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A Systematic Review of NHLBI-funded Cardiovascular Clinical Trials and the Impact of the NIH Revitalization Act on the Enrollment of Women and Reporting of Sex-Specific Outcomes in Primary Findings Publications

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A Systematic Review of NHLBI-funded Cardiovascular Clinical Trials and the Impact of the NIH Revitalization Act on the Enrollment of Women: Reporting of Sex-Specific Outcomes in Primary Findings Publications

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

A Systematic Review of NHLBI-funded Cardiovascular Clinical Trials and the Impact of the NIH Revitalization Act on the Enrollment of Women: Reporting of Sex-Specific Outcomes in Primary Findings Publications

By: Ebyan A. Addou Salah

The establishment of new laws and policies that address public health issues can serve as a powerful tool to initiate change in public health practice. The NIH Revitalization Act of 1993, was implemented to ensure the inclusion of women and underrepresented minorities in NIH funded clinical trials.

In the United States, cardiovascular disease (CVD) is the leading cause of death among women (T. Shah, Palaskas, & Ahmed, 2016). Historically the overriding belief in the biomedical community was the inclusion of women in clinical trials caused inconsistencies and invalid findings. Progress has been made in the inclusion of women in clinical trials since the passage of the 1993 NIH Revitalization Act, yet these changes have not translated to equity in the inclusion of women in cardiovascular clinical trials according to disease prevalence or the reporting of sex-specific outcomes in primary results publications.

In this systematic review, Clinical Trials.gov was accessed to identify NHLBI funded CVD clinical trials and the unique "NCT" Clinical trial.gov identification numbers were used to retrieve primary results publications in PUBMED. The primary results publications that were located were used to assess the enrollment of women in CVD clinical trials, whether there were outcomes by CVD area, prevention type, and if the clinical trials addressed sex-specific outcomes in the primary results papers.

Results showed a higher proportion of men (59.5%) enrolled in the NHLBI funded CVD clinical trials that were included in this systematic, compared to women (40.5%) (95% CI: 40.17%, 40.63%).

Only 20 of the 142 CVD trials (14.1%) reported on sex-specific outcomes in the results, discussion and/or conclusion sections and 122 (85.9%) of the 142 CVD trials with published primary results papers did not address sex outcomes in the results, discussion or conclusion sections.

The results suggest that improvements have been made with regards to the inclusion of women in CVD trials when compared to previously published systematic reviews, however the reporting of sex-specific outcomes in primary results papers still demonstrate that few publications report on sex-specific outcomes in CVD trials.

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Chapter 1 – Introduction

The establishment of new laws and policies that address specific public health issues can serve as a powerful tool to initiate change in public health practice (Burris et al., 2010). The implementation of public health policies can have far reaching effects on large segments of the population, and require consensus from various stakeholders (Moreland-Russell, Brownson, Eyler, & Chriqui, 2016). The National Institutes of Health (NIH) Revitalization Act of 1993, which was implemented to ensure representation of women and underrepresented minorities in NIH funded clinical trials, is an important example of how policy decisions can influence understanding of health conditions and influence the availability of interventions to improve health outcomes in more than half of the U.S. population.

The inclusion of women and underrepresented minorities in clinical research trials is essential to ensuring the generalizability of study results to the entire population and may contribute to the reduction of disparities in health by ensuring efficacy of interventions is well-understood (Brown et al., 2015). Generalizability of clinical research findings is contingent upon a variety of factors, including the investigators' ability to recruit and retain patients to participate in clinical trials (Mills et al., 2006). Determining the efficacy of an intervention does not depend only on the number of patients taking part in the clinical trial, but also on the representation of different segments of the population (Moye & Powell, 2001). The interventions proposed in a clinical trial may result in different health outcomes among different segments of the population, and so ensuring that the patients participating in a clinical trial include

specific subgroup populations is an important factor in determining the efficacy of an intervention proposed in a clinical trial (Sisk et al., 2008).

Gradual changes in population demographics can also greatly affect the incidence and prevalence data of diseases studied in clinical trials (Boden-Albala et al., 2015). And, preconceived notions regarding higher disease prevalence among specific groups or individuals who are believed to be most affected by a specific disease can result in selection bias in clinical trial design (Wenger, 2010). Many cardiovascular related diseases are more prevalent in women than in men, for example coronary microvascular disease, a form of heart disease in which the walls of the heart's small arteries are damaged or are diseased (NHLBI, 2014). Age is also an important risk factor for women and heart disease as women develop coronary heart disease, on average ten years later than men (NHLBI, 2014).

Yet, many clinical trials are unable to recruit and retain women and underrepresented minorities at rates comparable to the overall prevalence of many chronic diseases (Moye & Powell, 2001). This includes cardiovascular clinical trials (Melloni et al., 2010), despite cardiovascular disease being the most common cause of death in women in the U.S. (E. S. Kim & Menon, 2009).

Background Regarding Inclusion of Women in NIH Funded Research and the 1993 NIH Revitalization Act

The push to include female participants specifically in federally funded clinical research has been a recent development in biomedical research (Auerbach & Figert, 1995). The repercussions of serious adverse events in pregnant women related to the administration of medications such as thalidomide in the 1960s and diethylstilbestrol (also known as DES) in the 1970s led to FDA guidelines in 1977 that excluded childbearing women from participating in early phase clinical trials (Merkatz, 1998).

The establishment of the Public Health Service Task Force in 1983 and the release of the of the Public Health Services Task Forces report on Women's Health Issues in 1985 shed light on sex outcomes in the manifestation of disease symptoms and progression (Correa-De-Araujo, 2006) and that women are adequately represented in clinical trials that focus on drug interventions ("Women's health. Report of the Public Health Service Task Force on Women's Health Issues," 1985). Following the release of the Task Force Report, the NIH established policy in 1986 regarding the inclusion of women in clinical research that urged investigators receiving funding from NIH to include women in clinical research (Auerbach & Figert, 1995). The policy did very little to change the inclusion of women in NIH funded research despite the release of NIH inclusion policy in 1987 to the biomedical research community (Baird, 1999).

In 1990, the Government Accounting Office (GAO) issued a report detailing the NIH's progress in the inclusion of women in clinical research (Baird, 1999). The GAO report was presented in June 1990 during a House Subcommittee Meeting on Health and

the Environment (which oversaw the NIH) chaired by Rep. Henry Waxman (D-CA) and the authors found that the NIH Inclusion Policy first issued in 1986 was not widely enforced throughout the different institutes and centers in the NIH (Auerbach & Figert, 1995). As a consequence, an agency-wide system was not in place to monitor the number of women in NIH funded clinical trial (Auerbach & Figert, 1995). Members of the Congressional Women's Health Caucus (CCWI) which included Co-Chairs Pat Schroeder (Rep. D-CO) and Olympia Snowe (Rep. R-ME), highlighted the GAO Report's findings that many of the landmark clinical trials funded by the NIH did not include women participants, including the Physician's Health Study (a randomized clinical trial made up of 22,071 male physicians to test the effects of aspirin to prevent heart attack and the Multi-Risk Factor Intervention Trials (also known as "Mr. FIT") which examined the risk factors of Coronary Heart Disease in 15,000 men (Auerbach & Figert, 1995).

The disparities in the inclusion of women that were cited in the 1990 GAO Report helped accelerate programs and policies that fostered parity in NIH funded clinical research (Baird, 1999). The Women's Health Initiative, which was established in 1991 enrolled 150,000 women in over forty clinical centers in the U.S. over the course of 14 years and was the largest research study funded by NIH (Baird, 1999). The NIH's Outreach Notebook, which provided information regarding the inclusion of women and underrepresented minorities in clinical research and recruitment strategies (Baird, 1999). However, the most significant change that was initiated by the release of the 1990 GAO report was the NIH Revitalization Act (Auerbach & Figert, 1995).

The NIH Revitalization Act and NHLBI Inclusion Policy

The NIH Revitalization Act was signed into law by President Clinton in 1993 (Baird, 1999) and required that clinical research funded by the NIH include both women and members of underrepresented minority groups (Chen, Lara, Dang, Paterniti, & Kelly, 2014); specified outreach efforts to promote inclusion of women and underrepresented minorities in clinical research proposals; and, required the dissemination and analysis of research findings that address differences in women and underrepresented minorities (Baird, 1999).

Although the NIH Revitalization Act acknowledged that there were disparities in the participation of women and underrepresented minorities in clinical trials ("NIH Revitalization Act," 1993), the law did not provide the biomedical community with clear guidelines regarding the number of women and underrepresented minorities needed to determine whether the intervention proposed would result in differences in gender, racial, and ethnic subgroup populations ("NIH Revitalization Act," 1993). The NHLBI's inclusion policy for clinical research requires that the number of women and underrepresented minorities participating in a clinical trial reflect the disease prevalence ("Inclusion of Minorities and Women in Study Populations- Questions and Answers," 2011). If the disease's prevalence is not known, then the composition of the patients recruited in the clinical trial should be based on the most recent U.S. Census, i.e. for 2010, 51% women and 30% underrepresented racial and ethnic minorities ("Inclusion of Minorities and Women in Study Populations- Questions and Answers," 2011).

Exceptions to the NHLBI inclusion policy include for example, clinical trials that focus on diseases that are prevalent or occur in a specific population ("Inclusion of Minorities and Women in Study Populations- Questions and Answers," 2011).

Problem Statement

The primary purpose of the 1993 NIH Revitalization Act was to establish enforceable guidelines concerning the inclusion of women and members of minority groups in all clinical trials funded by the NIH. In essence, the 1993 NIH Revitalization Act, acknowledged that disparities in the inclusion and enrollment of women and underrepresented minorities in clinical trials affected the knowledge-base and health resources (Rochon et al., 2004). Quantifying the effects of the implementation of a policy can be a difficult endeavor. In the case of the NIH Revitalization Act, there may be different factors that prevent studies from recruiting sufficient numbers of women so that valid analyses can be made with regards to possible sex-specific outcomes in the intervention proposed in the clinical trial.

