trial she was participating in which is the same one as Bruce with the Vitamin D. But she would feel differently if she were participating in a trial where there was a chance that she might get randomized to placebo. It is that unknown factor that would make her a guinea pig in that case. So because she feels that there are fewer unknowns with the Vitamin D trial, she does not

currently feel like a guinea pig. She did admit though that being a guinea pig is a good thing because there is no other way to figure out whether a new medication works before giving it to the general public. So even though it does have a negative connotation, it serves a positive purpose and will benefit someone one day.

Another patient made a distinction between feeling like a guinea pig and being a guinea pig. "I never thought I was a guinea pig although I am. But I never felt like a guinea pig... If I felt like a guinea pig, I probably wouldn't have done it" (Sarah Tomas). Sarah explained that she never felt like a guinea pig because she was always treated humanely and has had a very positive experience throughout the four years she has been on her clinical trial. Although for her, the fact remains that she is a guinea pig since she is helping test out an experimental medication. So there is a component of her participation that requires that she submit herself, like a guinea pig, to testing of a new drug.

For patients who did feel like they were guinea pigs, there were also a variety of explanations provided. Surprisingly, even though these patients did feel like they were guinea pigs, this feeling had zero influence on their hypothetical declination of a clinical. Patients do feel like a guinea pig:

- But it is worth it to help with MS
- But that's what it takes to do research
- But you benefit from being in the study
- But you have a good handler and a deluxe wheel

This group of patients did not have any hesitation in admitting and acknowledging that they were, in fact, guinea pigs for participating in their respective clinical trials. Faye admitted, “I feel like a guinea pig but...It doesn't bother me. I don't care about that. I want to be a guinea pig in order to help somebody else deal with this illness because if I can be a guinea pig and help others with this, then I've done my job” (Faye Smith). She spoke of her role almost as if she were doing her duty to help someone else deal with the illness like she has to. She also approaches this role with no fear. “I'm not scared to be a guinea pig. I'm not scared to be a test dummy” (Faye Smith). In a sense, her sacrifice playing the role of guinea pig is worth it to her if it can help someone else in the future dealing with MS.

Jaime also freely admitted his guinea pig status and explained that it was the literal truth. People participating in clinical trials are literally guinea pigs because experimental drugs are being tested on human beings. However, doing testing on humans is what it takes to make progress in medical research to find better treatments, and hopefully a cure from MS. Research cannot test new drugs in animals forever. At some point if humans need to take the medication, the medication needs to be tested in humans. In a way, Jaime sees his guinea pig status as a logical outcome of the process new pharmaceutical agents are required to go through to gain FDA approval. Being a guinea pig is what it takes to do research.

Another patient who fully embraces her status as a guinea pig also freely posts that status on her Facebook page. There is no escaping being a guinea pig when signing up for a clinical trial. However, according to Isabelle, her guinea pig status does not go uncompensated. She feels that despite being a guinea pig, she reaps the benefits of participating in the clinical trial. Submitting herself to a clinical trial as a guinea pig is a minor effort compared with the many positive outcomes she experienced as a result of her participation. From Isabelle's perspective, in return for her service to science, she was able to go from wheelchair to walking without assistance. This would be a significant benefit from being a guinea pig, but a benefit that can never be expected or guaranteed.

Christine seemed to have the ability to be more calculating about becoming a guinea pig. She doesn't entirely like the fact that she is a guinea pig, but she weighed many factors that ultimately resulted in her participating in a clinical trial. One factor was that her clinical trial was a Phase II trial, so she already knew that this was not the first time the study medication was being looked at in humans and there was safety data available from the Phase I trial that put her more at ease. Additionally, she saw the level of care and extreme precautions required as part of the trial to monitor and prepare for any possible side effects in patients. There was also a level of expertise that was apparent in the research staff that was taking care of her throughout the trial. All of these factors combined to help solidify her decision to be part of the clinical trial, but

she felt secure in the fact that she would be well taken care of and watched over by expert staff. “Of course I'm a guinea pig, but I'm a guinea pig in pretty good hands so I'm alright. It's a nice cage. It's got the deluxe wheel from the deluxe pet store. I'm good” (Christine Rogers).

BAMC Mystique

Interview participants were asked whether recommendations from their doctor would make them more likely to participate in a clinical trial or if opinions from friends and family members would sway them to make one decision over another. Generally, most participants revealed that neither recommendations from their doctor nor opinions from their family and friends would significantly influence their decision to participate in a trial. Most patients appreciated the fact that when the clinical trial was first introduced to them by their neurologist, it was not recommended per se. Instead, patients described it as a free offering, explained in detail, but with no pressure to choose it. It was explained in a matter-of-fact way and left for the patient to decide whether or not they felt it was a good fit. Additionally, most participants admitted that any dissent from family and friends about participating in a trial would not be tolerated or influence them to choose differently. Those who did experience resistance from family and friends said it was merely their choice to make and their family would ultimately learn to accept it, which all of them did.

Surprisingly, these two reasons for participating in a trial did not seem to be significant factors when these MS patients were making their decisions about

entering a trial. However, an additional factor, which was not explicitly asked about in the semi-structured interview, did come up independently in 8 out of the 11 interviews. This factor was related to the perception that patients had of the hospital the trial was being conducted at, BAMC. Patients often expressed their fascination with and respect for BAMC's name, reputation, and high status compared with other regional hospitals. BAMC's mystique came up so often in the interviews that it is likely a bigger influence on patients deciding to participate in a clinical trial than originally accounted for. The status of BAMC is a factor that may play a role in potential clinical trial participants' decision-making process.

For Jaime, he came to BAMC specifically to start his clinical trial since he was being seen at the local community hospital for his regular medical care. What helped him feel more comfortable moving to BAMC and participating in a clinical trial was the fact that BAMC had a good reputation. So even though he was personally unfamiliar with the doctors that were going to take care of him, he knew he at least could trust the BAMC name.

The place makes a lot of difference because people can trust this place you know, trust the hospital itself just by the name, the reputation that it has. That can make a lot of difference. It does make a lot of difference. Especially because you can't trust the doctors at the beginning, you don't know what you're getting yourself into so you have to be secure about something. [Jaime Alarcon]

Regarding the unknown risks inherent to participating in a clinical trial, Jaime felt secure in the fact that even if something bad happened to him as the result of the trial, BAMC would be able to take care of him. Jaime had complete

trust in the BAMC name. “You can't really distrust BAMC. You know, it's a well-known hospital. You can't really say, Oh they're going to mess up my health and stuff. And if they do, they'll find something to be able to get you back on your feet” (Jaime Alarcon).

Similar to Jaime, Edward felt that BAMC's name and reputation for conducting medical research and being a teaching hospital put him at ease when he decided to participate in his clinical trial. “BAMC does a lot of research in general, but you know, medically, BAMC is well known to be a great place for medical research, a teaching hospital, things like that so I feel like any concerns they might have are very much allayed by the name of the institution” (Edward Foster).

In Isabelle's descriptions of BAMC, her language was much more extreme and seemed to have a significant influence on her decision to participate in a clinical trial. Keeping in mind that Isabelle had an amazing recovery of her walking ability that she attributes to the experimental medication she was taking in her clinical trial, she compares the care she received at her local community hospital with the care she received at BAMC on the clinical trial. “I mean I went through a lot of stuff that was very helpful at [the local community hospital] but it was almost like I graduated and now I'm in the BAMC program. I kind of see regular care as down here and the study and BAMC up here and if I was to back here [down] it would be like eating my vomit” (Isabelle Carbajal). Isabelle also remembers that when she was a child, her brother had gone to BAMC to get care

for a mysterious skin disease that they were able to treat and cure. She speculates that from that initial encounter, even though it was a long time ago, she must have formulated an opinion about the kind of hospital BAMC was. “I must have identified BAMC as being this great hospital with doctors in the sky or something” (Isabelle Carbajal).

Other patients seem to proclaim BAMC’s status as a foregone conclusion. Oftentimes patients, like Mary Conners, would just use the phrase, “Oh, well it’s BAMC,” as if the phrase itself was self-explanatory. When pressed to further explain what this statement meant, most had difficulty articulating the reason that BAMC had this status in their minds. For Carol Heuser, “This is BAMC that I’m going into, so it wasn’t like some little Podunk medical center in the middle of nowhere. It’s BAMC.” Christine Rogers explained that “BAMC is more deluxe.” Independent of each patient’s explanation, the commonality between all patients was that BAMC was held in high regard because of its reputation as a good medical hospital, a good research hospital, and a good teaching hospital which imbues an almost mystical quality to it, such that patients were put at ease when deciding to participate in a clinical trial conducted by BAMC. BAMC was perhaps even given collective biomedical authority by these MS patients, as well as the general public, who had heard of and accepted the reputation of the medical center as an additional guarantee of safety and security.

Trust and Distrust

As discussed previously, there are many studies that show minority groups distrust clinical research and the medical industry in general. This was definitely a theme that was worth exploring in more detail with the interview participants. Unfortunately, because patients who had declined a clinical trial were not easily accessible, the perspectives on trust in research from those that did participate in a clinical trial may be skewed toward a lack of distrust. By not interviewing those who declined participation in a trial, this study may be missing perspectives from those people who would agree that they distrust medical research and that it heavily influenced them to decline to participate. However, even though all of the interview participants had agreed to participate in a clinical trial, the patients may have a sense of whether or not there was a feeling of distrust that they were familiar with from their family or community.

With this limitation in mind, all 11 interview participants were asked about whether or not distrust in medical research would influence them to decline a clinical trial. Only 1 out of 11 said that distrust would influence him to decline a clinical trial. Interestingly, that one patient was Bruce who is Caucasian, not non-Caucasian as the medical literature would suggest. Bruce's reasons for distrusting research had to do with distrusting pharmaceutical companies and their motives. Ultimately, pharmaceutical companies are for-profit companies that have an obligation to their stakeholders. They have to report to Wall Street and send out their quarterly earnings reports. Bruce admits that they are trying

to make the world a better place, and he is all for a capitalistic society where the free market is the judge of success and failure, but inherently this design means that studies results will be biased. For example, even for the clinical trial he is participating in, if the study doesn't show a positive result for using Copaxone and Vitamin D to reduce MS relapse rates, the pharmaceutical company is not likely to report the negative findings to the public. Pharmaceutical companies will strategize ways to increase profit, perhaps by pushing sales which sometimes cause physicians to overprescribe medications unnecessarily, or they might be doing a clinical trial on a new drug because their patent on another drug is running out and they need to identify another revenue source.

This distrust in pharmaceutical companies described by Bruce was the only form of distrust that was uncovered during the interviews with all participants. Like Bruce, three additional patients brought up the distrust in pharmaceutical companies independently: Christine, Sarah, and Faye. Unlike Bruce, this distrust would not influence their decision to participate in a clinical trial. For Christine, she is extremely suspicious of the profit motive of pharmaceutical companies and how those without insurance are unable to benefit from great medical discoveries because the medications are so expensive and out of reach. Despite her distrust, she does differentiate between distrust for the pharmaceutical company itself and distrust for research. According to her, it is understandable to distrust the pharmaceutical companies, but not to distrust the research. In fact, it is good to have a healthy distrust for

the system into which the research is placed, but not the research itself and the positive intent behind it which is to find better treatments and a cure for MS.

Christine feels that being in a needful situation, like having a disease like MS and needing to find a better treatment for it through a clinical trial, would significantly increase someone's ability to trust research. Someone might consider that coercion, but the trial is also offering help to a patient who needs it.

