Trends in research with U.S. military service member participants: A population-specific ClinicalTrials.gov review

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A B S T R A C T

Background: ClinicalTrials.gov reviews have evaluated research trends for specific conditions and age groups but not for specific populations of research participants. No ClinicalTrials.gov reviews have evaluated research with military service member participants.

Purpose: Study objectives were (a) to use ClinicalTrials.gov to identify trends in biomedical research from 2005 to 2014 in which U.S. military service members actively participated as research participants and (b) to describe a search strategy for adaptation in future ClinicalTrials.gov reviews of specific participant populations.

Methods: A systematic review of ClinicalTrials.gov was performed to identify studies that included U.S. service members as participants, either exclusively or with other groups of participants.

Results: U.S. service members were identified as participants in 512 studies. Service members participated together with other groups in 392 studies, while 120 studies included only service members. The top five conditions of interest were post-traumatic stress disorder, traumatic brain injury, amputations, burns, and ocular injuries/disorders. The number of studies started each year peaked in 2011 and declined from 2012 to 2014. Twenty-five percent of studies exclusive to service members aimed to enroll 500 or more participants. Research exclusive to Guard and Reserve service members during this period was limited.

Conclusions: U.S. military service members participate in biomedical research. To address the health needs of U.S. service members, it is important to ensure there is not a prolonged decline in research among this population. The search strategy may be adapted to ClinicalTrials.gov reviews of specific participant populations for which straightforward searches are not possible.

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1. Introduction

Investigators often include U.S. military service members as participants in biomedical research. For example, several recently published studies included service members returning from deployments in Iraq and Afghanistan focused on war-related injuries such as traumatic brain injury (TBI) [1,2] and post-traumatic stress disorder (PTSD) [3,4]. Studies such as these, in which military service members actively participated as research participants, providing the required informed consent, are different from studies [5–8] in which medical records, databases, and registries with U.S. service member health information are reviewed and analyzed.

Understanding the types of studies in which U.S. military service members actively participate and identifying trends in such research can provide insights relevant to this population.

ClinicalTrials.gov is a Web-based clinical trials registry maintained by the National Library of Medicine. Registry entries contain detailed information about each study, provided by the sponsor or principal investigator, such as the purpose, methods, participant eligibility, estimated or actual enrollment, contact information, and locations [9]. ClinicalTrials.gov provides a robust, publicly available source of information about contemporary biomedical research worldwide.

Since the inauguration of ClinicalTrials.gov in February 2000, two important events have stimulated increased registration of studies. First, in 2004, the International Committee of Medical Journal Editors (ICMJE) announced that registration in a public clinical trial registry, such as ClinicalTrials.gov, would be a requirement for publication of a clinical trial in ICMJE member...
journals beginning in July 2005 [10]. After an initial period of adjustment, this requirement was reportedly well received by the scientific community [11], and it was continued in the most recent ICME guidelines [12]. Second, the U.S. Food and Drug Administration Amendments Act of 2007 required registration and results reporting for certain types of clinical trials [13], thus expanding trial registration requirements that had first been established in the Food and Drug Administration Modernization Act of 1997 [14].

Recent reviews of ClinicalTrials.gov have evaluated trends, characteristics, and status of research for various specialties [15–17], conditions of interest [18–20], and age groups [21–23]. No similar published reviews related to military-relevant biomedical research or research involving U.S. military service members have been identified. Additionally, we are unaware of any ClinicalTrials.gov reviews that have undertaken a review of a specific population that could not be searched directly by condition of interest or age group.

This study systematically reviewed studies registered in ClinicalTrials.gov that included U.S. military service members as research participants, either exclusively or with other groups of participants. The first aim was to identify the trends in and extent of U.S. military service members’ participation in biomedical research during the 10-year period from 2005 to 2014. The second aim was to describe a search and categorization strategy that may be adapted for future ClinicalTrials.gov reviews of specific populations of research participants for which no direct search strategy is available.

2. Methods

2.1. Search strategy

A search of ClinicalTrials.gov was performed using the registry’s advanced search function, with the search terms and specifications described in Table 1. Using the website’s Download Search Results function, 5159 studies, with all available data, were downloaded in extensible markup language (XML) format. The file was imported to Microsoft Excel.