Now in its twenty-third year, it is generally believed by people in the field that the implementation of the 1993 NIH Revitalization Act has resulted in an increase in the number of women recruited as participants in clinical trials. However, continuing low recruitment of women and their subpopulations in mixed-gender cardiovascular clinical trials continues to be a recurring theme in the biomedical literature (E. S. Kim, Carrigan, & Menon, 2008). To better understand the actual impact of the Act, I conducted a systematic review and content analysis of the primary results papers of cardiovascular clinical trials funded by the National Heart, Lung, and Blood Institute (NHLBI). The aim

of the review is to understand the extent to which women have actually been included in these clinical trials and to provide insights regarding the challenges that clinical trials face in disseminating primary research findings relevant to women and cardiovascular disease in accordance to the Act.

Theoretical Framework

The theoretical framework utilized for this systematic review and content analysis is the "Assessment of Evidence Base Policies"(Moreland-Russell et al., 2016). In this model, when a problem is identified and requires attention, policymakers and advocates look to evidence-based data as to whether or not a recommended policy will be effective, the costs involved, and ways in which the policy can be implemented (Moreland-Russell et al., 2016). The assessment of evidence-based policies rely heavily on scientific evidence and experience from previously proposed policies and over time, this framework can demonstrate whether the policies being examined resulted in progress with regards to a specific public health issue or problem (Moreland-Russell et al., 2016).

The Assessment of Evidence Base Policies can be initiated through the following six steps:

Step 1: Identify the components of evidence for the topic of interest (i.e. resources such as systematic review or other published research);

Step 2: Develop a method to quantify or categorize the components being analyzed;

Step 3: Create a tool for abstraction or the information being assessed by each policy;

Step 4: Collect policies of interest through tracking systems;

Step 5: Assess the content of each policy using the abstraction tool or checklist and use measures that ensure reliability; and,

Step 6: Compile and disseminate the results (Moreland-Russell et al., 2016).

Purpose Statement

The purpose of this research project is to conduct a systematic review and content analysis examining whether the primary results publications of NHLBI-funded cardiovascular disease clinical trials address sex-specific outcomes in accordance to the 1993 NIH Revitalization Act. The project will also analyze whether there are variances in the reporting of sex-specific outcomes in primary publication findings of NHLBI funded cardiovascular clinical trials based on the number of women enrolled in the clinical trial and the overall number of patients enrolled, the cardiovascular disease sub-category and whether the clinical trial focuses on primary versus secondary prevention of cardiovascular diseases.

Research Questions

The research questions that will be asked in this systematic review and content analysis are:

1) Are there variances in the reporting of sex-specific outcomes according to the disease area of the cardiovascular clinical trial?

2) In accordance to the NIH Revitalization Act, do the primary findings publications of NHLBI funded cardiovascular clinical trials report on sex-specific outcomes in the interventions proposed in the clinical trial?

3) Are there variances in the percentage of women reported in the primary finding of NHLBI funded cardiovascular clinical trials by year?

4) Based on the content analysis of the primary findings of cardiovascular clinical trials funded by the NHLBI, what can the analysis tell us about how effective the NIH Revitalization Act is being implemented in cardiovascular clinical trials?

Significance Statement

The dissemination of research findings has significant implications with regard to the development of treatment protocols and disease guidelines. If clinical trials are unable to recruit a diverse patient population, it may become difficult to implement these research findings to a wider patient population. The recruitment of women, particularly in NIH funded cardiovascular clinical trials can lead to a greater understanding of the effects of interventions used to treat cardiovascular diseases and the dissemination of research findings addressing sex-specific outcomes can contribute to the overall biomedical knowledgebase.

Term Definitions and Abbreviations

Abdominal Aortic Aneurysm
A condition whereby the walls of a blood vessel weaken and a dialation similar to a balloon in shape develops most commonly in the blood vessels that provide blood to the legs
(SVS)

Acute Coronary Syndrome
An umbrella term that refers to symptoms that are associated with acute myocardial ischemia, such as unstable angina (Kumar & Cannon, 2009).

Adverse Event
An unwanted effect that a subject experiences that is not while taking a drug or other intervention (Day, 2007)

Cardiac Arrest
Cardiac Arrest is defined as a sudden loss of heart function in an individual who may or may not have been diagnosed with heart disease (American Heart Association, 2016f)

Cardiac Surgery
An umbrella term used to describe surgical procedures to correct or mitigate damage caused by cardiovascular disease (American Heart Association, 2016c)

Cardiovascular Disease (CVD)
A term that encompasses several disease of the heart or blood vessels including: coronary heart disease, stroke, heart failure, hypertension and others(("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011)

Clinical Study
A study that is systematic in nature and includes human subjects, a clinical study does not necessarily focus on studying an intervention (Day, 2007)

Clinical Trial
A study that is systematic in nature and includes human subjects, and focuses on studying the effects of an intervention (Day, 2007)

Coronary Heart Disease
Is the most prevalent form of cardiovascular disease, this condition involves the narrowing of the arteries that are responsible for providing blood to the heart due to accumulating atherosclerotic plaque in the arterial walls ("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011)

Enrollment
The number of individuals who have been recruited into a clinical trial (Day, 2007)

Efficacy
A demonstration that an intervention is producing a desired effect in a participant (Day, 2007)

Generalizability
The ability to apply conclusive findings to large segment of a population (Day, 2007)

Heart Failure
Heart Failure is a condition that whereby the heart can no longer sufficiently pump blood to the body, and is characterixed by accumulation of fluid in the lungs, feet, legs, and other body parts("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011)

Heterogeneity
A term referring to variations in a metric or variable may be different among subgroup populations in a clinical trial (Day, 2007)

Incidence
During a specific time period, the total number of new cases of a disease (Day, 2007)

Inclusion Criteria
Requirements that a participant must fulfill in order to take part in a study, this often is based on whether or not the participant fulfills the health requirements to take part in the study (Day, 2007)

Intervention
The administration of a treatment or procedure with the intent of analysis for clinical research ("NIA Glossary of Clinical Research Terms,")

Myocardial Infarction
Also known as heart attack, this condition refers to the permanent damage of the muscles of the heart because of a lack of/reduction of blood supply to the heart that often results from the accumulation of atheroslectoric plaque and clots in the coronary arteries ("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011)

Principal Investigator
The person who is responsible for conducting the clinical research study (Day, 2007)

Participant
An individual taking part in a clinical study (Day, 2007)

Pediatric and Congenital Heart Diseases
A collection of heart diseases pertaining to children and heart diseases and conditions acquired at birth (American Heart Association, 2016a)

Power
Within the context of a statistical significance test, the likelihood that the null hypothesis is rejected, if the null hypothesis is not true (Day, 2007)

Prevalence
The total number of individuals in a population who have a disease (Day, 2007)

Primary Findings or Primary Results
The most critical results of a trial (Day, 2007)

Primary Prevention
The primary prevention of a disease at its origin, before individuals acquire a disease (Day, 2007)

Recruitment
The process by which individuals are enrolled in a clinical research study (Day, 2007)

Resuscitation
Refers to the act of attempting to sustain or restore life by initiating or sustaining air by breathing and circulation through CPR, a defibrillator or other emergency care methods (Jacobs et al., 2004)

Secondary Findings or Primary Results
A result or finding that is of secondary importance (Day, 2007)

Secondary Prevention
Prevention of the recurrence of a disease and its progression in individuals who have the disease of interest (Day, 2007)

Selection Bias
A form of bias that occurs when subjects that take part in a research study are not chosen at random (Day, 2007)

Study Design
The structure of a clinical trial or clinical study
(Day, 2007)

Strata
The act of sorting a sample or population by a specific category or group by a categorical value (Day, 2007)

Subgroup
The identification of participants in a clinical trial that are separately identified, often for further analysis (Day, 2007).

Systematic Review
A synopsis of the results of published studies and provides conclusive evidence with regards to the efficacy of an intervention (Cochrane Consumer Network, 2016)

Vascular Diseases
A group of diseases related to the vascular system (which includes the arteries, veins, and capillaries). Vascular Diseases include Hypertension, peripheral vascular disease, and abdominal aortic aneurysm and others illness related to the vascular system (MedlinePlus, 2016).

Abbreviations

AAA: Abdominal Aortic Aneurysm

AHA: American Heart Association

CVD: Cardiovascular Disease

GAO: Government Accounting Office

FDA: Food and Drug Administration

NHLBI: National Heart, Lung, and Blood Institute

NIH: National Institutes of Health

WHI: Women's Health Initiative

Chapter 2 - Literature Review

Introduction

This chapter reviews the pertinent literature that has been published regarding the representation of women in cardiovascular clinical trials funded by the NHLBI, inclusion of women in federally funded clinical trials and the impact of the implementation of the NIH Revitalization Act on the biomedical research community. Relevant articles discussing the disease etiology of cardiovascular disease in women, inclusion of women in clinical trials from a historical context, critique of the NIH Revitalization Act in the biomedical community, and past analysis focusing on the disparities of women participating in federally funded cardiovascular clinical trials are reviewed. This section concludes with a synopsis of the current public health problem and the relevance of this systemic review and content analysis regarding this issue.

Cardiovascular Disease in Women: Prevalence and Sex Differences

According to the World Health Organization, cardiovascular diseases (CVDs) encompass a group of illnesses primarily in the heart and blood vessels (WHO, 2015). These illnesses are often linked to atherosclerosis and can include ischemic stroke, hypertension, heart failure, arrhythmia, disease related to heart valve and heart attach (AHA, 2014a) and metabolic syndromes (AHA 2014b).