A patient who fell into the category of her needful situation increasing her ability to trust research was Sarah. Sarah does not trust pharmaceutical companies because all they care about is money. These companies just want to keep patients sick because that is how they make their money. If they find a cure, then their profit stream disappears. She believes that pharmaceutical companies are not really trying to cure anything. Given this extreme distrust, Sarah had to struggle with her decision to participate in her clinical trial. Her sister and family were against her participating in the trial at first too since they all had the same opinion about pharmaceutical companies as Sarah. Although Sarah Tomas felt like she was "...going to fall right into their web," she also needed an MS treatment that didn't have as many side effects as the FDA-approved medications currently available. Ultimately she came to the decision that she needed to participate in the clinical trial for herself and for the greater good of all the MS patients who would come behind her.

Like Sarah, Faye thinks that pharmaceutical companies are trying to figure out what causes MS and how people get it and how to treat it. However, she is

very negative about the prospect of pharmaceutical companies finding a cure, because if they do, they will go out of business. Why would they find a cure if they will lose money and jobs? Politics is a powerful force that works behind the scenes, so although she doesn't think that pharmaceutical companies will find a cure, she does think that they will continue to find different treatments for MS. Even if the pharmaceutical company doesn't cure her, at least they can keep her going. Given this less ambitious motive of finding better treatments instead of a cure, Faye does trust that they're doing it for the right reasons and that they are not going to harm you intentionally. So Faye trusts pharmaceutical companies in this regard. She also finds it incomprehensible when other MS patients have told her that they were scared to get their blood drawn, even as part of regular medical care, because they feared that their blood was being sold and distributed without their knowledge and that some researcher might be using their DNA to make a clone. Compared with Bruce, Christine, and Sarah, Faye seems to have a more tempered distrust of pharmaceutical companies that ends at their motives for finding a cure. Otherwise, they are trying to at least find better treatments and right now, that is good enough for Faye.

Out of the four patients who expressed distrust for pharmaceutical companies, three were Caucasian, Bruce, Christine, and Sarah, and one was African American, Faye. Although this is a small sample of interview participants, this result does not mirror studies suggesting that it should be non-Caucasian populations who have a higher distrust for medical research. For the four non-

Caucasian patients who did participate in the interviews, it could have been a quirk of their individuality that three out of four had no issues of trust with medical research. In a way, they were self-selected for by the nature of participating in a clinical trial. Non-Caucasian patients who did distrust research would likely not have participated in a clinical trial in the first place. In order to fully explore this idea at the end of the interview, all patients, both Caucasian and non-Caucasian, were specifically asked if they were familiar with the idea of medical distrust in minority populations and if they agreed or not based on their own experience and knowledge. They were also asked to share their thoughts about underrepresentation of minority groups in clinical trials.

Out of the four non-Caucasian interview participants, two were not familiar with the idea that there is medical distrust among minority populations and had never heard anyone mention it before. For Isabelle who identifies as Latina, she was surprised to hear that there were many studies showing that minorities were more likely to distrust medical research than Caucasians. In her experience, her family did not know much about clinical trials but they have been amazed to see the progress that she has made since starting her trial. In fact they are extremely happy for her because she has come so far in the past four years. She doesn't remember any resistance or negativity when she was first considering the trial. Ultimately, her family was supportive of her decision. Unfortunately, lack of knowledge about clinical trials may be one factor influencing trial participation rates that the family experienced personally. For Isabelle, it was only after she

educated herself about clinical trials and demanded to participate in one, that her neurologist gave her information about how to access a local clinical trial. If she had never made this demand, she might still be unaware that clinical trials are an option. Prior to her experience, Isabelle says her mother would have participated in a clinical trial for dementia if they had just known about it at the time. Although distrust was not an issue for Isabelle, her experience may point to how a lack of knowledge and access to clinical trials and provider bias might affect participation rates.

Faye, who identifies as African American, is the second non-Caucasian participant who had never heard that minorities are more likely to distrust research than Caucasians. Like Isabelle, Faye was also surprised by this statistic and she attempted to postulate reasons why this might be the case. She wondered if the individuals who didn't trust research might not trust anyone in general, so it might be less about a distrust of research specifically and more about having a distrusting disposition. She also wondered if lower minority participation rates in clinical trials might be related to logistical reasons, like transportation issues, instead of trust issues. These factors, she reasoned, should not be restricted to a particular race or ethnicity. Ultimately, Faye did not think that more distrust in non-Caucasian patients made any sense because if anyone, regardless of race or ethnicity, was in her situation, they would make the same decision to participate in a clinical trial.

The remaining two non-Caucasian interview participants, Jaime and Lydia who both identify as Latino, had heard of minority distrust of medical research, although it did not personally affect their decision to participate in a clinical trial. Jaime's explanation for the distrust and subsequent underrepresentation in clinical trials was that many minority groups do not like to go to the doctor and are extremely conservative. His sense was that people will go to the doctor when necessary, but will not do more than is necessary for their care, which would likely include participating in a clinical trial. Despite these characteristics, Jaime admitted that the problem of underrepresentation of minorities in clinical trials probably has less to do with being a minority and more to do with individual preference. In his view, even a high proportion of those in the majority (Caucasians) do not take the opportunity to participate in clinical trials.

Lydia has also heard of distrust of medical research in minority communities and has also had personal experience dealing with the consequences of this distrust. Many years ago, her grandmother was diagnosed with breast cancer but it had gone into remission twice. The third time, unfortunately, it came back and had spread to her liver. During her treatment, Lydia's grandfather already had a difficult time dealing with the fact that his wife had breast cancer. So when Lydia's grandmother was offered a chance to participate in a clinical trial for breast cancer, Lydia's grandfather would not allow her to participate. According to Lydia Ochoa, "he was a very old school Mexican man" who was having trouble accepting his wife's illness, so the idea of

participating in a clinical trial that might help other people he didn't know or care about was not first on his list. He was stubborn and if he didn't directly know who it was going to help, then it wasn't his problem. At the time, her grandmother was okay with not participating, but later expressed regret because she missed an opportunity to potentially help others. During the recruitment for the breast cancer trial, Lydia remembers her mother making a comment that there were more Caucasians than minorities being recruited into the trial and that they needed to make more of an effort to recruit Latinos since they are the minor majority. Lydia's explanation was that this distrust, at least from the Mexican community, might be due to a lack of information about medical research. Information that is provided needs to be translated carefully because it could have a negative effect on their decision to participate in a clinical trial. She suggests not focusing so much on the risks and presenting the benefits first.

For the remaining seven Caucasian interview participants, most (six out of seven) were not familiar with the idea that minority groups were more likely to distrust medical research and were under represented in clinical trials. Several of them offered up some potential reasons why this might be the case and most of the posited reasons had to do with logistical barriers that would create an illusion of distrust and measurable underrepresentation in clinical trial. Sarah wondered if the restrictive inclusion criteria listed in clinical trial protocols makes it difficult for many patients to qualify to participate. The protocols themselves could be inadvertently excluding particular populations of patients. Edward

suggested that decreased minority access to health care might contribute to the lower representation of minority groups in clinical trials. Time restraints and lack of knowledge about trials could also be factors. Carol speculated that location and proximity to a large medical center would limit access to studies and care. Bruce wondered if the lower rates of minority participation were only a reflection of the lower incidence rates of MS in minority populations.

The one Caucasian interview participant who was familiar with the idea that minorities are more likely to distrust medical research was Christine. Christine explains that minorities, but African Americans in particular, have every reason to distrust the medical system. It is a system that has excluded them, and when it does include them, provides them with improper medical care. They have a higher rate of mortality, a high rate of disease, and a lower rate of care. They often get lower care from the same doctor as their Caucasian counterpart. For Christine, the motive behind the distrust is completely understandable. Christine admits that it was a privilege for her to even have the choice to participate in a clinical trial.

Risk

As seen in both the electronic survey and interview responses, the concept of risk plays an important role in determining whether someone will decide to participate in a clinical trial. As discussed earlier, the interview participants were asked whether or not the following reason would influence their declination of clinical trial participation: “The risks are too great.” A majority of

interview participants, 8 out of 11, said that this reason would definitely influence their decision to decline a trial if they determined that the risks were too great. Although there was only one planned question about risk in the semi-structured interview, the concept of risk was a theme thread woven throughout all interviews in some way.

Placebo Risk

When patients say that they think the risks are too great to participate, the assumption is that the risks of the experimental drug, which is not FDA-approved and has only been tested in a small number of other humans, are the risks that patients are referring to. Although the risks of the experimental drug are not negligible, in these interviews it became clear that the most important risk a patient could take was the risk of NOT getting the experimental drug. Many MS clinical trial designs involve the possibility of being randomized to a placebo arm where a patient would not be receiving the experimental drug. It is this scenario, where a patient is randomized to receive placebo instead of the experimental drug, which is considered to be the ultimate risk. The 11 interview participants represent six different clinical trials being conducted at BAMC. Those six clinical trials are listed in Table 17 below.

The design of each trial is unique because some, like the Acorda Phase I trial, involve randomization to four different doses of the study drug or a placebo; thus, there was an 80% chance that a patient could be randomized to one of the study drug doses. This trial, which is rare for MS clinical trials, allowed patients

Table 17. Current MS Clinical Trials Being Conducted at BAMC

Trial	Phase	Drug	Study Design	Primary Side Effects	Trial Length
Acorda	I	Single IV infusion	Randomized to study drug or placebo (80% chance of study drug)	Allergic reaction, anaphylaxis	90 days
Actelion	II	Daily oral pill	Randomized to study drug or placebo for 6 months; then all pts on study drug (75% chance of study drug)	Cardiac issues, macular edema, increased risk of infection, liver problems, shortness of breath	4 years+
Biogen	II	IV infusion Q4W + Avonex	Randomized to study drug or placebo + Avonex (80% chance of study drug)	Allergic reaction, anaphylaxis	2 years + extension
Genzyme	III	IV infusion, yearly for 2 years or Rebif	Randomized to study drug or Rebif (50% chance of study drug)	Allergic reaction, anaphylaxis, immune thrombocytopenia, kidney disease, thyroid disorders, increased cancer risk	4 years+
Opera	III	IV infusion Q6M + Rebif	Randomized to either study drug or Rebif (50% chance of study drug)	Allergic reaction, anaphylaxis	2 years + extension
Vitamin D	N/A	Daily oral pill + Copaxone	Randomized to low or high dose study drug + Copaxone (50% chance high dose study drug)	Hypercalcemia	2 years

Adapted from: National Multiple Sclerosis Society, 2014, Treating MS: Medications, <http://www.nationalmssociety.org/Treating-MS/Medications>, accessed December 16, 2014.

to be on their current, FDA-approved MS medication in addition to being randomized to either the study drug or placebo. Thus, the risk of being randomized to the placebo arm in this trial may be minimized since MS patients do not need to go without their normal MS treatment for the duration of the trial.

In the Actelion Phase II study, patients could be randomized to one of three different doses of the study drug or a placebo for a 6-month period. After this period, all trial patients, no matter what arm they were initially randomized to, would be assigned to take the study drug for the remainder of the trial. With this trial, there is a potential that a patient could be completely off of all MS medications for a six-month period if they were randomized to the placebo arm. The Biogen Phase II trial required all patients to take the FDA-approved MS medication, Avonex, in addition to being randomized to the study drug or placebo. Even if a patient was randomized to placebo, they were still guaranteed to be taking Avonex. The Genzyme Phase III trial required that patients be randomized to either the study drug or Rebif, an FDA-approved MS medication. There was a chance for patients who were randomized to receive only Rebif to switch over to receive the study drug after spending a minimum of two years in the trial. The Opera Phase III trial was designed to randomize patients to either the study drug or Rebif. The Vitamin D trial is in a slightly different category since the study drug, Vitamin D, is not considered an experimental drug, but the study design still involved randomizing patients to receive either low or high-dose

Vitamin D with the added requirement of taking Avonex, another FDA-approved MS medication.

