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The diversity of participants in clinical trials involving allogeneic hematopoietic stem cell transplant recipients

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The Diversity of Participants in Clinical Trials Involving Allogeneic
Hematopoietic Stem Cell Transplant Recipients

by

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Thesis

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Abstract

This thesis set out to examine whether the demographic diversity of participants in clinical trials involving allogeneic stem cell transplant recipients matched the diversity of the actual allogeneic recipient population overall. It is important that clinical trials study new therapies in a population that represents characteristics of the overall treatment population in order to gain accurate safety and efficacy data. The actual diversity of the allogeneic transplant population was determined using data reported to the Center for International Blood & Marrow Transplant Research (CIBMTR) registry. Then, a comprehensive literature review was conducted to identify the population of allogeneic transplant recipients who took part in clinical research. In comparing the two populations, it was determined that women are well-represented in allogeneic transplant trials, while non-white minorities remain underrepresented. These findings demonstrate that there is more work to be done in order to ensure everyone has equal access to clinical trials.

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Introduction and Background

Hematopoietic stem cell transplantation (HSCT) is a widely recognized therapeutic option for treating a variety of hematologic malignancies and immunologic deficiencies. With more aggressive disorders, HSCT remains the only potentially curative option after exhausting chemotherapeutic treatments. There are two types of hematopoietic transplants: autologous and allogeneic. Simply defined, autologous HSCT involves removing the patient's stem cells once they achieve remission, giving the patient more chemotherapy, and subsequently re-infusing the stem cells in order to recover bone marrow function (NMDP, n.d.). Allogeneic transplants follow a similar path; however, they differ in stem cell source. Instead of stem cells coming from the patient's own system, they come from a healthy volunteer donor (NMDP, n.d.). While autologous transplantation remains a highly valued tool for treating patients with these serious conditions, this thesis will focus on allogeneic HSCT recipients.

In order to qualify for an allogeneic transplant, a patient must have a stem cell donor that can be considered a match (NMDP, n.d.). Both the patient and donor are tested for certain molecular markers found on the surface of most cells in the body. These markers are called human leukocyte antigens (HLA; NMDP, n.d.). Because these markers help the body identify which cells belong there and which do not, it is essential for donor stem cells to have a high degree of HLA match. It is often easier for patients to find matched donors within their own families because they share genetic traits (NMDP, n.d.). Without a related donor option, however, patients may turn to the National Marrow Donor Program (NMDP) for help. The NMDP is a nonprofit organization based in the United States that maintains a registry of volunteers who are willing to be donors for patients in need of HSCT.

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The NMDP's Be the Match Registry is vital for patients who need allogeneic transplants because they instantly have access to HLA information for millions of potential donors. Once the patient's HLA has been tested, a transplant center can quickly search the registry for donors that may be considered an HLA match (NMDP, n.d.). According to the NMDP (n.d.), Caucasian patients today have a 97% chance of finding a matched donor, yet minorities have a much lower likelihood. For instance, African Americans searching for a donor only have a 76% chance of finding one (NMDP, n.d.). If a donor cannot be identified from the pool of adult volunteers in the Be the Match Registry, the patient may be able to find one from the NMDP's umbilical cord blood registry.

Stem cells normally exist in the bone marrow or peripheral blood; however, they can also be found in the umbilical cord blood of a newborn baby. Before the child is born, the parents decide if they want to donate their child's umbilical cord blood and if so, the cells are collected from the cord after the baby is delivered. Once the stem cells are harvested, they undergo HLA testing and are cryopreserved in an umbilical cord blood bank. The cord blood registry is much smaller than the adult donor registry; therefore, the likelihood of finding a matched donor remains low. In fact, while there are approximately 126,000 white cord blood units, there are only 16,000 Black/African American cord blood units (H.R.S.A., n.d.). The search for cord blood units from American Indians or Pacific Islanders is even worse, with only 370 and 222, respectively (H.R.S.A., n.d.). Allogeneic HSCT using umbilical cord blood stem cells often have a high degree of HLA mismatch; and typically with more mismatch comes more post-HSCT complications for the recipient (Petersdorf et al., 1998). However, cord blood HSCT is somewhat unique from other stem cell sources since HLA differences are usually better tolerated for reasons that are not completely understood (Eapen et al., 2007).

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The NMDP is aware of the challenges facing non-white minorities in the donor search process and has implemented several programs focused on adding more racially and ethnically diverse unrelated donors and cord blood units to its registry (Johansen et al., 2008). While increased minority education, recruitment, and funding efforts have dramatically increased the odds of finding a matched unrelated donor, there remains an unfulfilled need (Johansen et al., 2008).

The NMDP registries are not the only instance where there exists an underrepresentation of select groups; it is also a significant problem in the clinical research realm (Murthy et al., 2004). For most of the twentieth century, the majority of clinical trial participants were white males. This led to a large gap in access for participation in clinical trials for minorities, women, and children (Emanuel et al., 2011). Without their participation, little was known about how novel therapies would affect these populations. Because variable therapeutic responses and toxicities can be potentially influenced by genetic differences, it is important to study therapies in a diverse population.

Participant diversity is also important from an ethical standpoint because everyone should be given equal opportunities to participate in clinical trials whenever possible. This is reflected in The Belmont Report issued by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research in 1979, which called for equal selection of participants to share in the burdens and benefits of clinical research (Emanuel et al., 2011). This landmark report brought to light ethical concerns in research and led the way to legislation that called for greater inclusion of minorities, women, and children in clinical research.