In the US, CVD prevalence exceeds one in three adults (Go et al., 2013) and is the leading actual cause of death among women (T. Shah, Palaskas, & Ahmed, 2016). Approximately 34.9% of women in the U.S. have some form of cardiovascular disease (Zhang, 2010). The American Heart Association estimated that in 2011, 388,606 male deaths were attributed to CVD while 398,035 female deaths were attributed to CVD

(Mozaffarian et al., 2015). Although deaths caused by CVD have declined among men and women in the US in recent years, declines in CVD mortality are not occurring at an equal rate in women as compared to men (Garcia et al., 2016).

Cardiovascular disease occurs in both men and women, but there are significant biological differences in the manifestation and symptoms of the disease (Westerman & Wenger, 2016). Women often have longer QT intervals and resting heart rates that are faster than men, they have increased risk of stroke due to atrial fibrillation, and women who have diabetes and smoke have a higher risk of developing coronary heart disease compared to men (Westerman & Wenger, 2016). Women, are also susceptible to cardiovascular diseases associated with pregnancy, and an estimated one in five women in the US has developed gestational diabetes, preeclampsia, and hypertension, which can also lead to the development of cardiovascular disease later with the advancement of age ("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011).

Psychosocial factors, which include depression, anxiety, stress, and lack of economic and social resources can have greater adverse effects on women with cardiovascular disease than men with cardiovascular disease ("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011)

Equity in the inclusion of women in cardiovascular clinical trials would provide critical information regarding differences in the efficacy of interventions proposed in clinical trials as well as sex differences in the treatment and prevention of CVD

(Dougherty, 2011). Because of inadequate representation of women in CVD clinical trials, evidence-based analyses that focus on sex differences in CVD must often draw on observation methods or rely on interventional clinical trials with low female enrollment (Taggu & Lloyd, 2007).

Underrepresentation of Women in Clinical Trials

In order to gain a better understanding of the implications of disparities in the inclusion of women as participants in federally funded clinical trials, it is important to examine the historical context that led to the establishment of policies such as the 1993 NIH Revitalization Act.

Since World War II and the years that followed, patients taking part in clinical trials were mostly male and the perception at the time was that predominantly male (specifically White Males) subjects represented the ideal patient population, because researchers believed that male subjects would not skew clinical trial results (Wizemann & Pardue, IOM 2001). The inclusion of female subjects in clinical trials, on the other hand, was believed by many in the biomedical research community to result in inconsistencies and thus yield invalid findings (Wizemann & Pardue, IOM 2001).

The practice of excluding female subjects from clinical trial participation has its origins in policies enacted to protect human subjects, such as the Nuremberg Code of Ethics of 1949, which addressed ethical, legal and moral issues that were violated by physicians in Nazi Germany (Wizemann & Pardue, IOM 2001). Subsequent ethical violations related to clinical research such as the Tuskeegee Syphilis Study and Willowbrook, promoted the need to protect patients believed to be vulnerable (Taylor,

1994), because of “their physical, mental or social circumstances” women were often excluded from clinical trials because of the potential harm to fetus (Shuster, 1996).

In the past, the biomedical research community had viewed women’s health issues primarily within the realm of breast and reproductive health and that there were no substantial or notable differences between the sexes when it came to disease and drug interventions (Wenger, 2004). The term “bikini medicine” has been used by women’s health experts such as Dr. Marianne Legato (Pinn, 2013) and Dr. Nanette Wenger to highlight the urgency of a more holistic approach to examining sex differences regarding disease etiology and to further elucidate the disparities in biomedical research projects that focus on sex differences.

The Institutes of Medicine Report, “Exploring the Biological Contributions to Human Health”, published in 2001, identified three reasons that women were not included as patients in clinical trials:
1) Sex differences between men and women were not significant, 2) the inclusion of women would result in variations in results due to women’s hormonal cycles (i.e. menstrual cycles and menopause), 3) women participating in clinical trials would result in the increase of the heterogeneity of the results (i.e. compromising the generalizability of the results) (Wizemann & Pardue, IOM 2001).

The importance of gender equity in biomedical research (Taylor, 1994) can be traced back to the women’s health movement of the 1960s and 1970s which focused mostly on access to reproductive health resources but over time expanded in scope to push for improvements in health care for women overall and an end to gender disparities

in access to health (Nichols, 2000). Most clinical trials that studied the efficacy of a drug were conducted on male participants; women were often excluded from clinical trials due to risks posed to their reproductive organs and to a fetus (Shuster, 1996).

In the years leading up to the enactment of the NIH Revitalization Act, the issue of generalizability of results, the acknowledgement of sex differences in the manifestation of disease (particular in clinical trial primary results papers) and health equity, were recurring themes in the biomedical literature pertaining to inclusion of women in clinical trials.

A 1991 report from the American Medical Association's Council on Ethical and Judicial Affairs stated that medical research results did not take sex differences into account and were applied to women without regard to the existence of evidence-based results examining the effects on women ("Gender disparities in clinical decision making. Council on Ethical and Judicial Affairs, American Medical Association," 1991).

In that same year, Dr. Bernadine Healy, former Director of the National Institutes of Health, published an editorial in the New England Journal of Medicine refuting the pervasive belief among the medical and research community that coronary heart disease was solely a male disease (Healy, 1991). In the New England Journal of Medicine editorial, Dr. Healy referred to the "Yentl Syndrome" (after the main character in the Isaac Bashevis Singer short story who disguises herself as a man in order to study the Talmud), to illustrate that the symptoms associated with diseases such as coronary artery disease present themselves differently in men than in women (Healy, 1991), which can in turn lead to fewer women being diagnosed and receiving treatment (Merz, 2011).

Equity in representation of women in clinical trials can also be examined in terms of the overall population, particularly since women represent half of the general population (Ramasubbu, Gurm, & Litaker, 2001). Rammasubbu and colleagues contended that as medical consumers, women often seek medical care more frequently than men and therefore they should be represented in clinical trials in greater numbers (Ramasubbu et al., 2001). Wenger et al. argued that because of disparities in the representation of women in cardiovascular trials, the ability of researchers to translate clinical trial findings into clinical care that is relevant to women with cardiovascular disease is difficult to ascertain (Wenger, Hayes, Pepine, & Roberts, 2013).

Criticism Regarding the 1993 NIH Revitalization Act

The introduction and implementation of sweeping changes in policies such as the 1993 NIH Revitalization Act require assurances that the policy changes in question are being implemented correctly by stakeholders. Freedman and colleagues interpreted the policy as a call for the representation of gender and racial and ethnic groups in biomedical research (Freedman et al., 1995).

Hohmann & Parron acknowledge the difficulties that NIH funded investigators faced in interpreting the requirements of the 1993 NIH Revitalization Act (Hohmann & Parron, 1996). They also pointed out that the costs associated with being in compliance with the policy, i.e. ensuring that adequate recruitment of women and racial and ethnic minorities may pose unanticipated obstacles with regards to conducting clinical trials (Hohmann & Parron, 1996). Added costs was a concern voiced in Buist and Greenlick's assessment of the 1993 NIH Revitalization Act, which would be attributed to increased

participant sample size and to meet the requirements of the policy (Sonia Buist & Greenlick, 1995).

Woolson and colleagues predicted difficulties in the design and planning of clinical research projects that seek federal funding with regard to interpretation of the policy, due to language pertaining to "appropriate representation" of women and minority population (Woolson, Jones, Clarke, & Torner, 1995). Woolson et al. argue that the policy does not provide the biomedical research community with a precise definition of "appropriate representation" in federally funded clinical research and that appropriate representation (in the case of racial and ethnic groups) can be measured in terms of the general U.S. population and/or the prevalence of the disease in the U.S. population (Woolson et al., 1995).

Another issue to consider in evaluating the effectiveness of the 1993 NIH Revitalization Act is whether adequate time has passed for the evaluation to be conducted (Legato, 2000). This is a point that Legato had made in an editorial published in 2000 discussing the progress made in women's health, the effectiveness of the 1993 NIH Revitalization Act could be assessed based on whether results papers published between1993-1998 reported on sex differences in results papers (Legato, 2000). Legato argues that analysis of the policy's impact based on a limited time span would not provide a complete picture of the progress made by NIH and other federal agencies when it came to inclusion of women in clinical research, although reporting of sex differences could be fostered by cooperation between the NIH and the biomedical research community (Legato, 2000).

In a commentary examining the disparities in sex and sex differences in biomedical research, Correa-de-Araujo argued that despite the establishment of federal policies such as the 1993 NIH Revitalization Act and reports such as the 2001 Institute of Medicine Report, sex differences are still not being reported in published results papers (Correa-De-Araujo, 2006).

Corbie-Smith and colleagues conducted a survey of 683 NHLBI investigators to assess the NIH revitalization act and its impact on their research (Corbie-Smith, Durant, & St. George, 2006). In their analysis of the investigators surveyed, Corbie-Smith and colleagues were in agreement that the policy requirements regarding adequate representation of women and underrepresented minorities in clinical trials improved the generalizability of study results to these subgroup populations (Corbie-Smith, Durant, & St George, 2006). In addition, a majority of the respondents, 68.8% found that the policy succeeded in increasing inclusion of women in clinical research (Corbie-Smith, Durant, & St George, 2006). Although the survey was conducted in a relatively small and limited population (i.e. NHLBI grantees as opposed to a wider NIH grantee population sample), Corbie-Smith and colleagues' findings are still significant as the focus of their study was made up of an important stakeholder group, NHLBI funded investigators and their assessment of the 1993 NIH Revitalization Act and its impact on their clinical research projects (Corbie-Smith, Durant, & St George, 2006).

Systematic Reviews Evaluating the 1993 NIH Revitalization Act

Since the implementation of the 1993 NIH Revitalization Act, there have been numerous systematic analyses published in peer review journals that focused on the inclusion of women in cardiovascular clinical trials. These systematic reviews approached the question of inclusion of women in clinical trials in different ways and how the 1993 NIH Revitalization Act impacted the reporting of sex differences in clinical trials.