Understanding the risk that a placebo poses requires consideration of what might cause harm to an MS patient. The biggest harm would be an increase in MS symptoms, having an MS attack, and/or experiencing disability progression. Having an MS attack while in a clinical trial can be difficult to deal with because there are many different factors at play and potential causes. One potential cause is the fact that the patient may have been randomized to the placebo arm, so if they are not taking any MS medications, they may be more likely to experience an MS attack. Another cause could be that the patient was randomized to receive the study drug, but it turns out that it is not as effective as other FDA-approved medications at reducing the relapse rate in MS patients. Another potential cause could be related to the nature of MS itself. For example, the patient may have been randomized to the study drug treatment arm, and the study drug could be just as effective as other FDA-approved medications, if not more effective, but the patient could still have an MS attack.

Remember that MS is extremely unpredictable in the frequency, duration, and severity of attacks. Even for FDA-approved MS medications, none of them are a cure, and all of them only reduce the rate of MS attacks in patients. Given that each individual MS patient will experience MS symptoms and attacks differently from the next, it can be almost impossible to determine whether a particular MS attack would have been due to the natural course of disease, the

ineffectiveness of a particular medication, or because the patient is actually on placebo. This is why MS clinical trials are so important because the only way to understand if an experimental medication has any effect on lowering the relapse rate is by gathering aggregate data and seeing if there are any differences in the actual relapse rate of MS patients in the study drug group compared with the placebo group (or currently approved MS medications). Unfortunately, parsing out the individual causation of MS attacks is impossible given our current understanding of the disease.

Despite this unknown, the risk of receiving placebo instead of an actual MS medication, whether it is approved by the FDA or not, still seems to be a very real concern for MS patients. It seems that the unpredictable nature of MS symptoms and attacks makes patients extremely wary of not being on any MS medication. Mary explains that she would not participate in a research study if she did not know whether she was on placebo or the study drug. First, she would blame herself and resent the fact that she chose to participate in a study if something happened to her, like an MS attack. Then, she might even blame the trial even though she is fully aware of the concept of randomization in clinical trials and the risk she incurred. If Mary experienced a relapse or other side effect while in the trial, it would be hard for her to justify participating in the trial at the expense of her own health. Even if she had the “good luck” to be randomized to the study drug, she wouldn’t know and neither would the research team or her doctors. “That would freak me out” (Mary Connors). Mary felt secure

participating in the Vitamin D clinical trial since she was only being randomized to a low or high-dose vitamin in addition to taking an FDA-approved MS medication.

Although most of the interview participants agreed that medical research and clinical trials are necessary in order to make advances in science and the treatment of MS, it is difficult to weigh that necessity with the potential of going without treatment for a certain amount of time. Similar to Mary, Carol speculated that if the clinical trial she was participating in, the Opera trial, had a placebo arm, she would have been less likely to participate. If there was a chance that she could get randomized to be on placebo, that would definitely be a risk to her since her neurologist had told her she needed to be on some type of MS medication. For her, not being on an MS medication would not be worth participating in a trial, even with the noble goal of trying to help MS patients find better treatments. The Opera trial offered Carol a way to participate in a clinical trial without the risk of being randomized to a placebo arm. Although she doesn't know which medication she is taking, Carol can be assured that she is actually on an MS medication, either Rebif or the study drug. Edward, who is also participating in the Opera trial, agreed that if there was a chance that he would be on placebo and he would have to go untreated for a certain amount of time, it would make him reconsider participation in the trial. Lydia even relates the risk of being on placebo as equivalent to being a guinea pig.

Risk of FDA-Approved MS Medications

Another surprising discovery that came out of the interviews was how some patients considered the risk of current FDA-approved MS medications to be the same if not worse than the experimental medications being tested in a clinical trial. The risk of current FDA-approved medications was often related to the number of side effects associated with taking these drugs. Oftentimes, even for patients who never participate in the medical research world, treating their MS is a choice between enduring different side effects. Although there are now 12 FDA-approved MS medications, all of which only slow the progression of MS (there is currently no cure for MS), most have a significant side effect profile that individual patients need to weigh against their tolerance for risk of MS disease progression. Table 18 lists the current FDA-approved MS medications and a brief side effect profile for each.

Patients who are risk-adverse tend to gravitate towards the MS medications that have been approved the longest. These medications have the longest track record, so in theory, more should be known about these drugs and their side effects than the most recently approved medications. Betaseron, Avonex, Copaxone, and Rebif are often referred to as platform MS therapy, or first-line MS therapy, because they have been around the longest, and are the most conservative MS medications available in terms of side effects. These medications are often used on patients in whom MS was diagnosed quickly (so they have little existing disease burden) and have little disease activity. If

Table 18. Current FDA Approved MS Medications

Brand Name (Chemical Name)	Administration	Frequency	Side Effects	Approval Year
Betaseron (Interferon beta 1b)	Self-injection, subcutaneous*	Every other day	Flu-like symptoms, injection site reactions or skin necrosis, depression, allergic reaction, liver problems	1993
Avonex (Interferon beta 1a)	Self-injection, intramuscular**	1x/week	Flu-like symptoms, depression, allergic reaction, liver problems, decrease in white blood cells, red blood cells and platelets	1996
Copaxone (Glatiramer acetate)	Self-injection, subcutaneous*	1x/day	Injection site reactions, hives, tremor, unusual tiredness or weakness, weight gain, post injection anxiety attack with flushing, chest tightness, heart palpitations, and difficulty breathing	1996
Novantrone (Mitoxantrone)	Intravenous*** infusion	Every 3 months	Cardiotoxicity, increase risk of acute myelogenous leukemia, nausea, hair loss, menstrual disorders in females, fever or chills, lower back or side pain, painful or difficult urination, swelling of feet or legs, black tarry stools	2000
Rebif (Interferon beta 1a)	Self-injection, subcutaneous*	3x/week	Flu-like symptoms, injection site reactions, depression, allergic reactions, liver problems, decrease in white blood cells, red blood cells and platelets	2002
Tysabri (Natalizumab)	Intravenous*** infusion	Every 4 weeks	Progressive multifocal leukoencephalopathy, liver damage, allergic reactions, anaphylaxis, increased risk for	2006

Brand Name (Chemical Name)	Administration	Frequency	Side Effects	Approval Year
			infections	
Extavia (Interferon beta 1b)	Self-injection, subcutaneous*	Every other day	Flu-like symptoms, injection site reactions and skin necrosis, depression, liver problems, allergic reactions, thyroid problems, decrease in white blood cells, red blood cells and platelets	2009
Gilenya (Fingolimod)	Oral	1x/day	Cardiac issues, macular edema, increased risk of infection, liver problems, shortness of breath	2010
Aubagio (Teriflunomide)	Oral	1x/day	Liver damage, significant birth defects if used during pregnancy, peripheral neuropathy, acute kidney failure, high levels of potassium, severe skin reactions, hair thinning	2012
Tecfidera (Dimethyl fumarate)	Oral	2x/day	Allergic reactions, anaphylaxis, angioedema (swelling under skin usually in throat and tongue), low white blood cell count, flushing, diarrhea, nausea, upper abdominal pain (one case of PML)	2013
Plegridy (Peginterferon beta-1a)	Self-injection, subcutaneous*	Every 2 weeks	Flu-like symptoms, allergic reactions, injection site reactions, cardiac problems, anemia, low white blood cell count, thyroid problems, seizures	2014
Lemtrada (Alemtuzumab)	Intravenous*** infusion	5-day cycle, Year 1 3-day cycle, Year 2	Allergic reaction, anaphylaxis, immune thrombocytopenia, kidney disease, thyroid disorders, increased cancer risk	2014

Brand Name (Chemical Name)	Administration	Frequency	Side Effects	Approval Year
*Subcutaneous = injected just under the skin **Intramuscular = injected directly into the muscle ***Intravenous = infused directly into the vein Flu-like symptoms = fatigue, chills, fever, muscle aches, and sweating Injection site reactions = swelling, redness, discoloration, and pain Depression = sadness, anxiety, loss of interest in daily activities, irritability, low self-esteem, guilt, poor concentration, indecisiveness, confusion, and eating and sleep disturbances Adapted from: National Multiple Sclerosis Society 2014.				

patients experience an increase in the frequency of MS attacks or they have accumulated a greater disease burden over time, usually they need to consider moving to different MS medications that might be more effective. Some of the more recently approved MS medications, like Gilenya and Tysabri, fall into that category of second-line MS therapy. These medications might be more aggressive in treating MS, but they usually also come with more dangerous side effects, some of which were not realized until after FDA approval.

Gilenya, for example, was approved by the FDA for public use in 2010. It was approved with the understanding that it caused patients to experience a slowed heart rate immediately after taking the first dose. Thus, prescribing instructions required that neurologists observe all patients for at least six hours after receiving their first dose of Gilenya. Unfortunately, in December 2011, an MS patient who received Gilenya died within 24 hours of receiving the first dose (Food and Drug Administration 2011). A review of all reported safety data that year revealed that ten more deaths had been reported in the European Union from apparent cardiovascular or unknown origin. Ultimately, it was determined that Gilenya's contribution to all of these deaths was unclear, but the potential

relationship between Gilenya and the patient deaths could not be ruled out. As a result, the FDA issued new prescribing guidance for Gilenya which requires six hour observation with continuous electrocardiogram, blood pressure, and heart rate monitoring, and extended cardiac monitoring for up to 24 hours in patients who have pre-existing cardiac conditions (Food and Drug Administration 2012).

Tysabri, originally approved by the FDA in November 2004, is another example. In February 2005, the drug was pulled off the market because three patients developed progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection fatal in about 20% of cases (Kappos, et al. 2011). It wasn't until June 2006 that Tysabri was re-approved by the FDA for use in MS but only through a risk minimization plan that all patients receiving Tysabri are required to register in. The plan provides close monitoring for the occurrence of PML and other opportunistic infections. Tysabri continues to be used today despite the risk of PML. Over time, the risk of developing PML while on Tysabri has been better understood. A patient's risk of developing PML increases the longer they have been on Tysabri, especially after 2 years, if the patient tests positive for the John Cunningham (JC) virus, and if the patient has previously been on any immunosuppressant medication (Food and Drug Administration 2010).

It may not be such a surprise that MS patients might consider FDA-approved MS medications to be risky, if not riskier than some of the medications being tested in clinical trials. Even just making decisions about normal medical

care for MS can be a difficult choice for patients because their choice depends on how much risk they are willing to shoulder, how tolerable the method of administration is (can they do self-injections three times a week?), how severe their MS symptoms are, and, of course, what their insurance companies are willing to cover. Despite not being approved by the FDA, MS experimental medications being studied in clinical trials usually have some kind of information about the safety of the medication and its efficacy to date. This information is built upon numerous animal studies required to better understand how the drug works and how safe it is before administration to human subjects. Phase I clinical trials provide the first safety information about the experimental drug in humans, while Phase II and III studies further refine data about both safety and efficacy. The most current safety and efficacy data is made available to potential clinical trial participants so they can make informed decisions.