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Improving the Inclusion of Minorities in Clinical Research

Recognizing the need to demonstrate the safety and efficacy of new therapies in a wide variety of patients, the United States government took action to ensure the inclusion of women, children, and minorities in clinical research. As detailed by Emanuel et al. (2011), the U.S. Food & Drug Administration (FDA) updated its guidance to allow for the inclusion of women of childbearing potential in clinical research in 1993 and issued new guidance stating that the overall diversity of research participants “should, in general, reflect the population that will receive the drug when it is marketed” (Emanuel et al., 2011). The Women’s Health Equity Act was also passed in 1993, calling for “greater equity in the delivery of health care services to women through expanded research on women’s health issues, improved access to health care services, and the development of disease prevention activities responsive to the needs of women” (Emanuel et al., 2011). In accordance with congressional mandate, the FDA then created the Office of Women’s Health in 1994.

Though children had previously been allowed to participate, the real push for the inclusion of children in clinical research didn’t begin until 1998. That year, the U.S. National Institutes of Health (NIH) urged researchers to include children unless there were scientific or ethical reasons to exclude them (Emanuel et al., 2011). The Pediatric Equity Act of 2003 also marked a milestone because it required pharmaceutical companies to perform clinical research in pediatrics when investigating new drugs and biologic products (Emanuel et al., 2011).

With regard to HSCT legislature, the Stem Cell Therapeutic and Research Act of 2005 and the Stem Cell Therapeutic and Research Reauthorization Act of 2010 are two laws that helped HSCT research make great strides. As discussed on the website for the Health Resources and Services Administration (HRSA), the Stem Cell Acts of 2005 and 2010 are responsible for

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both the creation of the NMDP and the expansion of the requirements of the registry to increase its number of donors and cord blood units (H.R.S.A., n.d.). Also in accordance with these laws, all allogeneic HSCT recipients must be registered with the Center for International Blood & Marrow Transplant Research (CIBMTR). In doing so, the CIBMTR collects information to track outcomes of HSCT recipients in order to large scale outcomes data and practice trends in the field that influence clinical research approaches for future transplant candidates. The incredible amount of data gathered by the CIBMTR has led to pivotal retrospective analyses that contribute to the development of new treatment guidelines for hematologic malignancies and immunologic disorders.

Determining the Study Population

Autologous transplants do not require donors as the recipients receive their own cells. However, allogeneic transplants are complicated by the need for an HLA-matched donor to donate stem cells to the recipient. A large amount of HSCT research is performed in patients undergoing allogeneic transplants in order to prevent malignant relapse and help mitigate the effects of post-transplant complications. Also, since non-white minorities often face riskier transplant courses because they are unlikely to find matched donors, they ideally should be included in clinical trials in order to prevent, treat, and alleviate the burden of post-transplant complications. With those facts in mind, it was determined that only clinical trials involving allogeneic HSCT recipients would be included in the investigation for this thesis.

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Purpose and Hypothesis

As previously detailed, much time and effort have been dedicated to ensuring that everyone has equal access to clinical research, regardless of gender, race, and age. Though clinical research participants were primarily white men just decades ago, there have been legislative improvements calling for the inclusion of participants who would not have been allowed previously. The primary purpose of this thesis was to examine whether those allogeneic transplant recipients who participate in clinical research are representative of the overall allogeneic transplant recipient population as a whole. Gender and race were the main focus of the investigation while age played a minor role.

This thesis sought to utilize information contained in the CIBMTR database in order to determine demographic characteristics of allogeneic transplant recipients in recent years. Once the characteristics of allogeneic HSCT recipients were known, a comprehensive review of literature surrounding the results of HSCT clinical trials facilitated the investigation into whether the diversity of participants in those trials truly reflected the population of allogeneic transplant recipients in the United States.

The hypothesis of this thesis was that the diversity of the participants enrolled in HSCT clinical trials would not accurately represent the makeup of the population of allogeneic transplant recipients. By investigating this in detail, this thesis sought to demonstrate whether or not more work needs to be done to increase the inclusion of underrepresented minorities into clinical trials that may help save lives in the future.

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Methods

Prior to beginning the investigation, the formal thesis proposal and study plan were submitted to the Eastern Michigan University Institutional Review Board (IRB). Also submitted was documentation that included study team training and a formal request to the University Human Subjects Review Committee for approval to conduct research involving human subjects. This study was concluded to be exempt from IRB oversight due to the minimal risk of harm to the humans involved in the study.

The investigation into the diversity of participants in allogeneic HSCT clinical trials required two steps: identification of the participants who were eligible to enroll in the clinical trials and determination of the diversity of the actual clinical trial participants.

Identifying the Potential Clinical Trial Participants

In order to understand who is participating in allogeneic HSCT clinical trials, the pool of eligible subjects had to be identified. The CIBMTR maintains a database of allogeneic transplants performed in recent decades and, as the name implies, it is dedicated to improving HSCT outcomes through research. In keeping with that goal, the CIBMTR allows investigators to submit requests for data from its expansive database. Therefore, a Custom Information Request Form was submitted through the CIBMTR webpage for allogeneic transplants performed in the United States between January 1, 2010 and December 31, 2014, a total of five complete years. The data requested was meant to define the traits of the allogeneic HSCT recipient population.