No single search term proved to be adequate for broadly locating registered studies that were relevant to U.S. military service members as research participants. An extensive list of search terms was developed to identify a comprehensive and inclusive search in which each resulting item could then be reviewed for inclusion or exclusion on a study-by-study basis. Combining all search terms using the operator OR served to eliminate the duplication of studies that would have occurred in independent searches of unique search terms [24].

2.2. Inclusion criteria

Each study was evaluated for the following inclusion criteria: (a) The study start date was between 01/01/2005 and 12/31/2014 as specified in ClinicalTrials.gov. For studies with no start date provided, we used the first received date, also between 01/01/2005 and 12/31/2014. (b) The study involved active participation. (c) Of the estimated or actual number of participants sought for enrollment, at least 10% or at least 30 participants were U.S. military service members. U.S. military service members were defined as active duty, Reserve, or Guard members of any service. Studies were eliminated as reported in Fig. 1.

The 2005 to 2014 study start date timeframe was selected (a) to limit the search to a manageable volume of data while maintaining the ability to identify trends over time, (b) to correspond with studies that may have been initiated in response to increased military operations and casualties in Iraq and Afghanistan, and (c) because studies were not registered in ClinicalTrials.gov consistently prior to this time due to lack of formal guidelines [10] or regulations [13].

ClinicalTrials.gov defines study start date as the date a study is first able to enroll participants in the study protocol [25]. Study start date was the most appropriate date to use for determining inclusion criteria in this review, due to the focus on service members’ participation in biomedical research. However, the ClinicalTrials.gov advanced search function did not provide an option for searching by study start date [24]. Instead, we used first received date, with an expanded date range from 01/01/2003 to 08/01/2015, to select for review any eligible studies with actual study start dates between 01/01/2005 and 12/31/2014.

Active participant involvement was required for a study to be included in this review. For example, retrospective chart reviews and safety surveillance studies were eliminated if the study did not involve contact with individuals and/or there was no direct data collection from individuals.

The thresholds of a minimum of 10%, or at least 30, U.S. military service member participants aimed to eliminate studies that did not involve a substantial proportion or number of service members. The intention was to avoid simply including all studies in which one or more service members could conceivably participate, and instead to examine studies that included U.S. military service member participants to an extent that was substantially meaningful.

The search was not limited to studies performed in the United States. Studies performed at overseas U.S. military installations that included U.S. military service members were also included. The review was limited to United States military service members due to the authors’ familiarity with this specific population.

2.3. Review process

Studies outside the start date parameters were eliminated first. Next, the title of each study was reviewed to determine inclusion or exclusion. When a determination could not be made based on title alone, other data fields were evaluated, such as condition being investigated, lead sponsor, collaborators, or study location. Fig. 1

Table 1

| Item      | Specification |
|-----------|---------------|
| Search type | Advanced terms |
| Search terms | military OR “active duty” OR soldier OR sailor OR airman OR marine OR guardsman OR Army OR Navy OR “Air Force” OR “Marine Corps” OR “Coast Guard” OR “National Guard” OR “service member” OR deployment OR combat OR war OR TBI OR PTSD OR reintegration |
| Age group  | Adult (18–65) |
| First received | From 01/01/2003 to 08/01/2015 |

Note: We tested and verified that for compound words in quotes (e.g., “Marine Corps,” “active duty”), the use of capital versus lower-case letters did not change search results. Similarly, plural and singular search terms (e.g., soldiers vs. soldier) also provided identical results.
shows the first reason found for determining a study ineligible for inclusion. (Many studies were excluded for more than one reason.)

One-third of the studies (n = 1,721, 33.4%) required further evaluation to determine if they met inclusion criteria. To accomplish this, the study hyperlink, a data field included in the downloaded search results, was used to review the complete registry entry on the ClinicalTrials.gov website. Each study record was reviewed with close attention to the reported participant eligibility and participant inclusion and exclusion criteria to determine if the study met criteria for inclusion in this review.