Given the current treatment options available to MS patients, it was intriguing to discover that experimental medications in clinical trials were given just as much consideration as FDA-approved medications by many of the interview participants. In fact for Mary, who seems to be the most risk-averse patient out of the 11 interview participants, she would not even consider taking some of the FDA-approved MS medications. It is too much of a risk because they have only been on the market for a few years. “Even my mom was like, ‘They have all these pills now.’ But even those are almost too new for my comfort...they've already gone through the trials and they've already been tested

and they're approved but for me I'm like, it's only been out two years. I don't know if I'm comfortable" (Mary Connors). One of the reasons she likes her clinical trial so much is that she is on an FDA-approved medication, Copaxone, that was approved almost 20 years ago, and she has to take a low or high-dose Vitamin D pill. For her, this is as low risk as she can get for a clinical trial and for her regular MS treatment.

Sarah was all too familiar with Tysabri being pulled off of the market in 2005. She was just about to start her Tysabri infusions as recommended by her neurologist, but the day after her insurance approved the medication, it was taken off the market due to PML risk. So Sarah decided to go on Rebif and remained on it for four years and endured flu-like symptoms three times a week. The side effects were awful for her, but she was stable on Rebif and had no MS attacks. She remained on Rebif until her body started developing antibodies to it in 2009, so she needed to find a different drug that her body would not reject. At this point she had moved her medical care to BAMC and they suggested Tysabri. She went through the process of getting insurance approval, but something stopped her from getting that first infusion. Sarah remembers keeping track of the number of PML cases which seemed to grow by the day. It was at that point that her neurologist recommended the Actelion clinical trial to her and she was immediately intrigued. At the time there were no FDA-approved oral medications for MS, so this seemed like a great alternative to the Rebif injections her body was rejecting and the high risk Tysabri carried which Sarah was not quite willing

to accept. When asked about her current tolerance of MS medications now, Sarah explained that she would not try any of the currently approved oral MS medications but might reconsider taking Tysabri. However, if she tested positive for the JC virus which increases your risk of developing PML, she would not start Tysabri. It is important to note that JC virus is a common infection that is found in approximately 50-90% of healthy adults but there are often no associated symptoms (Bellizzi, et al. 2013).

The JC virus factor is a common concern for MS patients considering Tysabri for treatment. Most MS patients, even if they are not taking Tysabri, are aware of the PML risk associated with it and how testing positive for JC virus increases that risk. Faye admitted that she was considering going on Tysabri before she was able to qualify for participation in a clinical trial. She had even had the blood test and found out that she did have the JC virus. Her neurologist was trying to explain the risk statistics to her, but she wasn't convinced even though she apparently had a greater chance of dying in a car accident than dying from PML. Ultimately, she remained on Avonex for almost 9 years and then switched to Rebif a few months before entering her clinical trial in 2013.

Understanding how MS patients conceptualize risk requires taking a comprehensive look at the treatment options available to them for regular medical treatment and then comparing them to the risk profiles of experimental MS medications. Many times, patients chose to enter clinical trials rather than deal with the FDA-approved medications available to them. As discussed

previously, both Jaime and Christine had experienced unbearable side effects related to their FDA-approved medications. Jaime had to endure severe flu-like symptoms every week that left him bed ridden for 24 hours after each injection, while Christine found her injections to be extremely painful and sometimes caused skin necrosis at the injections sites. One thing is clear: comparing the side effect profiles of the current FDA-approved medications with those from the experimental medications in clinical trials requires significant effort and deliberation no matter how risk-averse or risk-seeking a patient is. It seems that many patients considered FDA-approved medications to be risky, if not riskier than some of the clinical trial options.

Risk Perception of Current Clinical Trial

When asked to rank the risk level of their clinical trial, all 11 interview participants rated their clinical trial as low risk. Even though it would be difficult to objectively rank which of the trials was more risky than the others, it is obvious that all the clinical trials listed in Table 14 do not have the same risk level. The Vitamin D trial for example is the lowest risk because it involves the administration of an FDA-approved MS medication combined with low or high dose Vitamin D. Some participants gave a general risk level (low) while others placed the risk level on a scale of one to ten, with one being the least risk and ten being the highest risk they could think of. When using this scale, none of the patients ranked their clinical trial over a score of three.

For the three patients interviewed participating in the Vitamin D trial, Mary, Lydia, and Bruce, all considered this trial to be extremely low risk because the experimental drug was Vitamin D combined with a first-line MS medication, Copaxone, approved by the FDA almost 20 years ago. Mary always thought of the Vitamin D study as the least intrusive way to conduct a trial since she was going to go on Copaxone regardless of her participation in the trial, and she was going to take Vitamin D supplements which are often recommended to MS patients by neurologists in normal medical care. The trial mirrored what she was going to do during her medical care anyway, so she reasoned that a researcher might as well collect data during this process in order to try and get information out of it that could help future MS patients. For Bruce, the only risk he mentioned for this trial was related to confidentiality. His biggest concern was someone finding out at work that 1) he has MS, and 2) he is participating in a clinical trial. He is very aware of the potential for workplace discrimination if coworkers or supervisors were made aware of either situation. As a CRC, I was always careful to try and schedule Bruce's trial appointments as early in the morning or late in the afternoon as possible to minimize the amount of time he had to ask off of work without raising any suspicions.

Both Ronald and Faye participated in the Acorda trial, which was a Phase I, first in human trial looking at a new medication that has the potential to actually repair damaged nerve cells in the CNS. The repair of nerve cells in MS is something that none of the currently FDA-approved medications do and is

considered the “holy grail” of new MS medications. Despite this experimental drug only being tested in animals previously, both patients ranked this trial as low risk. Ronald did not consider it to be risky after discussing the trial with the lead neurologist who put him at ease. He did admit that he thought about the unknown risks, but did not dwell on this. However, he specifically omitted this information when discussing it with his wife so she didn’t dwell or stress over the risks. When asked if anything about the Acorda trial concerned her, Faye Smith said, “No. Nothing. I’m a ride or die chick. I’m gonna do whatever I’ve gotta do.”

After the Acorda trial, Faye also participated in the Biogen trial, a Phase II trial, also looking at a potential nerve repair medication combined with an FDA-approved medication, Avonex. She ranked this study a two or three out of ten and thought it was not a very dangerous study and in fact hoped that she was getting the study drug. When prompted, it did not concern her that the study drug was not yet approved and was experimental. She reasoned that all drugs had to be experimental drugs at one point, and there would be no way for them to get approved if they weren’t being studied first.

The three participants in the Actelion study, Isabelle, Christine, and Sarah, all rated this study as low risk. Isabelle explained that she was so intent on qualifying for this study and receiving the experimental drug that she could not remember any specific risk concerns when she first entered the trial; however, she understood enough about clinical trials and unknown risk to be willing to die over her participation if there were any unpredictable side effects. She does

remember that BAMC did do a good job at informing her about the study phases and her rights as a clinical trial participant, so she felt confident that she was going to be taken care of in the trial. This was a theme that both Christine and Sarah echoed. Christine took comfort in the study because of how meticulous the protocol was for monitoring side effects and collecting data. For example, her blood pressure had to be taken from a blood pressure machine that required annual calibration (to be reported to the pharmaceutical company), on her left arm, after she was supine for a minimum of five minutes. Similarly, Sarah was comforted by the detailed monitoring required during her participation. “So they didn't just give me a pill and send me home” (Sarah Tomas).

Christine ranked the Actelion study a three out of ten explaining that it was definitely below a five but as high as a three because the study drug was affecting her white blood cell count. Still she described the study as very low risk with high benefit. Although she elaborates that her risk perception has remained the same level over her four year participation, at first that level was dominated by fear of the unknown. Now that she's been in it for four years, the concern is for long-term side effects, although those do not keep her up at night. Her biggest fear right now, more than the long-term side effects, is getting kicked off of the study or not being let back on the study if she decided to have a baby. Sarah ranked the Actelion study three out of ten when she initially started. She knew that “horrible” things could happen to her because there are unknown risks, but she still felt pretty comfortable that it wasn't really that dangerous. Since she

has also been participating in this trial for over four years and nothing has happened, she no longer thinks that anything can happen and ranked the Actelion study a one out of ten.

For the Phase III Genzyme trial, Jaime did not consider this trial a risk at all. Although the study drug, which was recently FDA-approved in 2014, does have a significant side effect profile with a high percentage of patients (33%) developing thyroid disorders, Jaime included. It was difficult to get him to elaborate and perhaps remember since he had been on his trial for almost five years. When prompted, he said that he didn't consider the possibility of being randomized to Rebif a risk, because if he wasn't in the study, that's what he was going to have to take anyways. If he was randomized to Rebif, that would be fine, but if he was randomized to the study drug (which he was), that would be even better.

The Phase II Opera trial was an interesting case in risk perception because the two participants, Carol and Edward, had been participating in the trial for about three to six months when two deaths were reported and all trial participants had to be informed and re-consented. For Edward, he ranked the Opera trial as low risk because he felt satisfied with the way the trial was first explained to him, both the positives and the negatives, so this alleviated any concerns he had about potential study drug side effects. When he was informed about the two deaths of patients who were participating in the same study, he also felt that the situation was explained to him extremely thoroughly and

ultimately he decided it was not a big risk because there were mitigating factors. Edward feels that he made a rational decision considering all of the facts available to him at the time. He even compared the risk of death in this study, two out of one thousand, to another study he was familiar with where the risk of death was one in five.

Carol also saw the risk of this study as low. She did not see it as a risk to get randomized to either Rebif or the study drug because both were thought to treat MS and reduce MS relapse rates. Although, she admitted that she did prefer to be randomized to the study drug. When asked if she saw an experimental drug not yet approved by the FDA as a risk, she replied, “Do you know how much stuff I put in my body that probably isn't approved by the FDA?” (Carol Heuser). Carol clearly did not have any concern about the study drug in her clinical trial. Regarding the two deaths, similar to Edward, she considered the circumstances surrounding the deaths and made a calculation that the number of people who died on the study out of the total was a small percentage, so she continued to consider the drug to be low risk.

Although all interview participants ranked their clinical trial risk as low, they also understood that participating in clinical trials was not without risk. Submitting oneself to a clinical trial means accepting the unknown risks of the study drug and most of the interview participants admitted that the unknown was a real risk of research. However, this risk seemed to be outweighed by different factors for each patient, most related to the benefit they feel that they received

from their trial. As discussed earlier, some actually saw the risk of the unknown study drug as comparable to the risk of FDA-approved medications, as well as other non-MS medications. Faye explained that she doesn't see the risks of research because there are risks with taking Tylenol or other over-the-counter medications. During her study, Lydia was taking an FDA-approved medication for toe fungus and she ended up having abnormal liver function and had to stop taking it. Lydia sees the risk of a clinical trial in the context of the risks of life. There's a risk that you will get hit by a car. There's a risk that the stove will explode when you turn it on. There is risk in everything that we do every day.

Looking back at Table 14, it is apparent that different trials carry different levels of risk, but attempting to draw conclusions about which of the MS trials is the least or most risky from an objective standpoint is problematic because some patients are more concerned about method of administration, some are concerned about side effects, and some about the study design. What can be said is that Phase I trials have the least amount of data on human safety and efficacy available and Phase III trials have the most amount of data available. Experimental drugs must progress through these phases, with FDA approval required between each phase. If a trial does not have favorable data at any point along this path, it is not allowed to move to the next trial phase. Despite this regulatory requirement, patients did not seem overly concerned with the phase their trial was in, except that they knew it was more likely to have more information available about the drug the farther the drug was in the process.