In correspondence with the CIBMTR, however, it was discovered that the analysis of its 2014 data was not yet complete and it would not release that information at this time. It instead provided this researcher with the CIBMTR's Annual Progress Report for 2013 (CIBMTR, 2013),

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which included information about the allogeneic transplant population. In addition, the Health Resources and Services Administration—an agency of the United States' Department of Health and Human Services—publishes information utilizing CIBMTR data (H.R.S.A., n.d.). It was through these two resources that the allogeneic transplant recipient diversity was determined for this thesis. In keeping with the proposed plan, five years' worth of data was used that included transplants performed between January 1, 2009 and December 31, 2013.

Determining the Diversity of Clinical Trial Participants

After identifying the pool of eligible research participants, a literature review explored who among HSCT recipients were actually enrolling in clinical trials. Included in the review of recent publications of HSCT research studies were prospective trials with an intervention; any retrospective or purely observational studies were discounted. For the purposes of this thesis, an intervention was defined as a drug, survey, or other specialty procedure. To be included in this analysis, the study must have obtained each patient's consent to participate in the trial.

Observational and retrospective studies often rely on a patient providing consent to have their data collected with the purpose of it being used in any studies the researcher deems necessary. Because there are no planned interventions in this case, there is rarely any exclusion criteria for the study, so all patients are approached for inclusion.

The CIBMTR patient population was determined using only allogeneic HSCT recipients who were transplanted in the United States. Therefore, both single-center and multi-center trials were included in this step of the analysis; however, studies with international centers were not. Clinical trials in the literature search could be randomized, blinded, or placebo-controlled, though no specific study designs were required. If the intervention was a drug, it could be in any

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phase of development. For studies involving both autologous and allogeneic HSCT recipients, only the allogeneic patients were considered for analysis.

The most important criteria used to determine whether a clinical study could be involved in the analysis for this thesis was whether or not the publication included the demographic information for its participants. If race was not at least partially reported, the article was discounted from the analysis. If just one group was reported (i.e., white: 90%, etc.), then the remaining patients were classified as “unknown.” Race information was recorded as detailed as possible but was then simplified in order to report the most accurate data, as not all publications reported information that corresponded to the same CIBMTR race categories. The simplified categories were White, Non-White, and Unknown.

Google Scholar was instrumental in searching for publications that fulfilled all of these criteria. Publications were reviewed from scientific journals such as, but not limited to, *New England Journal of Medicine*, *Blood*, *Cancer*, *Biology of Blood and Marrow Transplantation*, and *Bone Marrow Transplantation*. For two HSCT-specific journals—*Biology of Blood and Marrow Transplantation* and *Bone Marrow Transplantation*—each monthly issue from 2011–2015 was examined.

Once a possible study was identified, the results contained in the publication were reviewed by this researcher to determine its eligibility. If an article was deemed eligible for inclusion, information about the publication was recorded into a Microsoft Excel database. Among the data collected was the intervention of the study, how many centers were involved, and the demographics of the patients in the trial. A copy of each article was then saved in a PDF format to allow for revisiting in the future.

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Statistical Analysis

Statistical analyses were done to determine whether recently published HSCT clinical trials demonstrated a reasonable degree of diversity with respect to the total population of allogeneic transplant recipients. Analyses utilized data collected in the Microsoft Excel database of publication information. Calculations themselves were also done with the help of functions in Microsoft Excel. The proportion of minorities in the study (publication) population was compared to the proportion of the same minority in the CIBMTR population using a two-proportion z-test (Jekel et al., 2007). Statistical significance was determined using the P value calculated from the z-test. If the P value was less than 0.05, the result was considered to be statistically significant.

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Results

Combining information from the CIBMTR and HRSA, a five-year allogeneic transplant recipient population of 37,768 was identified. A total of 46 clinical studies were identified from publications that fulfilled the criteria to be included in the race analysis, 44 of which also had corresponding gender data. The articles reported results from both single-center (n=19) and multi-center (n=27) trials. This mix of large and small trials led to a total of 4,780 patients that were included in the study population.

Race

The CIBMTR allows for patient race information to be collected into five categories: (1) American Indian/Alaska Native, (2) Asian, (3) Black or African American, (4) Native Hawaiian or Pacific Islander, and (5) White. This does not account for people of mixed race, those who chose to consider themselves to be only of Hispanic descent, and those who chose not to report their race. If a patient reported their heritage in one of these or another non-categorized fashion, they were reported by the CIBMTR in a sixth group: Data Not Available. Authors of published clinical trial manuscripts, however, may report their patients' diversity in any way they choose as it is optional for them to report racial characteristics at all. Due to the highly specific criteria needed in order to be included for analysis in this thesis, only a small number of articles were identified which had any sort of racial information.

With the CIBMTR reporting specific race categories and study authors reporting very little information, it was necessary to simplify and standardize the data between the two groups so they could be analyzed for comparison. The detailed CIBMTR information can be found in Tables 1 and 2. Data for the study population can be found in Tables 4 and 5 in Appendix B. The Data Not Available and Unknown race patients (n=945 for CIBMTR population and n=219 for

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study population) were discounted from analysis because there was no way to tell what their race was or why they were unreported. This left a total of 36,823 and 4,564 thesis participants for the CIBMTR and study populations, respectively. Non-white minority patients accounted for 13.3% (n=5,003) of the remaining CIBMTR population and 10.3% (n=472) of the study population. The differences in those proportions was found to be statistically significant ($p < 0.000001$).