2.4. Final categorization

The studies meeting inclusion criteria were further categorized into three groups based on the proportion of U.S. military service member research participants compared to other study participants: (a) studies with approximately 10%–24%, or at least 30, service member participants; (b) studies with at least 25%, but not exclusively, service member participants; and (c) studies with exclusively U.S. military service member participants. For ease of reading, in this paper these groups will be discussed as including (a) few, (b) many, or (c) all U.S. military service member participants, respectively.

Individual study registry entries were reviewed closely and information was manually collected to determine the types of participants and to categorize by proportions of participants. Items taken into consideration included but were not limited to lead sponsor, collaborators, location of the research, specific inclusion and exclusion criteria, number and types of civilian and military facilities for multi-location studies, estimated or actual enrollment, condition being studied, and age groups most commonly affected by a given condition. Study methods or findings publications, recruitment materials, and study websites were reviewed when available.

2.5. Excluded studies comparison group

A group of 512 studies was randomly selected from studies that had been excluded from the initial search results. These 512 studies, the excluded studies comparison group, were used in the analyses of study type, anticipated enrollment, and number of studies started by year for comparison with the 512 studies that met criteria for inclusion in the review. The studies in the excluded studies comparison group were limited to research performed in the U.S. with adult participants and with study start dates between 01/01/2005 and 12/31/2014. All studies in the excluded studies comparison group included no or very few (less than 10%) service member participants.
2.6. Data analysis

Descriptive statistics, including frequencies and percentages of categorical variables, were performed using IBM SPSS Statistics Version 23. When appropriate, cross tabulations of two categorical variables were performed with weighted cases using two-sided Fisher’s exact test to calculate p-value with level of significance $\alpha = 0.05$. Conditions of interest were ranked using Microsoft Excel.

3. Results

As of August 1, 2015, ClinicalTrials.gov contained 196,305 registered studies from all U.S. states and 190 countries. A total of 512 studies were identified as including U.S. military service members, as defined by the inclusion criteria. These studies were further categorized into three groups to differentiate between the proportions of U.S. service members included as participants. Nearly a quarter of the studies ($n = 120, 23.4\%$) had study inclusion criteria limiting participation exclusively to U.S. service members. The remaining 392 studies (76.6\%) included U.S. service members and other participants such as Veterans, military retirees, military health care beneficiaries, U.S. Department of Defense employees, and other civilians. Of the total 512 studies, 182 (35.5\%) included at least 25\% but not exclusively U.S. service member participants, and 210 (41.0\%) had at least 10\% but less than 25\%, or at least 30, U.S. service member participants (see Fig. 2 and Table 2). A complete list of included studies is available in Supplementary Material File 1.

3.1. Participant type

Among all 512 included studies, 500 (97.7\%) included active duty service members as participants, while only 168 studies (32.8\%) included Guard or Reserve service members as participants (Table 2). Among the studies that included 100\% service members, more than half ($n = 64, 53.3\%$) specifically limited participation to active duty service members, while 40.8\% ($n = 49$) permitted a combination of active duty and Reserve and/or Guard service members. Among studies exclusive to service members, significantly fewer studies ($n = 7, 5.8\%, p < 0.001$) were specifically limited to Reserve or Guard service members compared to those limited to only active duty service members.

Roughly half of the studies also included military health care beneficiaries ($n = 281, 54.9\%$) and military retirees ($n = 249, 48.6\%$) in addition to service members. Approximately one-fifth of studies overall also included U.S. Veterans ($n = 117, 22.9\%$) and other civilians ($n = 110, 21.5\%$).

3.2. Conditions of interest

The top five conditions of interest among all 512 studies were post-traumatic stress disorder (PTSD; $n = 100, 19.5\%$), traumatic brain injury (TBI; $n = 56, 11.0\%$), amputation care ($n = 22, 4.3\%$), burns ($n = 22, 4.3\%$), and ocular injuries/disorders ($n = 21, 4.1\%$). Studies had between one and six conditions of interest. Table 3 summarizes the top 20 conditions of interest for all included

![Study Start Year by Group](image-url)

**Fig. 2.** Number of studies started per year, by study group. If study start date was not reported in ClinicalTrials.gov, then study first received date was used.
Table 2
Participant type by study group.