Chapter 7 – Discussion

Underrepresentation Exists

Conducting a systematic review of the ClinicalTrials.gov website revealed that there are significant reporting deficits of MS clinical trial participants by race and ethnicity. Of the 475 completed MS trials, only 134 (28%) reported results. Of these, even fewer, 22 trials (16.4%) reported their results by race and ethnicity. Additionally, of those 22 clinical trials that did report participants by race and ethnicity, significant underrepresentation of racial and minority groups was revealed. Across the US, clinical trials favor Caucasian participation, significantly making up 95.7% of reported trial participants, African Americans making up 2.7%, and all other racial groups combined making up 1.7% of trial participants. In other words, the participation rate of Caucasian MS patients is approximately 36 times the participation rate of African American MS patients and almost 57 times the participation of MS patients from all other racial categories. When comparing the ethnicity categories of Latinos to Non-Latinos, Non-Latinos dominate clinical trial participation at 97.0% versus 3.0% participation. Although the prevalence rate reported by Noonan et al (2010) for Caucasians, African Americans, and the remaining racial and ethnic categories is a 2:1:1 ratio, actual clinical trial participation is far from matching this racial and ethnic proportion.

These results disprove the assertion that is often offered by clinicians, researchers, and patients (even some of the patients interviewed for this project),

to explain underrepresentation of minority groups in MS clinical trials.

Specifically, because racial and ethnic minority groups are less likely to develop MS, they are also less likely to participate in clinical trials. While this logic is generally accurate, the proportion of racial and ethnic group participation is vastly different from actual prevalence rates. Racial and ethnic minorities would require significant increases in participation rates in order to match the prevalence rates reported by Noonan et al (2010).

BAMC does a better job at representing racial and ethnic minority groups in its MS clinical trials, but disparities still remain. For example, approximately 38.4% of BAMC MS trial participants are non-Caucasian. Although this is also significantly higher than the proportion of non-Caucasian patients participating in clinical trials nationally, this rate still does not match the national prevalence rates by race and ethnicity. Again, if comparing the racial and ethnic the prevalence rates reported by Noonan et al (2010) for Caucasians, African Americans, and the remaining racial and ethnic categories which is a 2:1:1 ratio, for BAMC that ratio is approximately 13:1:7. Interestingly, this ratio seems to indicate that the representation of all other racial and ethnic categories combined, excluding African Americans, may approximate the MS prevalence rates observed nationally. Unfortunately, this also means that African Americans are severely underrepresented in BAMC MS clinical trials.

For clinical trials nationally and at BAMC, participation rates for males and females seemed to reflect the MS gender prevalence rates observed nationally.

In the US, women are 2.5 times more likely than men to develop MS, while women were 2.2 times more likely than men to participate in a clinical trial nationally. At BAMC, women were 2.4 times more likely than men to participate in a clinical trial. Although these rates approximate the national gender prevalence, the small differences may indicate a slightly heavier participation of males in clinical trials relative to the general MS population.

Despite the 1993 NIH Revitalization Act mandate to increase women and minority participation in research and the 2007 FDA Amendments Act which required submission of clinical trial results by race and ethnic categories, under-reporting and underrepresentation seem to persist in MS clinical trials.

Apparently not unique to MS, since much of the literature indicates this is also the case for cancer, cardiac, HIV/AIDS, asthma, diabetes and pain disorder clinical trials, the question still remains whether tracking trial participation by race and ethnicity are appropriate proxies for including and measuring the range of biological difference. The inclusion-and-difference paradigm seems to forge ahead without much thought to the consequences of this “black box” categorization. On the one hand, medical researchers want to remedy any underrepresentation of minority groups in clinical trials in order to generate results that are more generalizable to the public. On the other hand, the way they conceive of making trial results generalizable is by grouping individuals into racial and ethnic categories that may not actually represent biological difference. In fact, much of the research shows that race and ethnicity are not accurate

representations of biological categories and instead, are constructed by social, cultural, and historical forces (American Anthropological Association 1998; Jablonski 2004; Kuzawa and Sweet 2009; Race Ethnicity and Genetics Working Group 2005).

This racial and medical profiling of potential clinical trial participants creates more difference in its attempt at inclusion. Clinicians, medical institutions, pharmaceutical companies, and regulatory bodies remain the gatekeepers to clinical trial participation through their ability to pass binding research regulations, design clinical trial protocols, allow access to medical care, and offer invitations to potential study participants. This ability to shape the context of clinical trial participation gives these entities significant power over social actors who may or may not seek clinical trial participation on their own accord. The politics of communicability requires that particular individuals become enveloped in particular categories, for purposes prescribed by those in power. In this case, racial and ethnic minorities become passive victims of underrepresentation, who require assistance by gatekeepers who can grant access to the desired clinical trials. However, access can only be granted to “sanitary citizens” who are demonstrably compliant, proactive, and communicative patients. In contrast, “unsanitary subjects” are those patients incapable of adopting these characteristics and are thus deemed unfit for clinical trial participation (Briggs 2005). A successful patient is an individual who successfully learns how to be a “good trial patient” and is rewarded with clinical

trial access. Inherent in this acceptance of terms is the patient's categorization into the appropriate racial and ethnic category in an attempt to alleviate minority underrepresentation and lack of generalizability of trial results.

Foucault's (1975) conception of "docile bodies" may also help to describe how particular clinical trial patients are shaped by the needs of the clinical research industry. Docile bodies are those that "may be subjected, used, transformed, and improved...and can only be achieved through strict regiment of disciplinary acts" (Foucault 1975: 136). Importantly, clinical trial patients are not forced or coerced into proper trial behavior, but are shaped by increments of discipline. In fact, this discipline creates a new form of individuality for bodies that enable them to perform their duty within the confines of those disciplinary intuitions. Unfortunately, this arrangement is not something that an individual can choose to enter, but this control is exerted upon an individual absolutely through technology and power. "Docile bodies" in the research world translate to clinical trial patients who are agreeable, punctual, responsible, communicative, and proactive in order to maintain the rigorous requirements of a clinical trial protocol. Those who do not fall into this category are not fit for participation and lose their utility to the clinical research industry.

In an attempt to better recruit minority groups to clinical trials, recruitmentology endeavors to scientifically engineer recruitment efforts for "hard to recruit" populations. Unfortunately, this engineering does not serve to change the power dynamic inherent in the provider-patient relationship. Ultimately, the

problem of minority recruitment in clinical trials is a problem to be solved and engineered by the researcher, rather than a problem of power and positionality of all social actors involved in shaping the context of trial participation. Further, the use of race as a biological construct may undermine the larger goal of eliminating health disparities which are mostly due to sociopolitical causes rather than biological. Although the goal of inclusion is a worthy cause, the current discourse surrounding improvement of minority participation may only serve to maintain the paternalistic relationship between researchers and potential clinical trial participants. This is particularly true when much of the medical literature focuses on distrust as a reason for minority underrepresentation. As discussed previously, distrust is a nuanced concept, and there is conflicting evidence regarding the role distrust plays in preventing minority groups from participating in clinical trials.

Distrust is Real but Not Absolute

It would be wrong to discount the influence of distrust on participation rates of racial and ethnic minority groups in clinical research. Real and tragic abuses in research have transpired (e.g., Tuskegee) and should not be ignored. However, the medical community may not be considering the entire picture, when focusing on minority distrust as a reason for low clinical trial participation rates. There is significant evidence questioning the absolute contribution of distrust to influencing clinical trial participation. For example, Wendler, et al. (2006) found that minorities are just as willing to participate in trials but they are

asked to participate less often. Specific studies have looked at the influence of Tuskegee on willingness to participate, and many have found that knowledge of Tuskegee does not influence minority participation rates and, in fact, they were just as willing to participate as their Caucasian counterparts (Brandon, et al. 2005; Durant, et al. 2011; Katz, et al. 2009). When specifying particular types of distrust among the African American community, such as societal and interpersonal distrust, it becomes less clear that distrust is a singular notion that has absolute influence on participation rates (Durant, et al. 2011). Conflicting evidence even suggests that minority groups are actually overrepresented in Phase I clinical trials versus Phase III clinical trials, pointing to increased burden of risk for those participating in Phase I trials (Fisher and Kalbaugh 2011).

As previously discussed, there are many other potential reasons for low participation rates relating to structural barriers, such as provider bias and access to care. The continuous recycling of distrust as a reason minority groups do not participate in clinical research only serves to “blame” the disparity of participation on a particular attitude of the minority group in question. Again, this is not to discount the contribution of distrust in influencing minority participation rates, but to question the identification by research of a singular concept that contributes to low participation. In a sense, laying the blame on the group in question frees researchers from this responsibility, and prevents them from having to endure significant reflection to remedy the causes of low participation. Even the discourse surrounding strategies for minority recruitment revolve around

overcoming this minority distrust by providers and researchers becoming more trustworthy. Again, while strategies to improve relationships between researchers and potential patients are not fruitless, the strategy may ignore the inherent positionality of each party and how the unchanging and perpetual power positions of social actors will continue to create this distrust, rather than eliminate it. Importantly, Epstein (2008) suggests that building trust can be accomplished by using a variety of methods that involve a reciprocal relationship with a mutually beneficial exchange of knowledge and resources. The community is treated as a true partner in research rather than research subjects that passively accept the agenda of the researchers.

Distrust of research was not found to influence any of the electronic survey respondents when making a decision about clinical trial participation. In addition, no patterns were identified relating to the influence of distrust between racial and ethnic groups. For the interview participants, only one out of 11 said that distrust in research would influence his participation in a clinical trial. Contrary to what the literature might predict, that one patient was Caucasian and his reason for distrusting research had to do with distrusting pharmaceutical companies and their profit motives. Three additional interview participants, two Caucasian and one non-Caucasian, admitted that they also had a distrust of pharmaceutical companies, but said it would not influence their decision to participate in a trial. Their biggest fear was that these companies did not have

patients' best interests in mind as they strategized how to minimize losses and maximize revenue through the provision of experimental medications.

Independent of their distrust of pharmaceutical companies, only three of the 11 interview participants, two non-Caucasian and one Caucasian, were familiar with the notion that minority groups had more distrust of research than Caucasians. The two non-Caucasian interview participants who had heard of distrust also had personal experience of distrust in their families; however, one participant suggested that it was more likely that individual differences rather than race or ethnicity would dictate how trusting someone would be toward research. The other participant's grandfather had a distrust of research, while her grandmother, mother, and she were far more amenable to trial participation based on the concept of altruism. The Caucasian interview participant who was familiar with minority distrust admitted that her ability to decide to participate in her clinical trial was a privilege that few were offered, indicating a parallel cause of underrepresentation related to structural barriers.

Although trust of individual doctors did not seem to matter for the 11 interview participants, trust in BAMC as a medical institution did. Although this would require further examination, if these participants did not have the same trust in a medical institution as they do in BAMC, they may have been less likely to participate in a clinical trial, but the degree of this influence is yet unexplored. The role of distrust in explaining low participation rates of minority groups does seem to be present in some form, but the exact influence it has on minority

participation rates is uncertain. It may be that distrust is a convenient way to blame low participation rates on minority populations rather than consider the structural violence that exists and contributes to the participation disparities experienced by potential trial participants as biopolitical citizens. This research points to another factor that may help mediate participation in clinical trials: risk perception.