Table 1

Detailed Race Information for Allogeneic Transplant Recipients Reported to the Center for International Blood and Marrow Transplant Research

Race	2009	2010	2011	2012	2013	Total	%
American Indian or Alaska Native	40	31	32	35	57	195	0.5
Asian	271	287	323	321	364	1,566	4.2
Black or African American	573	559	610	635	726	3,103	8.2
Native Hawaiian or Pacific Islander	28	25	32	22	32	139	0.4
White	5,876	6,072	6,390	6,599	6,883	31,820	84.3
Data Not Available	142	134	188	195	286	945	2.5

Note: Data was unavailable for those recipients who declined to share information regarding their race or for those whose racial information did not fit into one of the five major categories.

Table 2

Simplified Race Information for Allogeneic Transplant Recipients Reported to the Center for International Blood and Marrow Transplant Research

Race	2009	2010	2011	2012	2013	Total	%
Non-White	912	902	997	1,013	1,179	5,003	13.3
White	5,876	6,072	6,390	6,599	6,883	31,820	84.3
Unknown/Other	142	134	188	195	286	945	2.5

Note: Race categories were simplified for statistical analysis.

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Gender

Since there were only two categories (men and women) for gender reporting from both the CIBMTR and study populations, it allowed for a simpler analysis. Detailed gender information for the CIBMTR population can be found in Table 3 and the information for the study population can be found in Table 6 in Appendix B. All patients included in the analysis had a gender association, with no one being categorized as Unknown. There were 44 studies that provided gender information, with a total of 4,755 patients (n=37,768 for CIBMTR population). Higher numbers were reported for men in both populations, where they accounted for 58.5% (n=22,079) of the CIBMTR population and 55.6% (n=2,644) of the study population; women made up only 41.5% and 44.4% (n=15,689; n=2,111), respectively. These proportions showed statistical significance ($p < 0.006$).

Table 3

Gender Information for Allogeneic Transplant Recipients Reported to the Center for International Blood and Marrow Transplant Research

Gender	2009	2010	2011	2012	2013	Total	%
Men	4,029	4,117	4,417	4,574	4,942	22,079	58.5
Women	2,901	2,991	3,158	3,233	3,406	15,689	41.5

Limitations

This thesis hoped to include analysis of the differences in age between the CIBMTR and study populations. However, this proved to be difficult to analyze due to non-standardized reporting practices. The CIBMTR categorizes patients by decade (i.e., 0–10 years, 11–20 years, etc.), whereas most publications will report, at most, the age range and median age of the clinical

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trial's cohort. Also, the current policy in the United States is to conduct clinical research in children only when necessary and only after safety and efficacy have been proven in adults. This means clinical trials will often focus on either children (under the age of 18) or adults, rarely both in the same study. Also worth noting is the fact that disorders requiring HSCT may differ between children and adults. With all of these issues in mind, it was unfeasible to examine age differences more closely.

Due to the reliance on data from outside sources, this investigation was limited in the scope of analyses it could perform. For instance, there was no way to identify both the race and gender for individual patients. As such, it was not feasible to analyze multi-dimensional information (i.e., how many non-white women were in a population). Also limiting the investigation was the small number of publications that reported race information. This resulted in a small sample size of studies eligible for inclusion. A larger sample size is desired in order to ensure a better reflection of clinical trial participants.

Discussion

While there has been progress for equal inclusion of women and minority patients into clinical trials over the last few decades, it seems there is still work to be done in both the allogeneic transplant realm and clinical research as a whole.

Women in Clinical Research

The data from this investigation demonstrates that the proportion of women in the study population is different from the proportion of women in the CIBMTR population; however, that is not an unfavorable result. The results indicate that a larger proportion of women are participating in clinical trials than is necessary to appropriately reflect the allogeneic HSCT population (44.4% for the study population vs. 41% for the CIBMTR population). Unfortunately, this is not the case in many other clinical research specialties. For instance, in 2013, Kwiatkowski, Coe, Bailar and Swanson examined how the number of women in cancer-related clinical trials had changed since 1990. They found that “the actual inclusion of women remain[ed] low, making up only 40.2% of participants in cancer treatment trials and 26.5% of participants in cancer prevention trials (excluding sex-specific trials)” (Kwiatkowski et al., 2013, p. 2961). This is especially relevant to allogeneic HSCT recipients because the large majority of these transplants are performed in patients with hematologic malignancies. So, while data from this thesis demonstrated an appropriate representation of women in allogeneic transplant trials, it is not indicative of a similar trend in clinical research as a whole.

Although the proportion of women in the study population appeared to accurately reflect the CIBMTR population, this investigation was limited with regard to any further analysis. Because the CIBMTR and HRSA only provided information about broad demographic

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categories, it was impossible to tell the characteristics of individual patients. Similarly, the investigation encountered the same disadvantage with the study population due to authors' apathetic attitude towards reporting demographic details. If those details had been accessible, it would have been valuable to perform multi-dimensional analyses to investigate the proportions of non-white women in both populations.

Minorities in Clinical Research

The results from this investigation demonstrate that while the number of non-white minorities who received allogeneic transplants between 2009 and 2013 was relatively low (13.6%), the number of non-white minorities who participated in clinical research was even lower (9.9%). This is particularly worrisome as non-white minorities often face riskier transplant courses and would most likely benefit from new therapies to help prevent, mitigate, or treat the effects of post-HSCT complications.