In a systematic analysis of 121 cardiovascular clinical trials from 1965 through 1998 funded by the NHLBI, Harris and Douglas found that the cumulative rate of enrollment for women in cardiovascular clinical trials during this time period was approximately 54% (Harris & Douglas, 2000). However, the data also showed that almost half the women enrolled in NHLBI-funded cardiovascular clinical trials were enrolled in two landmark single-sex clinical trials—The Women's Health Study and the Women's Health Initiative (Harris & Douglas, 2000). With the exclusion of the two single-sex clinical trials, Harris and Douglas found that enrollment rates of women in clinical trials was approximately 38% (Harris & Douglas, 2000). Harris and Douglas acknowledged the importance and significance of single-sex clinical trials but also argued that the single-sex clinical trials should not be seen as the only solution for low recruitment of women in clinical trials that enroll both sexes (Harris & Douglas, 2000).

Ramassubu and colleagues conducted a systematic review of clinical trial results papers published in the New England Journal of Medicine from 1994-1999 and were analyzed for the number of women enrolled, disease focus of the clinical trial, source of

funding, and how specific gender analysis data was used (Ramasubbu et al., 2001). In their analysis, Ramasubbu and colleagues found that just 24.6% of clinical trial participants were women and that the greatest number of female participants were found in vascular medicine clinical trials (46%) (Ramasubbu et al., 2001). The systematic review that was published by Ramassubu and colleagues could be deemed as being rather limiting since the clinical trials analyzed were within a very short time span (Legato, 2000).

Vidaver and colleagues conducted a systematic review of clinical trials in four high impact biomedical journals in the years 1993, 1995, 1997, and 1998 —1) New England Journal of Medicine; 2) Journal of the American Medical Association; 3) Circulation; and 4) the Journal of the National Cancer Institute (Vidaver, Lafleur, Tong, Bradshaw, & Marts, 2000). In their analysis of clinical trials funded by the NIH, Vidaver and colleagues found that 66%-75% of the clinical trials that focused on diseases occurring in both men and women did not mention sex differences in the intervention proposed in the study (Vidaver et al., 2000). In this study, Vidaver et al. concluded that a concerted effort was needed to recruit, retain, and report on the inclusion of women in federally funded clinical trials (Vidaver et al., 2000).

The systematic review conducted by Johnson and colleagues focused on the accessibility of interventions recommended in cardiovascular clinical trials relevant to women (Johnson, Karvonen, Phelps, Nader, & Sanborn, 2003). Johnson and colleagues analyzed systematic reviews from the Cochrane Library database (Johnson et al., 2003), particularly data collected by three Cochrane Collaborative review groups—1) Heart; 2) Hypertension; and, 3) Peripheral Vascular review groups. Johnson and colleagues

analyzed a total of 196 mixed gender cardiovascular clinical trials (Johnson et al., 2003). At the conclusion of the systematic review, Johnson and colleagues found that women made up only 27% of the total cardiovascular trial participant population of the 258 trials that were examined (Johnson et al., 2003). Interestingly, Johnson and colleagues found that the implementation of the 1993 NIH Revitalization Act did not result in a significant increase in the dissemination of gender-based differences in clinical trial results papers (Johnson et al., 2003).

Kim and colleagues conducted a systematic review of federally funded cardiovascular clinical trials funded by the NHLBI (E. S. Kim et al., 2008). A total of nineteen cardiovascular randomized clinical trials (RCTS) were analyzed and enrollment rates for women range from 10%-47% (E. S. Kim et al., 2008). Essentially, Kim and colleagues argued that despite the 1993 NIH revitalization, not much had changed regarding the inclusion of women and reporting of sex differences in cardiovascular clinical trials (E. S. Kim et al., 2008).

In a 2009 analysis published in circulation, Melloni and colleagues examined 156 randomized clinical trials cited in the American Heart Association's 2007 guidelines for CVD prevention in women by the year the results were published (1970-2006), intervention drug type (i.e., Aspirin, Beta Blockers, Statins), cardiovascular disease type (hypertension, heart failure), prevention category (primary versus secondary prevention) , and funding resources (government entities versus pharmaceutical industry funded randomized clinical trials) (Melloni et al., 2010).

In this analysis of 156 randomized clinical trials, Melloni and colleagues examined the proportion of women enrolled in randomized clinical trials focusing on

cardiovascular disease by publication year, therapeutic class, clinical indication (i.e., CVD area), prevention type, location (CVD clinical trials in the U.S. vs. other countries) , and funding source (Melloni et al., 2010). Melloni and colleagues found that there was a steady increase in women participating in studies (9% women in 1970 compared to 41% women in 2006); trials using aspirin as a thereapeutic intervention for prevention of cardiovascular disease had the highest enrollment of women (49%); randomized clinical trials focusing on hypertension had the highest rate of female enrollment by cardiovascular disease area (44%); government funded CVD trials had a slightly higher enrollment than privately funded trials were comparable (31.9% versus 31.5%); and, published findings of randomized clinical trials with the highest proportion of women were published in 1990-1994 (35.5% women) (Melloni et al., 2010). Melloni and colleagues concluded that women represented just 30% of patients enrolled in CVD randomized clinical trials and recommended that randomized clinical trials should be designed to include the reporting of results pertaining to sex differences in the intervention proposed in the trial (Melloni et al., 2010).

Tsang and colleagues conducted an analysis of cardiovascular clinical trials in three journals: New England Journal of Medicine, The Lancet, and Journal of the American Medical Association published between 1997-2009 examining enrollment of women in cardiovascular clinical studies (Tsang, Alter, Wijeysundera, Zhang, & Ko, 2012). In their analysis of 325 cardiovascular clinical trials, Tsang and colleagues argued that although 1 out of 3 participants in cardiovascular clinical trials were women, greater participation rates for women in cardiovascular clinical trials could be achieved if clinical trials recruit greater numbers of older women in clinical trials (Tsang et al., 2012). Often,

cardiovascular diseases occur in women much later in life than in men. Tsang and colleagues argued that women would be eligible to participate in a cardiovascular trial at a later age when compared to male participants, and their findings suggested that greater efforts should be made to recruit older women in cardiovascular clinical trials in order to achieve equity in recruitment with male participants (Tsang et al., 2012).

Summary of Current Problem and Study Relevance

Significant progress has been made with regard to the inclusion of women in clinical trials since the passage of the 1993 NIH Revitalization Act, yet these changes have not translated to equity in the inclusion of women in cardiovascular clinical trials and the reporting sex-specific outcomes in primary result of cardiovascular clinical trials.

The systematic reviews that were featured in this review of the literature concluded that improvements were still needed in order to achieve equity in the inclusion of women and reporting of sex differences, these changes included but were not limited to the design of the clinical trial, outreach and recruitment efforts to enroll more women, and ensuring that the results papers reported on sex differences.

Systematic reviews can serve as a critical tool for assessing public health policies such as the 1993 NIH Revitalization Act. The addition of newly completed cardiovascular clinical trials and published findings within the biomedical research knowledgebase warrant the need to conduct frequent systematic reviews and content analysis to assess whether the 1993 NIH Revitalization Act has improved inclusion of women in cardiovascular clinical trials over time and to determine whether or not there has been an increase in the number of primary findings that report on sex-specific outcomes since the policy was implemented.

Chapter 3 – Methodology

Introduction

A systematic review approach was used to assess whether or not cardiovascular clinical trials adhered to the inclusion of women in clinical trials according to the 1993 NIH Revitalization Act. Because many studies result in multiple publications, for the purposes of this systemaic review, primary result publications were used to assess whether or not the clinical trials addressed sex-specific outcomes in cardiovascular clinical trial interventions. This section details the methods that were used.

Background on Clinical Trials.gov

Clinical trials.gov is a publically accessible website that was launched by the NIH in 2000 and is used by patients and their families, researchers, and healthcare providers to access information regarding public and privately funded clinical trials (clinicaltrials.gov, 2016). The creation of the clinical trials.gov website stemmed from the 1997 FDA Modernization Act that required the Department of Health and Human Services (through the NIH) to provide accessible information regarding federal and privately funded clinical trials to the public. NIH's National Library of Medicine (NLM) is responsible for the maintenance of the Clinical Trials.gov website and information is entered and updated by the sponsor or principal investigator of the trial and is monitored by NLM staff.

Population and Sample

The systematic analysis used information on clinical trials retrieved through clinical trials.gov and the website served as the primary resource utilized to identify cardiovascular clinical trials. The sites reporting capabilities, particularly with regards to the disease category; participant population (number of women enrolled); and, the listing of primary findings associated with clinical trials were all conducive in the preliminary phases of data collection for this project.

Research Design and Procedure

Because Clinical Trials.gov data is updated on a daily basis and results papers are constantly being published, it was necessary to conduct the retrieval of the clinical trials at a specific point in time. The retrieval of the clinical trials.gov search was conducted on March 25, 2016.

In order to capture the NHLBI funded cardiovascular clinical trials, six separate advanced targeted searches were performed on the Clinical Trials.gov website. The rationale for conducting the multiple searches was due to the website's limited Boolean search capabilities, as well as the possibility of inadvertently excluding NHLBI funded cardiovascular searches from the search. The six searches that were conducted included: 1) Clinical Trials where NHLBI was listed as Sponsor/Collaborator – the term "NHLBI" was entered in the Sponsor/Collaborator field.

2) Clinical Trials where NHLBI was listed as the NHLBI Sponsor (Lead) – the term "NHLBI was entered in the Sponsor/Collaborator field.