Risk Perception

The most frequent reason that survey and interview participants alike said would influence them to decline participation in a clinical trial was that the risks of the trial were too great. Risk and risk perception is not a well explored topic in explanations for low minority group participation in clinical trials. However, risk is well known to epidemiologists looking to quantify risks and calculate probabilities in search of an “objective” and knowable risk profile. Many risk calculations have been made in an attempt to understand risk of current FDA-approved MS medications, but oftentimes, the calculated risks by the experts, does not match the risk perception of MS patients, nor their acceptance of risk (Clanet, et al. 2014; Heesen, et al. 2010; Hofmann, et al. 2013; Tur, et al. 2013).

Risk was a significant topic for the interview participants and it was explored at length during the majority of interviews. Risk seemed to be the most prominent consideration for MS trial participants, above trust or any other influence. Risk, like distrust, is also a nuanced concept and several surprising findings were made during the interviews with MS clinical trial patients. First was

the idea that the risk of being randomized to a placebo treatment arm was considered worse than the unknown risks of the study drug. I had made the assumption that the risk of an unknown, unapproved experimental medication being tested in humans would be the primary consideration for MS patients. To the contrary, fear of being off any kind of medication, whether it was FDA approved or not, far outweighed the fear of potential study drug side effects. Second, considerations of the current MS medication landscape was required to understand how MS patients also believed that currently FDA-approved MS medications were sometimes just as, if not more risky, than an experimental medication. Third, MS clinical trial patients all considered their own clinical trial to be low risk, despite the fact that they represented six different clinical trials with significant variability in trial design, study drug characteristics, and risk.

The influence of risk perception was a surprising finding since most of the literature focuses on the influence of distrust in clinical trial participation. Risk perception also seems to play an important but separate role from risk acceptance since a patient can perceive a high risk to be low, or can perceive a high risk to be high, yet accept the potential consequences of the high risk scenario. This may have been the case with Isabelle since she admits that she was willing to die by participating in her clinical trial, just for the chance to find something that would help improve her dire situation. In order to make that statement, she must have thought the clinical trial risks were high enough to potentially cause her lethal harm. So even though her risk perception of the

clinical trial was high, she also had a high tolerance for that level or risk because of her particular situation. This may point to another common denominator, in addition to risk, that may significantly influence trial participation rates. It seems that risks would not be worth taking without perceiving or hoping for a potential, direct benefit for the patient.

Why Participate in Clinical Trials?

When the 11 interview participants were asked what their primary reason was for participating in their clinical trial, all of them related their primary response to a “selfish” reason. Although advancing science and medicine and helping fellow MS patients were noble, bonus reasons for participation, the main reason for participation was contingent on a perceived benefit. Some patients saw their clinical trial as offering them a superior MS medication compared to the FDA-approved MS medications currently available, better medical care, receipt of free medication, improvement upon future health prospects, hope, and survival. It may be that for whatever potential benefit a clinical trial can offer a patient, it mediates the perception of risk and/or the acceptance of risk. In addition, there were no differences discovered in the survey or the interviews in reasons to participate in a clinical trial by race and ethnicity. There were several significant findings in the survey highlighting different reasons to accept and decline participation in a clinical trial, but these were not significant by race and ethnicity. Instead, they were significant based on education level and insurance type,

pointing again to structural barriers to participation in clinical trials rather than something inherent and strictly categorized by racial and ethnic group.

The most frequent response for survey participants on why they would participate in a clinical trial was “to advance science and medicine.” Although this may be the case for the general MS population, it could also be that the survey respondents were more inclined to produce responses that would be seen more favorably by the researcher conducting the survey. This provides evidence that trying to understand a topic as complex as clinical trial participation cannot be completed based on survey administration alone, like many of the research studies exploring distrust seemed to do. The semi-structured interviews allowed for a more honest discussion about true motivations for MS patients beyond what makes them look good. Of course, this is not to say that participating in a clinical trial for selfish reasons is bad. But a true understanding of the motivations of MS patients is required to fix any problems with underrepresentation of minority groups in clinical trials. Reducing the problem to one of minority groups categorized as distinct and absolute biological and even cultural divisions ignores the larger and more complex forces at play influencing clinical trial participation. It seems that the decision to participate in a clinical trial is mediated, not by arbitrary categories of race and ethnicity, but by a complicated interaction between distrust, risk perception and acceptance, and perceived benefits in combination with the many structural barriers that may prevent clinical trial participation (access to health care and clinician bias). Critical medical

anthropology reminds us of the “importance of political and economic forces, including the exercise of power, in shaping health, disease, illness experience, and health care” (Singer and Baer 1995) including the clinical trial experience, or lack thereof, of potential clinical trial participants.

References Cited

- Acquaviva, K. D., and M. Mintz
2010 Perspective: are we teaching racial profiling? The dangers of subjective determinations of race and ethnicity in case presentations. *Acad Med* 85(4):702-5.
- Adams, V., S. Miller, S. Craig, Sonam, Nyima, Droyoung, P. V. Le, and M. Varner
2007 Informed Consent in cross-cultural perspective: clinical research in the Tibetan Autonomous Region, PRC. *Cult Med Psychiatry* 31(4):445-72.
- Alonso, A., and M. A. Hernan
2008 Temporal trends in the incidence of multiple sclerosis: a systematic review. *Neurology* 71(2):129-35.
- American Anthropological Association
1998 American Anthropological Association Statement on "Race".
<http://www.aaanet.org/stmts/racepp.htm>, accessed December 17, 2014.
- 2011 RACE - Are we so different? A Project of the American Anthropological Association.
http://www.understandingrace.org/lived/global_census.html, accessed February 22, 2015.
- Anwuri, V. V., L. E. Hall, K. Mathews, B. C. Springer, J. R. Tappenden, D. M. Farria, S. Jackson, M. S. Goodman, T. J. Eberlein, and G. A. Colditz
2013 An institutional strategy to increase minority recruitment to therapeutic trials. *Cancer Causes Control* 24(10):1797-809.
- Azevedo, Kathryn, and Christopher Payne
2006 Scrutinizing the Clinical Trials Process for Improved Patient Protection—A New Role for Applied Anthropologists? *Practicing Anthropology* 28(1):35-39.
- Barnett, Clifford R.
1985 Anthropological Research in Clinical Settings: Role Requirements and Adaptations. *Medical Anthropology Quarterly* 16(3):59-61.
- Bartlett, C., L. Doyal, S. Ebrahim, P. Davey, M. Bachmann, M. Egger, and P. Dieppe
2005 The causes and effects of socio-demographic exclusions from clinical trials. *Health Technol Assess* 9(38):iii-iv, ix-x, 1-152.

- Bellizzi, A., E. Anzivino, D. M. Rodio, A. T. Palamara, L. Nencioni, and V. Pietropaolo
2013 New insights on human polyomavirus JC and pathogenesis of progressive multifocal leukoencephalopathy. *Clin Dev Immunol* 2013:839719.
- Benamer, H. T., E. S. Ahmed, A. S. Al-Din, and D. G. Grosset
2009 Frequency and clinical patterns of multiple sclerosis in Arab countries: a systematic review. *J Neurol Sci* 278(1-2):1-4.
- Berger, J. S., C. Melloni, T. Y. Wang, R. J. Dolor, C. G. Frazier, Z. Samad, E. D. Peterson, D. B. Mark, and L. K. Newby
2009 Reporting and representation of race/ethnicity in published randomized trials. *Am Heart J* 158(5):742-7.
- Bernard, H. Russell
2011 *Research Methods in Anthropology: Qualitative and Quantitative Approaches*. Lanham, MD: AltaMira Press.
- Block, Pamela, and Eva Rodriguez
2008 Team Building: An Anthropologist, An Occupational Therapist, and the Story of a Pediatric Multiple Sclerosis Community. *Practicing Anthropology* 30(3):6-9.
- Brandon, D. T., L. A. Isaac, and T. A. LaVeist
2005 The legacy of Tuskegee and trust in medical care: is Tuskegee responsible for race differences in mistrust of medical care? *J Natl Med Assoc* 97(7):951-6.
- Braunstein, J. B., N. S. Sherber, S. P. Schulman, E. L. Ding, and N. R. Powe
2008 Race, medical researcher distrust, perceived harm, and willingness to participate in cardiovascular prevention trials. *Medicine (Baltimore)* 87(1):1-9.
- Briggs, Charles L.
2005 Communicability, Racial Discourse, and Disease. *Annual Review of Anthropology* 34(1):269-291.
- Briggs, Charles L., and Clara Mantini-Briggs
2003 *Stories in the Time of Cholera: Racial Profiling During a Medical Nightmare*. Berkeley, CA: University of California Press.

Buchanan, R. J., M. A. Zuniga, G. Carrillo-Zuniga, B. J. Chakravorty, T. Tyry, R. L. Moreau, C. Huang, and T. Vollmer

2010 Comparisons of Latinos, African Americans, and Caucasians with multiple sclerosis. *Ethn Dis* 20(4):451-7.

Byrd, G. S., C. L. Edwards, V. A. Kelkar, R. G. Phillips, J. R. Byrd, D. S. Pim-Pong, T. D. Starks, A. L. Taylor, R. E. McKinley, Y. J. Li, and M. Pericak-Vance

2011 Recruiting intergenerational African American males for biomedical research Studies: a major research challenge. *J Natl Med Assoc* 103(6):480-7.

Cabral, D. N., A. M. Napoles-Springer, R. Miike, A. McMillan, J. D. Sison, M. R. Wrensch, E. J. Perez-Stable, and J. K. Wiencke

2003 Population- and community-based recruitment of African Americans and Latinos: the San Francisco Bay Area Lung Cancer Study. *Am J Epidemiol* 158(3):272-9.

Calderon, J. L., R. S. Baker, H. Fabrega, J. G. Conde, R. D. Hays, E. Fleming, and K. Norris

2006 An ethno-medical perspective on research participation: a qualitative pilot study. *MedGenMed* 8(2):23.

Cassell, Joan

2002 Perturbing the System: "Hard Science," "Soft Science," and Social Science, The Anxiety and Madness of Method. *Human Organization* 61(2):177-185.

Center for Information and Study on Clinical Research Participation

2014 Who We Are. <https://www.ciscrp.org/>, accessed December 14, 2014.

Chan, K. H., K. L. Tsang, P. W. Ho, C. T. Tse, J. S. Kwan, J. W. Ho, A. C. Chu, R. S. Chang, and S. L. Ho

2011 Clinical outcome of relapsing remitting multiple sclerosis among Hong Kong Chinese. *Clin Neurol Neurosurg* 113(8):617-22.

Clanet, M. C., J. S. Wolinsky, R. J. Ashton, H. P. Hartung, and S. C. Reingold

2014 Risk evaluation and monitoring in multiple sclerosis therapeutics. *Mult Scler* 20(10):1306-11.

Coakley, M., E. O. Fadiran, L. J. Parrish, R. A. Griffith, E. Weiss, and C. Carter

2012 Dialogues on diversifying clinical trials: successful strategies for engaging women and minorities in clinical trials. *J Womens Health (Larchmt)* 21(7):713-6.