Unfortunately, the lower proportion of non-white minorities participating in clinical trials was unsurprising as similar trends persist in other subspecialties of clinical research. For instance, in their investigation into strictly cancer-related trials, Kwiatkowski et al. (2013) found "whites still make up the significant majority (>80% of all participants in cancer clinical trials)" (p. 2961). They also determined that the "number of African Americans participating in cancer treatment trials actually declined over the previous 10 years, while there were slight increases in the inclusion of other minority groups. Within cancer prevention studies, African Americans represented 11.6% of all participants, with other minorities representing $\leq 4\%$ " (Kwiatkowski et al., 2013, p. 2961). These numbers are frighteningly low and the fact that African American participation had declined over the previous decade was alarming. With such low minority participation numbers, it is difficult for clinical trials to gather enough information about how the

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non-white population may be affected by new therapies. It is challenging to produce accurate safety and efficacy data for new therapies for a diverse population when they are only tested in a primarily white population. This could potentially lead to drugs that are dangerous or ineffective in the minority population even though they are proven to be safe and effective in the white population. It also suggests a barrier to investigational therapies that may have potential immediate direct benefit to minority populations.

There are several factors that may have contributed to a small number of minorities enrolling in clinical trials for allogeneic transplant recipients. First, it has been shown that the post-transplant survival of non-white minorities is lower than that of white patients (Hamilton et al., 2015). Therefore, the lower number of minority clinical trial participants may be related to the fact that those patients just aren't living long enough to enroll in studies. This is most likely due to a higher prevalence of post-transplant complications in the non-white population. However, this sort of "time bias" would not explain those clinical trials that are offered to potential participants at the time of their HSCT.

Another possible influence may be socioeconomic factors. For a typical allogeneic transplant course, the average medical costs for the first 100 days post-HSCT are approximately \$200,000 (Majhail et al., 2013). This is obviously a large undertaking for anyone to deal with but the out-of-pocket burden is lessened substantially for those patients with good health insurance coverage. Patients are forced to take a lot of time off from work and some even lose their jobs entirely. With medical bills piling up, some patients may decline to participate in clinical trials because they can't afford to take any more time away from work.

Yet another possible explanation for the low number of minority patients in HSCT clinical trials relates to access to quality medical care. Transplant centers are usually found in

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densely populated cities where there exists a large pool of potential patients. If non-white patients live in more rural areas, they will have to endure long journeys just to travel to the transplant center to receive routine care. If a clinical trial requires many study-related visits, geographic proximity will certainly play a role in patients' decision to enroll in the trial; it may even prevent the researchers from approaching the patient for possible enrollment.

It is also worth noting that there is a perception among minority patients, particularly African Americans, that “research is biased to benefit white people, resulting in a lack of trust” (Smith et al., 2007, p. 425). This is a major barrier to clinical research participation and it's a perception that exists on both on an individual and community level. While this is likely multifactorial, possible explanations could be lack of individual and community-wide education related to clinical research, as well as lingering effects of the highly unethical Tuskegee Syphilis Study performed in African American men under the guidance of the United States Public Health Service (Emanuel et al., 2011).

Future Directions

The data from this investigation demonstrated that there is still work to be done to increase the number of minority patients enrolling in clinical trials related to allogeneic transplants. And, while the numbers in this study indicated an appropriate number of women participants, it is important not to lose momentum. In order to maintain this progress, Mazure and Jones (2015) suggested that “the NIH should offer priority to grant applications addressing sex and gender differences, and the FDA should require sex-specific data for all drug and device applications”. They went on to hold all clinical researchers accountable for creating a culture to value men and women participants equally. The research community must implement changes,

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some of which include “requiring that medical and continuing medical education incorporates consideration of the influence of sex and gender on health” (Mazure & Jones, 2015).

Efforts should also be undertaken to recruit more minority patients into clinical trials. There were strategies identified by Smith et al. (2013) to help recruit and retain minority patients. First, community involvement in clinical research would be beneficial for recruiting and education efforts. Such involvement could emphasize the benefits of research and would go a long way toward building trust in medical establishments. Next, the clinical trial’s study team should have at least some minority representation to aid in building relationships with minority patients. Lastly, compensation or other incentives are highly desirable, so offer those whenever possible. This would help offset costs incurred during the life of the trial and would demonstrate to patients that their participation is valued (Smith et al., 2013).

Once researchers have completed their clinical trials and look to publish their results, it is imperative that they include the demographics of their participants. There is no other way to measure overall progress with regard to the inclusion of women and minorities in clinical research other than reviewing the literature. Demographic information is also necessary for physicians to know if a study drug in a publication can be safely prescribed to their patients. Clinical researchers must be diligent in reporting this information.

Finally, more work should be done in examining the representation of women and minorities in clinical trials, particularly in subspecialties like allogeneic transplantation. Clinical research is meant to advance scientific knowledge in order to help patients and society in the future. The only way to accomplish that goal is to perform studies in a diverse patient group which mirrors the makeup of society as a whole. The only means to determine where the

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research community is failing to meet that need is to identify where the deficiencies are and dedicate efforts to ensure they are corrected.