3) Clinical Trials where "HL" (NHLBI's two letter grant identifier) was listed as the Study ID – the term "HL" study was entered into the study ID field

4) Clinical Trials where "HV" (NHLBI's two letter cardiovascular contracts identifier) was listed as the Study ID – the term HV was entered into the study ID field

5) Clinical Trials where "HC" (NHLBI's two letter epidemiology and clinical applications contracts identifier) was listed as the Study ID – the term HC was entered into the study ID field

6) Clinical Trials where "HW" (NHLBI's two letter women's health initiative Contracts identifier) was listed as the Study ID – the term HW was entered into the study ID field. A flowchart briefly detailing the data retrieval process is provided (see Figure 1)

For record keeping purposes, snapshot files of the six advanced search results pages were saved as PDFs. The six separate searches data were downloaded into MS Excel files. Using the sort function in MS Excel, the data was sorted according to the two study type categories provided by Clinical Trials.gov: Observational Clinical Trials and Interventional Clinical Trials. Since the focus of the analysis was interventional clinical trials, observational clinical trials were removed.

Next, the clinical trials were sorted according to "Condition" (i.e. the disease or illness being studied in the clinical trial). The clinical trials records were sorted according to the unique Clinical Trials.gov identified or NCT Number and duplicate records were

removed. Three reviewers examined the list of clinical trials: the author of this paper and two NHLBI scientific staff members who were well versed in the cardiovascular field. The reviewers rated the clinical trials according to three categories—

1) Interventional Cardiovascular Focused/Related Clinical Trials – Clinical Trials that were deemed as a cardiovascular focused or related by the reviewers.

2) Interventional Clinical Trials that were not Cardiovascular focused or related – these clinical trials were not deemed as cardiovascular focused or related by the reviewers, these records were omitted from the list.

3) Unsure if the Interventional Clinical Trial was Cardiovascular focused or related. These included interventional clinical trials where it was not entirely clear whether the clinical trial was cardiovascular focused or related. The clinical trials in this category warranted further discussion by the reviewers to determine whether the clinical trial should be included in the interventional cardiovascular focused/related clinical trial or the interventional clinical trials that were not cardiovascular focused or related.

The reviewers met to examine topic areas where there was disagreement with regards to the cardiovascular focus of the trial.

Once a consensus was reached among the three reviewers, the remaining cardiovascular focused/related investigational clinical trials were then sorted according to the total patient recruitment number. Interventional cardiovascular clinical trials with a patient enrollment of 150 subjects or greater were included in the final list of clinical trials and this threshold was based on the monitoring guidelines detailed in the NHLBI's Accrual of Human Subject Policy (NHLBI, 2009). The NHLBI Accrual policy was

initiated in 2009 in order to monitor patient accrual and assess the feasibility of clinical studies to ensure the proper utilization of public funds for clinical research (NHLBI, 2009). As per the NHLBI Policy, clinical trials with 150 human subjects or greater are regularly monitored by the NHLBI (NHLBI, 2009). In this systematic review, clinical trials with patient enrollment less than 150 patients were omitted from the list.

NCT numbers for the cardiovascular interventional clinical trials were entered in PubMed and primary results publications were retrieved for content analysis specifically if the results addressed sex-specific outcomes in the intervention.

Data Analysis Methodology

This research project utilized a systematic review and content analysis approach. Although clinical trials.gov provided details regarding the number of participants recruited, patient recruitment by gender and the clinical trial disease area focus, the primary findings published in peer review journals served in providing information that was disseminated to the biomedical research community regarding clinical trial results.

Data Extraction

Information extracted for each of the primary results papers retrieved included:

1)The overall number of participants enrolled;

2) The percentage of women enrolled in the clinical trial;

3) The reporting of sex differences in the intervention proposed in the trial;

4) The cardiovascular disease area focus of the clinical trial; and

5) The prevention category of the clinical trial i.e. primary or secondary prevention.

Study Limitations and Delimitations

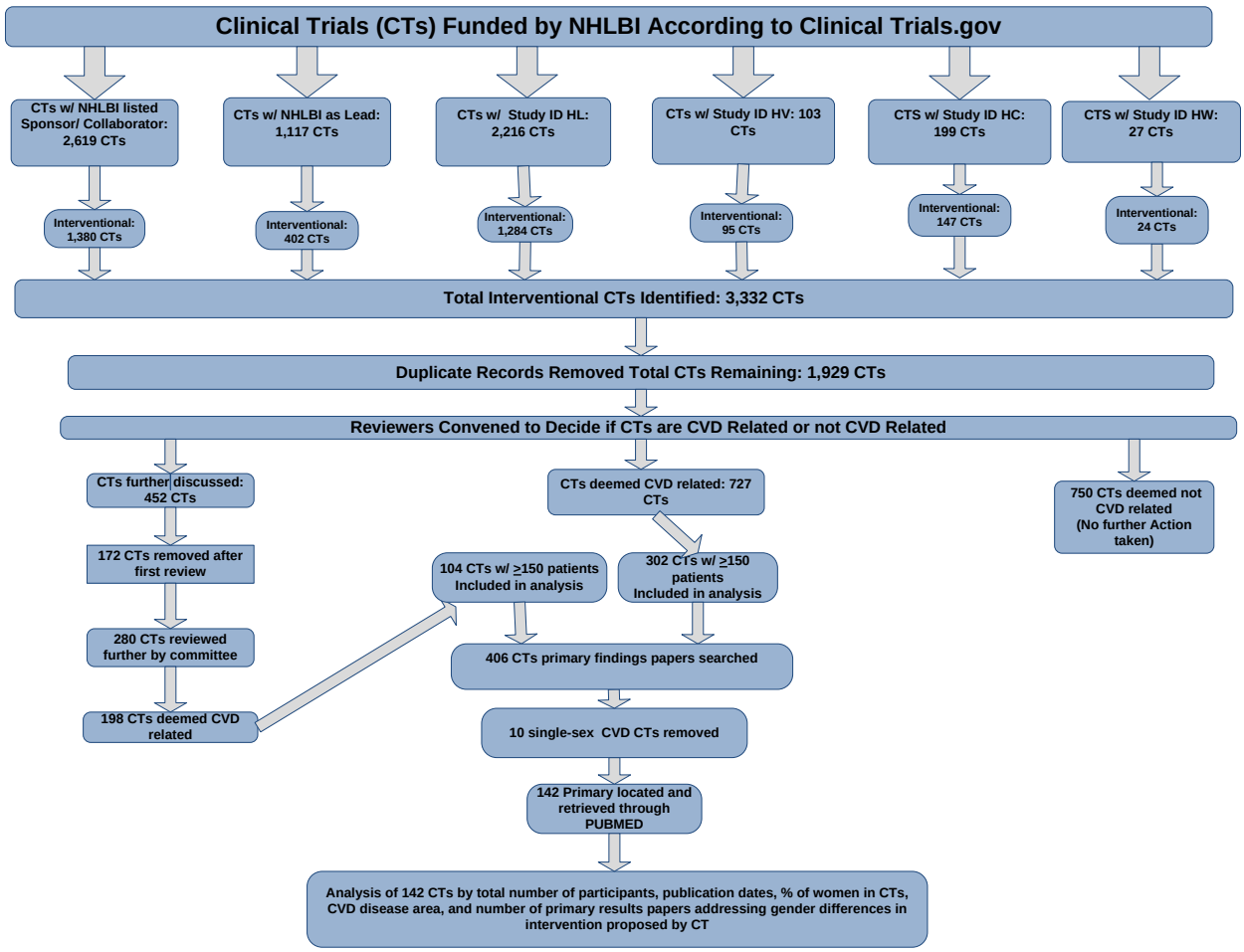
The project's reliance on clinical trials.gov as a primary resource for identifying NHLBI funded interventional cardiovascular clinical trials may result in clinical trials that were not included in the analysis due to institution's or study sponsors not providing information regarding the trial in clinical trials.gov. The possibility of errors in the reporting of disease categories patient enrollment numbers, and the clinical trial's status by the sponsor or principal investigator of the clinical trial could also affect the data that was analyzed for this project.

The delimitations of selecting the primary findings paper as the main resource for examining the reporting of sex differences in the clinical trials would identify those trials that did not report on sex difference. However, clinical trials that published findings on sex differences after the primary findings were published could be interpreted as the investigators or sponsors of the clinical trial not adhering to the 1993 NIH Revitalization Act.

The decision to set the number of participants at 150 patients or more was based on the NHLBI's Accrual of Human Subject Policy (NHLBI, 2009) which requires clinical trials with target enrollment greater than 150 patients to be monitored for meeting accrual plans and inclusion of subgroup populations (NHLBI, 2009). By setting the cut-off of the total patient enrollment to 150 patients or more, it would be difficult to ascertain whether the clinical trials in the lower patient enrollment range had

enough power to report on sex differences in the primary findings than those in the upper patient enrollment range. It is also difficult to determine whether or not clinical trials with larger patient enrollment enrolled more women or were more likely to address sex differences in the primary results papers, than those trials with smaller total patient recruitment numbers.

Figure 1: Systematic Review Flow Chart



Chapter 4 - Results

Introduction

The systematic review conducted in Clinical Trials.gov was a multi-step process that initially identified 6,281 clinical trials that were sponsored and/or led by the NHLBI, or referenced the NHLBI's NIH grants/contracts codes (i.e. "HL", "HV", "HC", and "HW" respectively). Observational trials were omitted from the cardiovascular clinical trials that were analyzed and 3,332 interventional trials remained, once duplicate records were removed this number decreased to 1,929 clinical trials. Using the descriptions provided in clinical trials.gov, a committee consisting of the author and two program officials convened to decide whether the clinical trials focused on cardiovascular diseases. A total of 750 clinical trials were deemed not cardiovascular disease focused by the review committee and thus omitted from the analysis. 727 clinical trials were deemed cardiovascular disease focused. A total of 452 clinical trials were set aside for further review by the committee, and when the committee convened to review these trials 172 were deemed not cardiovascular disease related and 198 were categorized as cardiovascular disease focused clinical trials.