- Cohen, J.W.
1988 Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates.
- Colon-Otero, G., R. C. Smallridge, L. A. Solberg, Jr., T. D. Keith, T. A. Woodward, F. B. Willis, and A. N. Dunn
2008 Disparities in participation in cancer clinical trials in the United States : a symptom of a healthcare system in crisis. *Cancer* 112(3):447-54.
- Corbie-Smith, G., D. M. St George, S. Moody-Ayers, and D. F. Ransohoff
2003 Adequacy of reporting race/ethnicity in clinical trials in areas of health disparities. *J Clin Epidemiol* 56(5):416-20.
- Corbie-Smith, G., S. B. Thomas, and D. M. St George
2002 Distrust, race, and research. *Arch Intern Med* 162(21):2458-63.
- Corbie-Smith, G., S. B. Thomas, M. V. Williams, and S. Moody-Ayers
1999 Attitudes and beliefs of African Americans toward participation in medical research. *J Gen Intern Med* 14(9):537-46.
- Corbie-Smith, G., I. C. Williams, C. Blumenthal, J. Dorrance, S. E. Estroff, and G. Henderson
2007 Relationships and communication in minority participation in research: multidimensional and multidirectional. *J Natl Med Assoc* 99(5):489-98.
- Coyle, P. K., and K. P. Johnson
2007 Relapses matter: the costs & consequences of multiple sclerosis relapses. *J Neurol Sci* 256 Suppl 1:S1-4.
- Cree, B., and E. Waubant
2010 Does race matter for multiple sclerosis? *Neurology* 74(7):532-3.
- Cristiano, E., L. Patrucco, and J. I. Rojas
2008 A systematic review of the epidemiology of multiple sclerosis in South America. *Eur J Neurol* 15(12):1273-8.
- De las Nueces, D., K. Hacker, A. DiGirolamo, and L. S. Hicks
2012 A systematic review of community-based participatory research to enhance clinical trials in racial and ethnic minority groups. *Health Serv Res* 47(3 Pt 2):1363-86.

- DiGiacomo, Susan M.
1999 Can there be a cultural epidemiology? *Medical Anthropology Quarterly* 13(4):436-457.
- Douglas, Mary
1992 *Risk and Blame: Essays in Cultural Theory*. London: Routledge.
- Durant, R. W., A. T. Legedza, E. R. Marcantonio, M. B. Freeman, and B. E. Landon
2011 Different types of distrust in clinical research among whites and African Americans. *J Natl Med Assoc* 103(2):123-30.
- Eggy, S., E. Barton, A. Winckles, L. A. Penner, and T. L. Albrecht
2013 A disparity of words: racial differences in oncologist-patient communication about clinical trials. *Health Expect*.
- Epstein, Steven
2007 *Inclusion: The Politics of Difference in Clinical Research*. Chicago, IL: The University of Chicago Press.
- 2008 The rise of 'recruitmentology': clinical research, racial knowledge, and the politics of inclusion and difference. *Soc Stud Sci* 38(5):801-32.
- Farmer, P. E., B. Nizeye, S. Stulac, and S. Keshavjee
2006 Structural violence and clinical medicine. *PLoS Med* 3(10):e449.
- Fisher, J. A., and C. A. Kalbaugh
2011 Challenging assumptions about minority participation in US clinical research. *Am J Public Health* 101(12):2217-22.
- Fitzgerald, Maureen H., and Kathryn A. Paterson
1995 The hidden disability dilemma for the preservation of self. *Journal of Occupational Science* 2(1):13-21.
- Food and Drug Administration
2010 FDA Drug Safety Communication: Risk of Progressive Multifocal Leukoencephalopathy (PML) with the use of Tysabri (natalizumab). <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm199872.htm>, accessed December 17, 2014.
- 2011 FDA Drug Safety Communication: Safety review of a reported death after the first dose of Multiple Sclerosis drug Gilenya (fingolimod).

<http://www.fda.gov/Drugs/DrugSafety/ucm284240.htm>, accessed December 16, 2014.

2012 FDA Drug Safety Communication: Revised recommendations for cardiovascular monitoring and use of multiple sclerosis drug Gilenya (fingolimod). <http://www.fda.gov/Drugs/DrugSafety/ucm303192.htm>, accessed December 17, 2014.

2014 Code of Federal Regulations Title 21. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=56>, accessed January 2, 2015.

Ford, M. E., L. A. Siminoff, E. Pickelsimer, A. G. Mainous, D. W. Smith, V. A. Diaz, L. H. Soderstrom, M. S. Jefferson, and B. C. Tilley

2013 Unequal burden of disease, unequal participation in clinical trials: solutions from African American and Latino community members. *Health Soc Work* 38(1):29-38.

Foucault, Michael

1975 *Discipline and Punish: the Birth of the Prison*. New York: Random House.

Frampton, G. K., J. Shepherd, and J. L. Dorne

2009 Demographic data in asthma clinical trials: a systematic review with implications for generalizing trial findings and tackling health disparities. *Soc Sci Med* 69(8):1147-54.

Frankenberg, Ronald

1993 Risk: Anthropological and Epidemiological Narratives of Prevention. *In Knowledge, Power, and Practice: The Anthropology of Medicine and Everyday Life*. S. Lindenbaum and M. Lock, eds. Berkeley, CA: University of California Press.

Goldade, Kate, and Mark A. Nichter

2010 Risk Perceptions and Knowledge of Sexually Transmitted Infections (STIs) and HIV Among Undocumented Nicaraguan Migrant Women in Costa Rica. *NAPA Bulletin* 34(1):195-212.

Gravlee, C. C., and E. Sweet

2008 Race, ethnicity, and racism in medical anthropology, 1977-2002. *Med Anthropol Q* 22(1):27-51.

- Grimen, H.
2009 Power, trust, and risk: some reflections on an absent issue. *Med Anthropol Q* 23(1):16-33.
- Gross, C. P.
2008 Racial disparities in clinical trial enrolment. *Lancet* 372(9651):1713-4.
- Hasnain-Wynia, R., D. W. Baker, D. Nerenz, J. Feinglass, A. C. Beal, M. B. Landrum, R. Behal, and J. S. Weissman
2007 Disparities in health care are driven by where minority patients seek care: examination of the hospital quality alliance measures. *Arch Intern Med* 167(12):1233-9.
- Heesen, C., I. Kleiter, F. Nguyen, N. Schaffler, J. Kasper, S. Kopke, and W. Gaissmaier
2010 Risk perception in natalizumab-treated multiple sclerosis patients and their neurologists. *Mult Scler* 16(12):1507-12.
- Hofmann, A., J. P. Stellmann, J. Kasper, F. Ufer, W. G. Elias, I. Pauly, J. Repenthin, T. Rosenkranz, T. Weber, S. Kopke, and C. Heesen
2013 Long-term treatment risks in multiple sclerosis: risk knowledge and risk perception in a large cohort of mitoxantrone-treated patients. *Mult Scler* 19(7):920-5.
- Holland, NJ, TJ Murray, and SC Reingold
2007 *Multiple Sclerosis: A Guide for the Newly Diagnosed*. New York, NY: Demos Medical Publishing.
- Howerton, M. W., M. C. Gibbons, C. R. Baffi, T. L. Gary, G. Y. Lai, S. Bolen, J. Tilburt, T. P. Tanpitukpongse, R. F. Wilson, N. R. Powe, E. B. Bass, and J. G. Ford
2007 Provider roles in the recruitment of underrepresented populations to cancer clinical trials. *Cancer* 109(3):465-76.
- Hunt, L. M., N. D. Truesdell, and M. J. Kreiner
2013 Genes, race, and culture in clinical care: racial profiling in the management of chronic illness. *Med Anthropol Q* 27(2):253-71.
- Hussain-Gambles, M.
2004 South Asian patients' views and experiences of clinical trial participation. *Fam Pract* 21(6):636-42.

- Hussain-Gambles, M., K. Atkin, and B. Leese
2004 Why ethnic minority groups are under-represented in clinical trials: a review of the literature. *Health Soc Care Community* 12(5):382-8.
- Irvine, H., C. Davidson, K. Hoy, and A. Lowe-Strong
2009 Psychosocial adjustment to multiple sclerosis: exploration of identity redefinition. *Disabil Rehabil* 31(8):599-606.
- Jablonski, Nina G.
2004 The Evolution of Human Skin and Skin Color. *Annual Review of Anthropology* 33:585-623.
- Joseph, G., and D. Dohan
2009 Diversity of participants in clinical trials in an academic medical center: the role of the 'Good Study Patient?'. *Cancer* 115(3):608-15.
- Kalafatova, O.
1987 Geographic and climatic factors and multiple sclerosis in some districts of Bulgaria. *Neuroepidemiology* 6(3):116-9.
- Kalb, R.
2007 The emotional and psychological impact of multiple sclerosis relapses. *J Neurol Sci* 256 Suppl 1:S29-33.
- Kampman, M. T., T. Wilsgaard, and S. I. Mellgren
2007 Outdoor activities and diet in childhood and adolescence relate to MS risk above the Arctic Circle. *Journal of Neurology* 254(4):471-477.
- Kanarek, N. F., H. L. Tsai, S. Metzger-Gaud, D. Damron, A. Guseynova, J. F. Klamerus, and C. M. Rudin
2010 Geographic proximity and racial disparities in cancer clinical trial participation. *J Natl Compr Canc Netw* 8(12):1343-51.
- Kappos, L., D. Bates, G. Edan, M. Eraksoy, A. Garcia-Merino, N. Grigoriadis, H. P. Hartung, E. Havrdova, J. Hillert, R. Hohlfeld, M. Kremenchutzky, O. Lyon-Caen, A. Miller, C. Pozzilli, M. Ravnborg, T. Saida, C. Sindic, K. Vass, D. B. Clifford, S. Hauser, E. O. Major, P. W. O'Connor, H. L. Weiner, M. Clanet, R. Gold, H. H. Hirsch, E. W. Radu, P. S. Sorensen, and J. King
2011 Natalizumab treatment for multiple sclerosis: updated recommendations for patient selection and monitoring. *Lancet Neurol* 10(8):745-58.

Katz, R. V., B. L. Green, N. R. Kressin, S. A. James, M. Q. Wang, C. Claudio, and S. L. Russell

2009 Exploring the "legacy" of the Tuskegee Syphilis Study: a follow-up study from the Tuskegee Legacy Project. *J Natl Med Assoc* 101(2):179-83.

Kira, J., T. Kanai, Y. Nishimura, K. Yamasaki, S. Matsushita, Y. Kawano, K. Hasuo, S. Tobimatsu, and T. Kobayashi

1996 Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. *Ann Neurol* 40(4):569-74.

Koch-Henriksen, N., and P. S. Sorensen

2011 Why does the north-south gradient of incidence of multiple sclerosis seem to have disappeared on the northern hemisphere? *J Neurol Sci* 311(1-2):58-63.

Kreatsoulas, C., and S. Anand

2009 Considering race/ethnicity and socio-economic status in randomized controlled trials. A commentary on Frampton et al.'s systematic review generalizing trial findings and tackling health disparities in asthma research. *Soc Sci Med* 69(8):1155-6.

Kuzawa, C. W., and E. Sweet

2009 Epigenetics and the embodiment of race: developmental origins of US racial disparities in cardiovascular health. *Am J Hum Biol* 21(1):2-15.

Langer-Gould, A., S. M. Brara, B. E. Beaver, and J. L. Zhang

2013 Incidence of multiple sclerosis in multiple racial and ethnic groups. *Neurology* 80(19):1734-9.

Launiala, A., and M. L. Honkasalo

2010 Malaria, danger, and risk perceptions among the Yao in rural Malawi. *Med Anthropol Q* 24(3):399-420.

Lupton, Deborah

1999 *Risk*. London: Routledge.

Marks, Jonathan

2002 *What it means to be 98% Chimpanzee: Apes, People, and Their Genes*. Berkeley, CA: University of California Press.