Conclusions

For the last few decades, much progress has been made for the inclusion of women and minority patients into clinical trials throughout the United States. This thesis set out to investigate the current representation of women and minorities in clinical trials that involved allogeneic transplant recipients in order to determine if their inclusion accurately reflected the transplant community as a whole. The findings concluded that while the proportion of women enrolled in clinical trials was better than anticipated, the number of minority participants remained low. This is worrisome because a lack of diversity within clinical trials will lead to a shortage of safety and efficacy data for novel therapies in minorities.

Though this thesis focused a critical eye on the allogeneic transplant recipient community, it is not the only specialty area to face these challenges. Now that the diversity deficiencies have been identified, the entire scientific community must continue to implement changes that promote the inclusion of women and minorities into clinical trials. This could mean differences in funding allocations, publication practices, or recruitment strategies; all of which could help the enrollment numbers of underrepresented populations throughout the United States. Clinical researchers throughout the country must continue to strive for greater inclusion of women and minorities in order to give them access to potentially life-saving therapies and to gain more insight into the safety and efficacy of new therapies in these populations.

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Appendix A: Glossary

Allogeneic transplant: type of stem cell transplant that involves volunteers donating stem cells to recipients in need.

Autologous transplant: type of stem cell transplant in which a recipient receives their own stem cells.

CIBMTR: Center for International Blood and Marrow Transplant Research. Registry responsible for collecting data about stem cell transplants and recipients.

HSCT: hematopoietic stem cell transplant. See “Autologous transplant” and “Allogeneic transplant” for different types of HSCT.

HLA: human leukocyte antigen. Molecules on the surface of human cells that help the body identify other cells that belong there.

HRSA: Human Resources and Services Administration. An agency of the United States’ Department of Health and Human Services responsible for reporting and tracking outcomes of stem cell transplants nationally.

NMDP: National Marrow Donor Program. An organization in the United States that maintains a registry of volunteers who are willing to act as stem cell donors for patients in need.

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Appendix B: Tables

Table 4

Detailed Race Information from Literature Review Publications

Author, Year	Total	White	%	B/AA	%	Asian	%	AI/AN	%	NH/PI	%	O/U	%
Amin, 2014	126	120	95.2	0	0.0	0	0.0	0	0.0	0	0.0	6	4.8
Anderlini, 2015	79	64	81.0	5	6.3	3	3.8	0	0.0	0	0.0	7	8.9
Baird, 2015	20	18	90.0	1	5.0	0	0.0	0	0.0	0	0.0	0	0.0
Ballen, 2012	13	10	76.9	0	0.0	1	7.7	0	0.0	0	0.0	2	15.4
Bashey, 2011	80	73	91.3	3	3.8	2	2.5	0	0.0	0	0.0	0	0.0
Besien, 2016	97	59	60.8	23	23.7	0	0.0	0	0.0	0	0.0	15	15.5
Devine, 2011	44	42	95.5	0	0.0	0	0.0	0	0.0	0	0.0	2	4.5
El-Jawahri, 2014	522	470	90.0	13	2.5	22	4.2	0	0.0	0	0.0	17	3.3
Fathi, 2016	30	27	90.0	0	0.0	0	0.0	0	0.0	0	0.0	3	10.0
Foster, 2012	164	143	87.2	16	9.8	0	0.0	0	0.0	0	0.0	5	3.0
Garcia, 2012	64	53	82.8	4	6.3	0	0.0	0	0.0	0	0.0	2	3.1
Gatza, 2014	34	30	88.2	0	0.0	0	0.0	0	0.0	0	0.0	4	11.8
Grosso, 2015	28	20	71.4	4	14.3	1	3.6	0	0.0	0	0.0	0	0.0
Halasa, 2016	44	44	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Jim, 2013	24	23	95.8	0	0.0	0	0.0	0	0.0	0	0.0	1	4.2
Kamani, 2012	8	0	0.0	7	87.5	0	0.0	0	0.0	0	0.0	1	12.5
Karras, 2013	65	53	81.5	0	0.0	0	0.0	0	0.0	0	0.0	12	18.5
Khera, 2014	268	246	91.8	0	0.0	0	0.0	0	0.0	0	0.0	13	4.9
Kimball, 2016	184	165	89.7	1	0.5	7	3.8	1	0.5	0	0.0	8	4.3
Ladas, 2015	30	16	53.3	12	40.0	2	6.7	0	0.0	0	0.0	0	0.0
Leen, 2013	50	38	76.0	7	14.0	0	0.0	0	0.0	0	0.0	5	10.0
Leung, 2011	190	139	73.2	0	0.0	0	0.0	0	0.0	0	0.0	51	26.8
Liesveld, 2013	19	17	89.5	1	5.3	0	0.0	0	0.0	0	0.0	0	0.0

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Table 4 (continued)