Trials with patient enrollment less than 150 patients according to the clinical trial.gov database were included in the analysis, which reduced the number of clinical trials analyzed to 406. Ten single-sex CVD clinical trials were also removed. A total of 142 primary findings publications were found in PubMed and analyzed for this systematic review. The results of the data analyzed for this systematic review are described in the next section.

Key Findings

Proportion of Women of Enrolled in the clinical trials

Overall, we found that the total proportion of women across all of the clinical trials identified for inclusion in this analysis, therefore, did not meet the requirements for 51% female participation as required by NHLBI's inclusion policy. A total of 171,198 patients were enrolled in the 142 cardiovascular disease clinical trials. Of these, 101,796 (59.5%) of the participants were male and 69,402 of the participants were female (40.2%). These results indicated that a higher percentage of men were enrolled across all *cardiovascular clinical trials than women (an approximate 19% difference)*

Table 1: Overall Enrollment in CVD Clinical Trials by Sex

Total Number of Cardiovascular Disease (CVD) Trials	Total Number of Participants in CVD Trials	Total Number of Men in CVD Trials	Total Number of Women in CVD Trials	Percentage of Men in CVD Trials	Percentage of Women in CVD Trials
142	171,198	101,796	69,402	59.5%	40.5%

Inclusion of Women in CVD Trials by CVD Area

There were significant differences in the number of women enrolled in the cardiovascular disease clinical trials analyzed for this systematic review by cardiovascular disease area. We grouped the cardiovascular disease areas into nine areas (listed below). Of these nine disease area categories, Acute Coronary Syndrome & Myocardial Infarction had the lowest percentage of women enrolled in the clinical trials (29.5% women versus 70.5% men), while the Primary Prevention of Cardiovascular Disease trials enrolled the largest number of women in (65.8% women versus 34.2% men). Table 2 provides a breakdown of the enrollment by gender for the nine categories. Further details regarding the proportion of women enrolled in the nine cardiovascular disease areas are also described.

Table 2 : Breakdown of the Enrollment by Sex for Nine Cardiovascular Disease Area Categories

Disease Area	# of CTs*	Total # of Participants	Total # of Male Participants	Total # of Female Participants	Total % of Male Participants	Total % of Female Participants	95% CI for Female Participants
Acute Coronary Syndrome & Myocardial Infarction	13	7,208	5,079	2,129	70.5%	29.5%	(28.45% , 30.55%)
Cardiac Arrest & Resuscitation	9	48,586	33,160	15,426	68.3%	31.7%	(31.29%, 32.11%)
Cardiac Surgery	12	8,888	6,114	2,774	69%	31.2%	(30.24% , 32.16%)
Coronary Heart Disease	10	26,676	17,499	9,177	65.6%	34.4%	(33.83% , 34.97%)
Heart Failure	20	14,947	9,163	5,784	61.3%	38.7%	(37.92% , 37.48%)
Pediatrics and Congenital Heart Diseases	5	2,586	1,530	1,056	59.2%	40.8%	(38.91% , 42.69%)
Primary Prevention of CVD	32	12,955	4,432	8,523	34.2%	65.8%	(64.98% , 66.62%)
Secondary Prevention of CVD	14	28,047	13,601	14,446	48.5%	51.5%	(50.92% , 52.08%)
Vascular Diseases	27	21,305	11,218	10,087	52.7%	47.3%	(46.63% , 47.97%)
Totals	**142**	**171,198**	**101,796**	**69,402**	**59.5%**	**40.5%**	(40.17%, 40.63%)

*** CT= Clinical Trials**

Acute Coronary Syndrome & Myocardial Infarction

A total of thirteen cardiovascular clinical trials were included in the Acute Coronary Syndrome and Myocardial Infarction (ACS& MI) category. There were 7,208 participants in these clinical trials with 5,079 men enrolled and 2129 female participants. The ACS & MI category had 29.5% women enrolled, the lowest percentage of women enrolled in the cardiovascular clinical trials categories. The percentage of women enrolled by trial in this category ranged from 16% to 54%.

It is interesting to note that two of the ACS& MI trials with higher percentages of women enrolled examined the issue of depression and mental health following ACS & MI and had fewer patients enrolled. This may suggest that a higher percentage of women were willing to report depression and other mental health related co-morbidities than the men enrolled in these clinical trials, or it may reflect a real sex-based difference in incidence of depressive symptoms. In a clinical trial reporting on sex differences in the reporting of depression in patients hospitalized for acute coronary syndrome, Frazier and colleagues found that 35 % of the female participants reported depressive symptoms more often than their male counterparts (22%) (Frazier et al., 2012). Overall, the ACS & MI clinical trials that reported on sex-specific outcomes between a proposed treatment and/or intervention had fewer women enrolled.

Cardiac Arrest & Resuscitation Trials

In the Cardiac Arrest & Resuscitation trials catergory, there were a total of nine clinical trials i with 48,586 participants overall, 68% of the participants were male and 32% of the participants were female. The percentage of women enrolled in the Cardiac

Arrest & Resuscitation trials ranged from 17% to 37%. The clinical trials that were included in this category focused on the use of devices such as external difibrillators or cardiopulmonary resuscitation (CPR).

In an analysis focusing on sex differences in prehospital management of out of hospital cardiac arrest, Mumma and Umarov found that men received more timely pre-hospital resuscitation (Mumma & Umarov, 2016). Kim and colleagues also reported on gender disparities in the treatment of cardiac arrest and found that of the 1,436,052 hospital discharge records for patients with cardiac arrest 45.4% were female and were less likely to receive coronary angiography, temperature management, and percutaneous coronary interventions and hypothesized that this would lead to higher in hospital mortality rates in women than in men (L. K. Kim et al., 2016). The low enrollment numbers for women enrolled in the cardiac arrest and resuscitation trials analyzed for this systematic review may reflect the sex differences that were reported by Mumma & Ummarov and Kim et al.

Cardiac Surgery

There were a total of thirteen clinical trials in the Cardiac Surgery trials category, and there were 9,819 participants overall, 67% of the participants were male and 33% were female. The percentage of women enrolled in the Cardiac Arrest & Resuscitation trials ranged from 12% to 57%. The clinical trials that were included in this category primarily focused primarily on coronary artery bypass grafting, drug-eluting stents, percutaneous coronary intervention, and mitral valve replacement.

It is important to note that the participants enrolled in the RECESS Trial were 57% women and consisted of patients undergoing complex cardiac surgery and leukocyte-reduced red cells stored for 10 days or less versus 21 days or more (Steiner et al., 2015). The high percentage of women in both these trials may have also been due to the advanced age of the participants (patients in this trial were mostly over the age of 70) (Steiner et al., 2015) and cardiac surgery is often performed on women who are older than their male counterparts (Hogue et al., 2001).

Coronary Heart Disease

There were a total of ten clinical trials in the Coronary Heart Disease category, with a total of 26,676 participants overall, 65.6% of the participants were men and 34.4% of the participants were women. The percentage of the participants enrolled in the Coronary Heart Disease clinical trials ranged from 15% to 53%. The clinical trials included in this group comprised of mostly drug interventions and efficacy on patients with Coronary Heart Disease. The two clinical trials with the highest percentage of women were the Clarification of Optimal Anticoagulation through Genetics (COAG) trial (49% women enrolled) (Kimmel et al., 2013) and the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial (53% women enrolled) (Douglas et al., 2015). The primary results papers for the COAG and PROMISE trials include participants with median ages greater than 55 (Kimmel et al., 2013) and 60 years of age (Douglas et al., 2015) respectively.

In the case of the PROMISE trial, a concerted effort was made by the investigators to enroll older women in the trial to reflect the age differences in the incidence of cardiovascular diseases in women versus men (Douglas et al., 2015).

In an American Heart Association statement on Cardiovascular Disease in Women, Mosca and colleagues reported that there is a lower age risk of Coronary Heart Disease in women when compared to men and women tend to experience Coronary Heart Disease ten years later than men (Mosca et al., 1997).

Heart Failure

There were a total of twenty clinical trials included in the Heart Failure category with a total of 14,947 participants overall, 61.3% of the participants were men and 38.7% of the participants were women. The percentage of the participants enrolled in the heart failure clinical trials ranged from 18% to 52%. The clinical trials included in this group encompassed a wide range of intervention strategies including surgery, behavioral modifications and patient education, and medications, and vital signs monitoring.

The Treatment of Preserved Cardiac Function with an Aldosterone Antagonist (TOPCAT) trial compared treatment with spironolactone versus placebo in patients with HFpEF and 52% of the participants enrolled were women with a mean age of 68.6 (S. J. Shah et al., 2013).

Although incidence of heart failure is lower in women than in men overall, women who have heart failure tend to be older in age, have preserved systolic function

(also referred to as Heart Failure with Preserved Ejaculation Fraction or HFpEF) and have nonischemic cardiomyopathy (R. U. Shah, Klein, & Lloyd-Jones, 2009).

The "Effectiveness of Peer Support in Improving Heart Failure Self-Management and Care" trial also had an enrollment rate of 52% women with the median age being 69 years and in this trial, heart failure patients were assigned to a group session led by a nurse practitioner and were encouraged to participate in weekly phone sessions (Michele Heisler et al., 2013). It cannot be determined whether or not gender played a role in the efficacy of the intervention, a peer support program for Heart Failure patients (M. Heisler et al., 2013).

Pediatric and Congenital Heart Disease

There were a total of five clinical trials included in the Pediatric and Congenital Heart Disease category with a total of 2,586 participants overall, 59% of the participants were male and 41% of the participants were female. The percentage of the female participants enrolled in the pediatric and congenital heart disease category ranged from 32% to 47%. The clinical trials included in this group comprised mostly of trials focusing on pediatric cardiac surgery, although one of the trials examined drug interventions in patients with congenital heart disease (Lacro et al., 2013) and enrolled 40% female participants (Lacro et al., 2013).