- Marrie, R. A., and R. I. Horwitz
2010 Emerging effects of comorbidities on multiple sclerosis. *Lancet Neurol* 9(8):820-8.
- Marrie, R., R. Horwitz, G. Cutter, T. Tyry, D. Campagnolo, and T. Vollmer
2008 Comorbidity, socioeconomic status and multiple sclerosis. *Mult Scler* 14(8):1091-8.
- McCann, S. K., M. K. Campbell, and V. A. Entwistle
2010 Reasons for participating in randomised controlled trials: conditional altruism and considerations for self. *Trials* 11:31.
- Melcon, M. O., L. Gold, A. Carra, F. Caceres, J. Correale, E. Cristiano, N. Fernandez Liguori, O. Garcea, G. Luetic, and M. Kremenchutzky
2008 Argentine Patagonia: prevalence and clinical features of multiple sclerosis. *Mult Scler* 14(5):656-62.
- Mendoza, D. B., M. T. Williams, L. K. Chapman, and M. Powers
2012 Minority inclusion in randomized clinical trials of panic disorder. *J Anxiety Disord* 26(5):574-82.
- Milo, R., and A. Miller
2014 Revised diagnostic criteria of multiple sclerosis. *Autoimmun Rev* 13(4-5):518-24.
- Minden, S. L., D. Frankel, L. Hadden, J. Perloff, K. P. Srinath, and D. C. Hoaglin
2006 The Sonya Slifka Longitudinal Multiple Sclerosis Study: methods and sample characteristics. *Mult Scler* 12(1):24-38.
- Multiple Sclerosis International Federation
2013 Atlas of MS 2013 - Mapping Multiple Sclerosis Around the World.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
1979 The Belmont Report: Ethical Principals and Guidelines for the Protection of Human Subjects of Research.
- National Institutes of Health
2001 NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research - Amended October 2001.
http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm.

- 2014a ClinicalTrials.gov: Learn About Clinical Trials.
<https://clinicaltrials.gov/ct2/about-studies/learn>, accessed January 2, 2015.
- 2014b NIH Clinical Research Trials and You.
<http://www.nih.gov/health/clinicaltrials/basics.htm>, accessed January 2, 2015.
- National Library of Medicine and National Institutes of Health
2014 ClinicalTrials.gov Background. <https://clinicaltrials.gov/ct2/about-site/background>, accessed December 31, 2014.
- National Multiple Sclerosis Society
2014 Treating MS: Medications.
<http://www.nationalmssociety.org/Treating-MS/Medications>, accessed December 16, 2014.
- Nichter, Mark
2001 Risk, Vulnerability and Harm Reduction: Preventing STIs in Southeast Asia by Antibiotic Prophylaxis, a Misguided Practice. *In* Cultural Perspectives on Reproductive Health. C.M. Obermeyer, ed. Oxford: Oxford University Press.
- Noonan, C. W., S. J. Kathman, and M. C. White
2002 Prevalence estimates for MS in the United States and evidence of an increasing trend for women. *Neurology* 58(1):136-8.
- Noonan, C. W., D. M. Williamson, J. P. Henry, R. Indian, S. G. Lynch, J. S. Neuberger, R. Schiffer, J. Trottier, L. Wagner, and R. A. Marrie
2010 The prevalence of multiple sclerosis in 3 US communities. *Prev Chronic Dis* 7(1):A12.
- Orton, S. M., L. Wald, C. Confavreux, S. Vukusic, J. P. Krohn, S. V. Ramagopalan, B. M. Herrera, A. D. Sadovnick, and G. C. Ebers
2011 Association of UV radiation with multiple sclerosis prevalence and sex ratio in France. *Neurology* 76(5):425-31.
- Penberthy, L., R. Brown, M. Wilson-Genderson, B. Dahman, G. Ginder, and L. A. Siminoff
2012 Barriers to therapeutic clinical trials enrollment: differences between African-American and white cancer patients identified at the time of eligibility assessment. *Clin Trials* 9(6):788-97.

- Petryna, Adriana
2002 *Life Exposed: Biological Citizens after Chernobyl*. Princeton, NJ: Princeton University Press.
- 2005 Ethical variability: Drug development and globalizing clinical trials. *American Ethnologist* 32(2):183-197.
- 2007 Experimentality: On the Global Mobility and Regulation of Human Subjects Research. *Political and Legal Anthropology Review* 30(2):288-304.
- Poser, C. M., and V. V. Brinar
2007 The accuracy of prevalence rates of multiple sclerosis: a critical review. *Neuroepidemiology* 29(3-4):150-5.
- Pucci, E., G. Giuliani, A. Solari, S. Simi, S. Minozzi, C. Di Pietrantonj, and I. Galea
2011 Natalizumab for relapsing remitting multiple sclerosis. *Cochrane Database Syst Rev* (10):Cd007621.
- Rabinow, Paul
1996 *Essays on the Anthropology of Reason*. Princeton, NJ: Princeton University Press.
- Race Ethnicity and Genetics Working Group
2005 The use of racial, ethnic, and ancestral categories in human genetics research. *Am J Hum Genet* 77(4):519-32.
- Rathore, S. S., and H. M. Krumholz
2003 Race, ethnic group, and clinical research. *BMJ* 327(7418):763-4.
- Ridker, P. M., N. R. Cook, I. M. Lee, D. Gordon, J. M. Gaziano, J. E. Manson, C. H. Hennekens, and J. E. Buring
2005 A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 352(13):1293-304.
- Risco, J., H. Maldonado, L. Luna, J. Osada, P. Ruiz, A. Juarez, and D. Vizcarra
2011 Latitudinal prevalence gradient of multiple sclerosis in Latin America. *Mult Scler* 17(9):1055-9.

- Robinson, I.
1990 Personal narratives, social careers and medical courses: analysing life trajectories in autobiographies of people with multiple sclerosis. *Soc Sci Med* 30(11):1173-86.
- Rook, G. A.
2012 Hygiene hypothesis and autoimmune diseases. *Clin Rev Allergy Immunol* 42(1):5-15.
- Rosati, G.
2001 The prevalence of multiple sclerosis in the world: an update. *Neurol Sci* 22(2):117-39.
- Ryan, R. E., M. J. Prictor, K. J. McLaughlin, and S. J. Hill
2008 Audio-visual presentation of information for informed consent for participation in clinical trials. *Cochrane Database Syst Rev* (1):Cd003717.
- Sankar, P.
2004 Communication and miscommunication in informed consent to research. *Medical Anthropology Quarterly* 18(4):429-46.
- Schmotzer, G. L.
2012 Barriers and facilitators to participation of minorities in clinical trials. *Ethn Dis* 22(2):226-30.
- Schumacher, George A., Gilbert Beebe, Robert F. Kibler, Leonard T. Kurland, John F. Kurtzke, Fletcher McDowell, Benedict Nagler, William A. Sibley, Wallace W. Tourtellotte, and Thomas L. Willmon
1965 Problems of Experimental Trials of Therapy in Multiple Sclerosis: Report by the Panel on the Evaluation of Experimental Trials of Therapy in Multiple Sclerosis. *Annals of the New York Academy of Sciences* 122(1):552-568.
- Schwartz, R. S.
2001 Racial profiling in medical research. *N Engl J Med* 344(18):1392-3.
- Shabas, D., and M. Heffner
2005 Multiple sclerosis management for low-income minorities. *Mult Scler* 11(6):635-40.
- Shavers, V. L., C. F. Lynch, and L. F. Burmeister
2000 Knowledge of the Tuskegee study and its impact on the willingness to participate in medical research studies. *J Natl Med Assoc* 92(12):563-72.

- 2002 Racial differences in factors that influence the willingness to participate in medical research studies. *Ann Epidemiol* 12(4):248-56.
- Sheikh, A., L. Halani, R. Bhopal, G. Netuveli, M. R. Partridge, J. Car, C. Griffiths, and M. Levy
2009 Facilitating the recruitment of minority ethnic people into research: qualitative case study of South Asians and asthma. *PLoS Med* 6(10):e1000148.
- Simpson, S., Jr., L. Blizzard, P. Otahal, I. Van der Mei, and B. Taylor
2011 Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. *J Neurol Neurosurg Psychiatry* 82(10):1132-41.
- Singer, Merrill, and Hans Baer
1995 *Critical Medical Anthropology*. Amityville, NY: Baywood Publishing Co., Inc.
- Sommerfeld, Johannes, Mamadou Sanon, Bocar A. Kouyate, and Rainer Sauerborn
2002 Perceptions of Risk, Vulnerability, and Disease Prevention in Rural Burkina Faso: Implications for Community-Based Health Care and Insurance. *Human Organization* 61(2):139-146.
- Svensson, K., O. F. Ramirez, F. Peres, M. Barnett, and L. Claudio
2012 Socioeconomic determinants associated with willingness to participate in medical research among a diverse population. *Contemp Clin Trials* 33(6):1197-205.
- Symonds, R. P., K. Lord, A. J. Mitchell, and D. Raghavan
2012 Recruitment of ethnic minorities into cancer clinical trials: experience from the front lines. *Br J Cancer* 107(7):1017-21.
- Trostle, James A.
2005 *Epidemiology and Culture*. New York: Cambridge University Press.
- Tsai, Ching-Piao, Chih-Lun Yuan, Hsiang-Yu Yu, Chien Chen, Yuh-Cherng Guo, and Din-E Shan
2004 Multiple Sclerosis in Taiwan. *Journal of the Chinese Medical Association* 67(10):500-505.
- Tur, C., M. Tintore, A. Vidal-Jordana, D. Bichuetti, P. Nieto Gonzalez, M. J. Arevalo, G. Arrambide, E. Anglada, I. Galan, J. Castillo, C. Nos, J. Rio, M. I. Martin, M. Comabella, J. Sastre-Garriga, and X. Montalban

- 2013 Risk acceptance in multiple sclerosis patients on natalizumab treatment. *PLoS One* 8(12):e82796.
- Van der Geest, Sjaak , Susan Reynolds-Whyte, and Anita Hardon
1996 The Anthropology of Pharmaceuticals: A Biographical Approach. *Annual Review of Anthropology* 25:153-178.
- Van der Werf, S. P., A. Evers, P. J. Jongen, and G. Bleijenberg
2003 The role of helplessness as mediator between neurological disability, emotional instability, experienced fatigue and depression in patients with multiple sclerosis. *Mult Scler* 9(1):89-94.
- Van Ryn, M., and J. Burke
2000 The effect of patient race and socio-economic status on physicians' perceptions of patients. *Soc Sci Med* 50(6):813-28.
- Vollmer, Timothy
2007 The natural history of relapses in multiple sclerosis. *Journal of the Neurological Sciences* 256:S5-S13.
- Wallin, M. T., W. F. Page, and J. F. Kurtzke
2004 Multiple sclerosis in US veterans of the Vietnam era and later military service: race, sex, and geography. *Ann Neurol* 55(1):65-71.
- Wasay, M., I. A. Khatri, B. Khealani, and M. Sheerani
2006 MS in Asian countries. *Int MS J* 13(2):58-65.
- Wendler, D., R. Kington, J. Madans, G. Van Wye, H. Christ-Schmidt, L. A. Pratt, O. W. Brawley, C. P. Gross, and E. Emanuel
2006 Are racial and ethnic minorities less willing to participate in health research? *PLoS Med* 3(2):e19.
- World Health Organization and Multiple Sclerosis International Federation
2008 Atlas - Multiple Sclerosis Resources in the World.