Author, Year	Total	White	%	B/AA	%	Asian	%	AI/AN	%	NH/PI	%	O/U	%
Liu, 2011	45	32	71.1	9	20.0	0	0.0	0	0.0	0	0.0	4	8.9
Loggers, 2014	18	18	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Mahadeo, 2015	22	3	13.6	5	22.7	3	13.6	0	0.0	0	0.0	2	9.1
Majhail, 2012	25	24	96.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Marty, 2013	230	207	90.0	0	0.0	0	0.0	0	0.0	0	0.0	23	10.0
Muffly, 2013	166	154	92.8	8	4.8	0	0.0	0	0.0	0	0.0	4	2.4
Oberg, 2012	80	25	31.3	16	20.0	5	6.3	0	0.0	0	0.0	34	42.5
Pasquini, 2016	1013	896	88.5	54	5.3	29	2.9	5	0.5	5	0.5	24	2.4
Pidala, 2015	12	12	100.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Shea, 2011	44	32	72.7	0	0.0	0	0.0	0	0.0	0	0.0	12	27.3
Shook, 2015	8	4	50.0	2	25.0	0	0.0	0	0.0	0	0.0	1	12.5
Simmons, 2011	26	18	69.2	0	0.0	0	0.0	0	0.0	0	0.0	8	30.8
Stieglitz, 2014	85	67	78.8	3	3.5	7	8.2	0	0.0	0	0.0	8	9.4
Syrjala, 2011	92	87	94.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Thakar, 2011	6	4	66.7	1	16.7	0	0.0	0	0.0	0	0.0	0	0.0
Triplett, 2015	17	7	41.2	3	17.6	0	0.0	0	0.0	0	0.0	7	41.2
Wallace, 2015	134	116	86.6	0	0.0	0	0.0	0	0.0	0	0.0	18	13.4
Weisdorf, 2012	24	15	62.5	6	25.0	1	4.2	0	0.0	0	0.0	2	8.3
Williams, 2014	166	152	91.6	8	4.8	3	1.8	0	0.0	0	0.0	0	0.0
Windreich, 2016	19	15	78.9	1	5.3	2	10.5	0	0.0	0	0.0	1	5.3
Wood, 2013	22	18	81.8	2	9.1	1	4.5	0	0.0	0	0.0	0	0.0
Wood, 2016	310	284	91.6	10	3.2	5	1.6	1	0.3	3	1.0	7	2.3
Zhang, 2016	33	29	87.9	2	6.1	2	6.1	0	0.0	0	0.0	0	0.0
Totals	4,780	4,089	85.5	227	4.7	96	2.0	7	0.1	8	0.2	306	6.4

Note: This table includes detailed race information gathered from articles in scientific journals that were identified during a review of recent literature. Only allogeneic transplant recipients were included. If race reporting was incomplete in an article, patients were reported as Other/Unknown. Race abbreviations: AI/NA: American Indian or

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Native Alaskan; B/AA: Black or African American; NH/PI: Native Hawaiian or Pacific Islander; O/U:
Other/Unknown.

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Table 5

Simplified Race Information from Literature Review Publications

Author, Year	Total	White	%	NW	%	Unk	%
Amin, 2014	126	120	95.2	0	0.0	6	4.8
Anderlini, 2015	79	64	81.0	8	10.1	7	8.9
Baird, 2015	20	18	90.0	2	10.0	0	0.0
Ballen, 2012	13	10	76.9	1	7.7	2	15.4
Bashey, 2011	80	73	91.3	7	8.8	0	0.0
Besien, 2016	97	59	60.8	23	23.7	15	15.5
Devine, 2011	44	42	95.5	0	0.0	2	4.5
El-Jawahri, 2014	522	470	90.0	35	6.7	17	3.3
Fathi, 2016	30	27	90.0	0	0.0	3	10.0
Foster, 2012	164	143	87.2	16	9.8	5	3.0
Garcia, 2012	64	53	82.8	9	14.1	2	3.1
Gatza, 2014	34	30	88.2	0	0.0	4	11.8
Grosso, 2015	28	20	71.4	8	28.6	0	0.0
Halasa, 2016	44	44	100.0	0	0.0	0	0.0
Jim, 2013	24	23	95.8	0	0.0	1	4.2
Kamani, 2012	8	0	0.0	8	100.0	0	0.0
Karras, 2013	65	53	81.5	0	0.0	12	18.5
Khera, 2014	268	246	91.8	20	7.5	2	0.7
Kimball, 2016	184	165	89.7	14	7.6	10	5.4
Ladas, 2015	30	16	53.3	14	46.7	0	0.0
Leen, 2013	50	38	76.0	7	14.0	5	10.0
Leung, 2011	190	139	73.2	51	26.8	0	0.0
Liesveld, 2013	19	17	89.5	2	10.5	0	0.0
Liu, 2011	45	32	71.1	9	20.0	4	8.9
Loggers, 2014	18	18	100.0	0	0.0	0	0.0
Mahadeo, 2015	22	3	13.6	18	81.8	1	4.5
Majhail, 2012	25	24	96.0	1	4.0	0	0.0
Marty, 2013	230	207	90.0	0	0	23	10.0
Muffly, 2013	166	154	92.8	8	4.8	4	2.4
Oberg, 2012	80	25	31.3	21	26.3	34	42.5
Pasquini, 2016	1013	896	88.5	93	9.2	24	2.4
Pidala, 2015	12	12	100.0	0	0.0	0	0.0
Shea, 2011	44	32	72.7	0	0.0	12	27.3
Shook, 2015	8	4	50.0	3	37.5	1	12.5
Simmons, 2011	26	18	69.2	0	0.0	8	30.8
Stieglitz, 2014	85	67	78.8	10	11.8	8	9.4
Syrjala, 2011	92	87	94.6	5	5.4	0	0.0
Thakar, 2011	6	4	66.7	2	33.3	0	0.0
Triplett, 2015	17	7	41.2	10	58.8	0	0.0
Wallace, 2015	134	116	86.6	18	13.4	0	0.0
Weisdorf, 2012	24	15	62.5	9	37.5	0	0.0
Williams, 2014	166	152	91.6	14	8.4	0	0.0

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Table 5 (continued)

Author, Year	Total	White	%	NW	%	Unk	%
Windreich, 2016	19	15	78.9	4	21.1	0	0.0
Wood, 2013	22	18	81.8	4	18.2	0	0.0
Wood, 2016	310	284	91.6	19	6.1	7	2.3
Zhang, 2016	33	29	87.9	4	12.1	0	0.0
Totals	4,780	4,089	85.5	472	9.9	219	4.6

Note: In order to simplify representation calculations, this table reclassified the detailed race information found in articles from the literature review. Calculations were done based on White/Non-White/Unknown categories, with the patients of unknown race discounted from the analysis.