The trial with the highest female enrollment in this category, Safe Pediatric Euglycemia in Cardiac Surgery (SPECS) trial (47% female enrollment) examined whether tight glycemic controls lowered morbidity in pediatric patients (as it has been

demonstrated in adult patients) proceeding cardiac surgery (Agus et al., 2012).

Although the enrollment of female participants is higher in the pediatric and congenital heart disease trials were higher when compared to the adult cardiovascular disease trials that were examined in this systematic analysis, it is important to note that the pediatric and congenital heart disease group had the fewest number of trials (just five when compared to categories such as heart failure, acute coronary syndrome and myocardial infarction and vascular diseases).

In a 2004 editorial examining sex differences in pediatric cardiac surgery, Miller –Hance and Tacy contended that issues pertaining to gender may not be of great importance to pediatric cardiologist and congenital heart surgeon (Miller-Hance & Tacy, 2004). However, gender may be an important factor in the care and outcomes of patients with congenital heart diseases and larger studies (i.e. registries) may provide critical information regarding the role of gender and pediatric and congenital heart diseases (Miller-Hance & Tacy, 2004).

Primary Prevention of Cardiovascular Disease

There were a total of thirty-two clinical trials included in the Primary Prevention of Cardiovascular Diserase category, with a total of 12,955 participants overall, 34.2% of the participants were male and 65.8% of the participants were female. The percentage of the female participants enrolled in the primary prevention of cardiovascular disease category ranged from 25% to 92%. The clinical trials included in this category comprised of trials that focused on the prevention of cardiovascular disease in at risk patients and examining the effects of behavioral and dietary interventions.

It is interesting to note that the clinical trial in this category with the highest percentage of women enrolled was 92% (Evaluating the Health Benefits of Workplace Policies and Practices) (Hurtado et al., 2016). The participants in this trial were comprised of nursing home workers who were recruited to examine the effects of smoking cessation programs that were based on a work-family supportive organizational intervention strategy. (Hurtado et al., 2016) In the primary results paper for this trial, the investigators acknowledged that their study population was predominantly female as most of the certified nursing assistants employed in US nursing homes were female (Hurtado et al., 2016).

Secondary Prevention of Cardiovascular Disease

There were a total of fourteen clinical trials included in the Secondary Prevention of Cardiovascular Disease category, with a total of 28,047 participants overall, 48.5% of the participants were male and 51.5% of the participants were female. The percentage of the female participants enrolled in the primary prevention of cardiovascular disease category ranged from 26% to 76%. The clinical trials included in this category comprised of trials that focused on the secondary prevention of cardiovascular disease in patients with cardiovascular disease and examining the effects of behavioral and dietary interventions.

The clinical trial with the highest percentage of women enrolled, the Transfusion Trigger Trial for Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) with 76% women and an older mean age (81.6 years of age) (Carson et al., 2011). In the case of the FOCUS trial, the participants that were

enrolled had to have had undergone hip surgery which is performed more frequently in women and increases by age (Maradit Kremers et al., 2015).

Vascular Diseases

There were a total of twenty-seven clinical trials included in the Vascular Disease category, with a total of 21,305 participants overall, 52.7% of the participants were male and 47.3% of the participants were female. The percentage of the female participants enrolled in the primary prevention of cardiovascular disease category ranged from 8% to 72%. The clinical trials included in this category comprised mostly of trials that focused on hypertension and peripheral arterial disease. It is interesting to note that within the Vascular Disease category, the Exercise Therapy to Treat Adults With Abdominal Aortic Aneurysms trial had the lowest female enrollment (8%) (Myers et al., 2014). This trial examined the benefits of exercise therapy in patients with abdominal aortic aneurysm (AAA) versus usual care (physical activity was not tracked in the usual care group) (Myers et al., 2014). Although AAA is a condition that is more prevalent in men than in women, the case fatality rate for women who undergo surgery for AAA is estimated as being 35-50% higher than in men (Norman & Powell, 2007).

It is important to mention the relation between the participants age and proportion of female participants that were enrolled in the CORAL (Cardiovascular Outcomes in Renal Atherosclerotic Lesions) trial which examined atherosclerotic renal artery stenosis and the efficacy of renal-artery stenting versus medical therapy as this study had a patient enrollment that was mostly over 65 years of age and 50% of the participants were female (Cooper et al., 2014).

Two of the trials with the highest percentage of women enrolled in this category focused on hypertension with a patient enrollment of 72% women (Kronish et al., 2016) (Ogedegbe et al., 2014). Although hypertension is a condition that effects both men and women, the prevalence of disease increases with age (particularly after the age of 50) in women (Igho Pemu & Ofili, 2008).

Enrollment of Women in CVD Clinical Trials by Prevention Type

The primary results papers, specifically the methods and interventions proposed, were analyzed to determine whether the trials proposed a primary or secondary prevention of CVD. 31 of the 142 (21.8%) CVD trials were categorized as primary prevention (i.e. trials that were preventing CVD from occurring in patients that had not developed or were at risk of developing CVD. 111 of the 142 (78.2%) clinical trials were categorized as secondary prevention (i.e. trials with patients that had CVD but interventions were aimed at reducing the impact of CVD).

The table below provides a breakdown of the number of participants and enrollment by gender for the primary prevention and secondary prevention CVD Trials.

Table 3: Total Enrollment by Sex for Primary Prevention CVD Trials

Total # of CVD Trials	Total # of participants	Total # of Male participants	Total # of Female participants	% Male participants	% Female participants
32	12,955	4,432	8,523	34.2%	65.8%

Table 4: Total Enrollment by Sex for Secondary Prevention CVD Trials					
Total # of CVD Trials	**Total # of participants**	**Total # of Male participants**	**Total # of Female participants**	**% Male participants**	**% Female participants**
110	158,243	97,364	60,879	61.5%	35.8%

Enrollment of Women in CVD Clinical Trials by Primary Findings Publications Year

The publication years for the primary findings publications for the cardiovascular clinical trials examined for this systematic review spanned from 2006-2016, however the number of papers published by year were not evenly distributed as shown in the table below (see Table 5)

Table 5: Primary Results publication dates of CVD Clinical Trials and Enrollmentby Sex						
Publication Year of Primary Findings Paper	**Number of Trials with papers published**	**Total Number of Participants**	**Total Number of Male Participants**	**Total Number of Female Participants**	**Percentage of Male Participants**	**Percentage of Female Participants**
2006	**1**	**248**	**172**	**76**	**69.4%**	**30.6%**
2007	**2**	**5,394**	**2,125**	**3,269**	**39.4%**	**60.6%**
2008	**6**	**21,641**	**14,704**	**6,937**	**67.9%**	**32.1%**
2009	**12**	**8,928**	**5,132**	**3,796**	**57.5%**	**42.5%**
2010	**11**	**17,426**	**11,433**	**5,993**	**65.6%**	**34.4%**
2011	**18**	**21,678**	**13,364**	**8,314**	**61.6%**	**38.4%**
2012	**20**	**11,185**	**5,889**	**5,296**	**52.7%**	**47.3%**
2013	**20**	**12,427**	**6,842**	**5,585**	**55.1%**	**44.9%**
2014	**17**	**7,491**	**3,948**	**3,543**	**52.7%**	**47.3%**
2015	**25**	**56,065**	**32,972**	**23,093**	**58.8%**	**41.2%**
2016	**10**	**8,715**	**5,215**	**3,500**	**59.8%**	**40.2%**

Because of the variances in the number of primary results papers published, the Chi-Square values were calculated to determine if there was an association between the publication date and the proportion of women in the CVD trials. Publication dates were grouped into two categories: Early Years (2006-2012) and Late Years (2013-2016).

Table 6: Publication Year Groupings for CVD Trials and Enrollment by Sex				
Publication Category	**Male Participants**	**Female Participants**	**Totals Participants**	
Early Years: 2006-2012 (70 primary publications)	52,819	33,681	86,500	**Percentage of Women: 38.9% (Early Years)**
Later Years: 2013-2016 (72 primary publications)	48,977	35,721	84,698	**Percentage of Women 40.9% (Late Years)**
Totals	**101,796**	**69,402**	**171,198**	

The proportion of women enrolled in the CVD trials with primary publication in the early years was 38.9% and the proportion of women enrolled in the CVD trials with primary publications in the later years was 40.9 %. The absolute difference in the proportion of women enrolled in the two publication categories was 2% and the calculated probability or p-value was $p<0.001$ and was statistically significant.

Primary Publications Papers Reporting on Sex-Specific Outcomes

The results of the 142 papers analyzed for this systematic review indicated that only 20 (14.1%) CVD trials reported on sex differences in the results, discussion and/or conclusion sections and 122 (85.9%) primary results papers did not address sex differences in the results, discussion or conclusion sections. For the primary results papers that reported on sex differences, the proportion of women enrolled in the trials was 43.2% (95% CI, 42.66 to 43.74%). For the primary results papers that did not

address sex differences in the results, discussion, or conclusions sections, the proportion of women enrolled in the trials was 39.9% (95%CI= 0.26, 39.64% to 40.16%).

CVD Clinical Trials with Subsequent Paper Published After Primary Findings and Sex-Specific Outcomes

The results of a search in PubMed of the NCT Numbers or Unique Clinical Trials.gov found that their were two clinical trials that reported on sex differences in both the primary results papers and subsequent publications. Of the 124 clinical trials that did not report on sex differences in the primary findings, just 13 or 11% of the cardiovascular disease clinical trials (including the two that reported on sex differences in the primary results papers and the subsequent findings papers) had published subsequent papers that reported reported on sex differences in the results, discussion and/or conclusion sections.

Summary

The NHLBI funded cardiovascular disease clinical trials that were analyzed for this systematic review showed that the overall the proportion of women participating in these trials was not equal to the number of men enrolled in the clinical trials.