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Table 6

Gender Information from Literature Review Publications

Author, Year	Total Patients	Men	%	Women	%
Amin, 2014	126	86	68.3	40	31.7
Anderlini, 2015	79	40	50.6	39	49.4
Baird, 2015	20	14	70.0	6	30.0
Bashey, 2011	80	49	61.3	31	38.8
Besien, 2016	97	60	61.9	37	38.1
Devine, 2011	44	16	36.4	28	63.6
El-Jawahri, 2014	522	297	56.9	225	43.1
Fathi, 2016	30	18	60.0	12	40.0
Foster, 2012	164	81	49.4	83	50.6
Garcia, 2012	64	42	65.6	22	34.4
Gatza, 2014	34	26	76.5	8	23.5
Grosso, 2015	28	19	67.9	9	32.1
Halasa, 2016	44	27	61.4	17	38.6
Jim, 2013	24	12	50.0	12	50.0
Kamani, 2012	8	2	25.0	6	75.0
Karras, 2013	65	39	60.0	26	40.0
Khera, 2014	268	136	50.7	132	49.3
Kimball, 2016	184	104	56.5	80	43.5
Ladas, 2015	30	16	53.3	14	46.7
Leen, 2013	50	33	66.0	17	34.0
Leung, 2011	190	114	60.0	76	40.0
Liesveld, 2013	19	7	36.8	12	63.2
Liu, 2011	45	30	66.7	15	33.3
Loggers, 2014	18	8	44.4	10	55.6
Mahadeo, 2015	22	7	31.8	15	68.2
Majhail, 2012	25	13	52.0	12	48.0
Marty, 2013	230	132	57.4	98	42.6
Muffly, 2013	166	108	65.1	58	34.9
Oberg, 2012	80	51	63.8	29	36.3
Pasquini, 2016	1,013	503	49.7	510	50.3
Shea, 2011	44	35	79.5	9	20.5
Shook, 2015	8	5	62.5	3	37.5
Simmons, 2011	26	16	61.5	10	38.5
Stieglitz, 2014	85	56	65.9	31	36.5
Syrjala, 2011	92	43	46.7	49	53.3
Thakar, 2011	6	4	66.7	2	33.3
Triplett, 2015	17	11	64.7	6	35.3
Wallace, 2015	134	87	64.9	47	35.1
Weisdorf, 2012	24	11	45.8	13	54.2
Williams, 2014	166	76	45.8	90	54.2
Windreich, 2016	19	9	47.4	10	52.6
Wood, 2013	22	11	50.0	11	50.0
Wood, 2016	310	173	55.8	137	44.2
Zhang, 2016	33	19	57.6	14	42.4
Totals	4,755	2,644	55.6	2,111	44.4

Note: This table includes gender information gathered from articles in scientific journals that were identified during a review of recent literature.

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Appendix C: Human Subjects Exemption Letter

UHSRC Determination: EXEMPT

DATE: May 25, 2016

**TO: Tracey Churay
Department of Clinical Research Administration
Eastern Michigan University**

**Re: UHSRC: # 906305-1
Category: Exempt category 4
Approval Date: May 25, 2016**

Title: The Diversity of Participants in Clinical Trials Involving Allogeneic Hematopoietic Stem Cell Transplant Recipients

Your research project, entitled **The Diversity of Participants in Clinical Trials Involving Allogeneic Hematopoietic Stem Cell Transplant Recipients**, has been determined **Exempt** in accordance with federal regulation 45 CFR 46.102. UHSRC policy states that you, as the Principal Investigator, are responsible for protecting the rights and welfare of your research subjects and conducting your research as described in your protocol.

Renewals: Exempt protocols do not need to be renewed. When the project is completed, please submit the **Human Subjects Study Completion Form** (access through IRBNet on the UHSRC website).

Modifications: You may make minor changes (e.g., study staff changes, sample size changes, contact information changes, etc.) without submitting for review. However, if you plan to make changes that alter study design or any study instruments, you must submit a **Human Subjects Approval Request Form** and obtain approval prior to implementation. The form is available through IRBNet on the UHSRC website.

Problems: All major deviations from the reviewed protocol, unanticipated problems, adverse events, subject complaints, or other problems that may increase the risk to human subjects **or** change the category of review must be reported to the UHSRC via an **Event Report** form, available through IRBNet on the UHSRC website.

Follow-up: If your Exempt project is not completed and closed after **three years**, the UHSRC office will contact you regarding the status of the project.

Please use the UHSRC number listed above on any forms submitted that relate to this project, or on any correspondence with the UHSRC office.

Good luck in your research. If we can be of further assistance, please contact us at 734-487-3090 or via e-mail at human.subjects@emich.edu. Thank you for your cooperation.

Sincerely,

Sonia Chawla, PhD
Research Compliance Officer