When analyzing the enrollment of women by cardiovascular disease area there were specific disease areas with disparities in the proportion of women enrolled, for example, in the Acute Coronary Syndrome & Myocardial Infarction category there were 29.5% women enrolled. There were just two cardiovascular disease area categories that had a higher proportion of women enrolled than men: primary prevention of

cardiovascular disease (65.8% women enrolled) and secondary prevention of cardiovascular disease (51.5%).

The proportion of primary findings papers that reported on sex-specific outcomes in the results, discussion and/or conclusion was just 14.1%. The publication year of the primary findings did hav a significant impact on the proportion of women enrolled , clinical trials with primary findings published between 2006-2012 (Early Years) enrolled 38.9% women, while clinical trials with primary findings published between 2013-2016 enrolled 40.9% women. The differences in the proportion of women enrolled in the early versus late years would imply that there is a temporal in the proportion of women enrolled in cardiovascular clinical trials funded by the NHLBI.

Chapter 5 - Discussion

Introduction

Despite the fact that Cardiovascular Disease is the primary cause of mortality in women in the U.S., disparities still exist with regards to the enrollment of women in cardiovascular clinical trials (Melloni et al., 2010) even with enactment of the NIH Revitalization Act (Harris & Douglas, 2000) . The dissemination of the results of clinical trials in biomedical publications is crtitical in establishing treatment protocols and guidelines (Melloni et al., 2010). The need to elucidate sex differences, within the context of the pathology of cardiovascular disease in women, has been discussed numerous times by experts within the the field of cardiovascular health (Wenger, 2004). Ensuring that clinical trials enroll women at rates that reflect the prevalence of cardiovascular disease and reporting on sex-specific outcomes in the intervention proposed in cardiovascular clinical trials are important steps in ameliorating cardiovascular health outcomes in women (Westerman & Wenger, 2016).

Summary of Study

The enactment of the NIH Revitalization Act was an important juncture in biomedical research, as this federal mandate required the inclusion of women and underrepresented minorities in NIH funded clinical trials (E. S. Kim et al., 2008). Determining the success of the NIH Revitalization Act since its implementation in the 1990s with regards to the enrollment of women in areas in which there had been limited representation (i.e. cardiovascular disease) is a difficult task. A systematic analysis and review of the primary findings publications for cardiovascular clinical trials funded by

NHLBI can provide quantitative data regarding the number of women enrolled in the cardiovascular clinical trials as well show whether or not the primary findings report on sex-specfic outcomes in the interventions proposed in the trial.

The aim of this project was to perform a systematic review and content analysis of primary results papers reporting on the number of women enrolled in the clinical trials and whether sex differences were discussed based on the stipulations detailed in the NIH Revitalization Act. There have been many published systematic reviews that analyzed the inclusion of women in cardiovascular clinical trials and how the NIH Revitalization Act has had very little effect on the enrollment of women in cardiovascular disease clinical trials and the reporting of sex-specific outcomes (Melloni et al., 2010). The results of these systematic reviews and analysis provide insightful milestones in comparing the data collected for this project.

The data collected for this project required a multi-step systematic approach in which clinical trials were retrieved through clinical trials.gov based on inclusionary criteria such as: the type of clinical trial (intervention vs. observational), the review of the trials by a committee consisting of the author of this paper and NHLBI scienitific staff, the number of participants based on the NHLBI's Accrual Policy for Clinical Research, and if the unique clinical trials.gov identifying numbers had reported primary findings published in PubMed.

The results demonstrated that there was a higher proportion of men enrolled in the NHLBI funded cardiovascular clinical trials that were included in this systematic, compared to women. The data also showed that according to cardiovascular disease area, there were areas that showed higher proportions of enrollment of men in cardiovascular

disease clinical trials compared to women. However in the categories of primary and secondary prevention of cardiovascular disease there was a higher proportion of women enrolled than men. There was also a higher percentage of primary findings papers that did not report on sex differences in the intervention proposed.

The conclusions that can be drawn from the results of this systematic review and analysis is that despite the implementation of the NIH Revitalization Act, there are still disparities in the enrollment of women in NHLBI funded cardiovascular clinical trials, regardless of the specific disease areas in which the proportion of women enrolled in these clinical trials is higher than men. Also, the reporting of sex differences in primary results papers was not a common occurrence among the primary results papers analyzed.

Limitations

There were several limitations in the extraction of data utilized in this systematic review and analysis.

While Clinical Trials.gov served as a useful resource for retrieving NHLBI funded clinical trials, the reporting of up-to-date information was contingent upon the principal investigators and their respective institution reporting on the progress of the trials. There were many clinical trials that started several years earlier where enrollment information was not provided, and so the primary findings papers could not be found. Conversly, parameters with respect to the time in which the preliminary data was collected had to be set for a specific date as the information in Clinical Trials.gov was updated on a daily basis.

The variance in the reporting of sex differences for the clinical trials.gov, also placed limits regarding the analysis or comparisons that could be drawn between the

enrollment of women in trials with published findings versus those that did not have published findings linked to the unique identifier numbers (NCTs) in PubMed.

The decision to categorize specific clinical trials into nine cardiovascular disease area categories could also be perceived as being a delimitation in this project as clinical trials were clustered according to the intervention and composition of the partipants that were part of the clinical trial.

Implications

The underrepresentation of women in cardiovascular clinical trials and the limited reporting of sex-specific outcomes in the primary findings publications of cardiovascular clinical trials has wide reaching implications to the field of public health. Women comprise more than half of the US population and have historically been underrepresented in clinical trials, particularly mixed-gender cardiovascular clinical trials (E. S. Kim et al., 2008). As there are sex-based differences in the etiology of cardiovascular diseases and specific female risk factors such as complications due to pregnancy that can effect cardiovascular health in women (Westerman & Wenger, 2016) , it is paramount that primary results papers report on variances in outcomes of the interventions recommended (Westerman & Wenger, 2016).

A recently published GAO Report showed that limitations exist with regards to accessibility of NIH's reporting of data pertaining to the enrollment of women in NIH funded clinical trials (U.S. Government Accounting Office, 2015). The GAO report also found that because the NIH does not examine enrollment data based on a specific disease area or illness, it is difficult to ascertain whether or not women are sufficientily enrolled

in NIH funded clinical trials (U.S. Government Accounting Office, 2015). Despite the strides and progress made in the inclusion of women in clinical trials since the implementation of the NIH Revitalization Act, the reporting of sex-specific outcomes and increasing the enrollment of women in specicific CVD area clinical trials with low female recruitment numbers are challenge that must be faced in order to ameliorate cardiovascular disease outcomes in women (Melloni et al., 2010).

Conclusion and Recommendations

The findings of this systematic review demonstrated that there was an overall improvement in the proportion of women enrolled in the cardiovascular clinical trials, when compared to previous systematic reviews cited in this paper. Yet there were variances in female enrollment in cardiovascular clinical trials by disease area, which for the most part showed that there were fewer women enrolled in the cardiovascular clinical trials when compared to men. Of the nine cardiovascular disease clinical trial categories, only two had a higher proportion of women enrolled than men: Primary Prevention of Cardiovascular Disease and Secondary Prevention of Cardiovascular Diseases, which demonstrates that trials that focus on the prevention of cardiovascular disease in general have a larger proportion of female participants enrolled than those cardiovascular trials focusing on a specific condition such as heart failure.

The low percentage of primary findings papers that reported on sex-specific outcomes in the results of the cardiovascular clinical trials is an important outcome of this analysis to report, as these primary findings form the basis for guidelines for treating cardiovascular disease (Blauwet, Hayes, McManus, Redberg, & Walsh, 2007).

Like most public health policy initiatives, the challenges in addressing low inclusion rates of women in cardiovascular trials and low rates in the reporting of sex difference in cardiovascular clinical trials requires input from various the examination of multiple options from various stakeholders. These may include:

Implementation of Frequent Systematic Reviews of Cardiovascular Trials that analyze the inclusion of women in cardiovascular clinical trials by NIH and Institute specific analysis (U.S. Government Accounting Office, 2015)

As more clinical trials are completed over time and as the primary results papers become available for newer studies, an increase in the frequency of systematic reviews performed by NHLBI could identify specific cardiovascular disease areas where the proportion of women enrolled are low and track cardiovascular disease areas that have improved over time.

Implement policies that require NHLBI funded cardiovascular trials to address sex differences in the primary results papers

To ensure that sex-specific outcomes are addressed in NHLBI funded cardiovascular clinical trials' primary results paper, it may be necessary to implement policies or conditions that requires investigators to report on sex differences in their primary results papers (Blauwet et al., 2007).

Implement policies that are initiated by the NHLBI that would require journals reporting on NHLBI funded cardiovascular clinical trials to report on the percentage of both men and women participants and the intervention results for both genders

Many of the primary findings papers that were retrieved for this systematic review reported on the number and proportion of male participants enrolled and the

number in the cardiovascular clinical trials. Although minimal arithmetic calculations were required to deduce the number of female participants when results tables only provided data for male participants in the primary findings, this practice of only reporting on data for male participants suggests that providing results for the female participants in the results of the intervention is not significant or is perhaps an afterthought(Heidari, Babor, De Castro, Tort, & Curno, 2016). Including data on the proportion of male and female participants and intervention results stratified by sex and making this information readily available may facilitate future systematic analysis and ancillary assessment of sex differences in cardiovascular clinical trials and other variables of interest.

Analysis of NHLBI funded CVD clinical trials and examine whether there is a correlation between the median age of participants and the proportion of women enrolled in NHLBI funded CVD clinical trials

Advanced age is a risk factor for women in the development of cardiovascular disease ("The 10Q Report: Advancing Women's Heart Health Through Improved ResearchTreatment and Diagnosis," 2011) and there were several studies cited in this paper that reported on sex-specific outcomes in the results, specifically with regards to age. The primary findings papers retrieved for this project can be used to conduct an analysis of median age and the proportion of female participants enrolled.

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