| Group                                | Participant type |
|--------------------------------------|-----------------|
|                                      | Military participants | Other participants |
|                                      | Active duty only | Reserve or Guard only | Active duty with Reserve and/or Guard | Veterans | Military retirees | Military health care beneficiaries | DoD employees | Other civilians |
| Exclusively military participants (n = 120) | n 64 | 7 49 | 0 0 0 | 0 | 0 0 0 |
|                                      | % 53.3 | 58 40.8 | 0 0 0 | 0 |
| At least 25% but not exclusively military participants (n = 182) | n 99 | 4 79 | 96 100 84 | 8 | 29 |
|                                      | % 54.4 | 2.2 43.4 | 52.7 54.0 46.2 | 4.4 |
| 10%–24% or at least 30 military participants (n = 210) | n 181 | 1 28 | 21 149 197 | 11 | 81 |
| All studies (N = 512)                 | n 344 | 12 156 | 117 249 281 | 19 | 110 |
|                                      | % 67.2 | 2.3 30.5 | 22.9 48.6 54.9 | 3.7 |

Abbreviation: DoD, Department of Defense.

Table 3
Top 20 conditions of interest.

| Condition                  | All included studies (N = 512) |
|----------------------------|-------------------------------|
| n | % of total | Rank |
|--------------------------------|
| PTSD                   | 100 | 19.5 | 1 |
| TBI                     | 56  | 11.0 | 2 |
| Amputation care          | 22  | 4.3  | 3 |
| Burns                    | 22  | 4.3  | 3 |
| Ocular injuries/disorders| 21  | 4.1  | 5 |
| Back pain                | 20  | 3.9  | 6 |
| Depression               | 19  | 3.7  | 7 |
| Sleep                    | 18  | 3.5  | 8 |
| Malaria                  | 17  | 3.3  | 9 |
| Cognitive performance    | 15  | 2.9  | 10 |
| Combat stress disorders  | 15  | 2.9  | 10 |
| Nutrition status         | 15  | 2.9  | 10 |
| Stress                   | 15  | 2.9  | 10 |
| Diabetes                 | 14  | 2.7  | 14 |
| Orthopedic trauma        | 14  | 2.7  | 14 |
| Post-concussive syndrome | 14  | 2.7  | 14 |
| Post-op pain             | 14  | 2.7  | 14 |
| Hemodynamic status       | 13  | 2.5  | 18 |
| CV disease               | 12  | 2.3  | 19 |
| Phantom limb pain        | 12  | 2.3  | 19 |

Note: Studies may indicate more than one condition of interest. Studies are listed alphabetically in the same cell when there are ties within a rank. More than 20 conditions are listed when the 20th-listed condition was tied with other conditions. Abbreviations: CV, cardiovascular; Post-op, postoperative; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury.

Table 4 summarizes the top 20 conditions of interest by study group. A complete list of conditions of interest overall and by study group is available in Supplementary Material File 2.

PTSD was the top-ranking condition of interest overall for all included studies (n = 100, 19.5%), and for the study groups with many (n = 67, 36.8%) and all service member participants (n = 27, 22.5%). In contrast, in the study group with few service members, PTSD ranked only tenth in conditions of interest (n = 6, 2.9%), tied with back pain, dengue fever, glucose control, influenza, orthopedic trauma, obstructive sleep apnea, and wound research.

TBI was the second ranked condition of interest overall for all included studies (n = 56, 11.0%), and for the study groups with many (n = 29, 16.0%) and all service member participants (n = 18, 15.0%). TBI was tied with cardiovascular disease as the fourth-ranked condition of interest for the study group with few military participants (n = 9, 4.3%).

Ocular injuries/disorders ranked in the top five conditions of interest when all 512 studies were combined but was not in the top five for any of the three study groups categorized by proportion of service members. The group with few service members had eight studies (3.8%) examining ocular injuries and disorders; the group with many service members had four studies (2.2%); and the group with all service members had nine studies (7.5%).

Ninety studies (17.6%) included pain as a condition of interest. Pain research was categorized as acute pain, chronic pain, back pain, postoperative pain, phantom limb pain, knee injuries/pain, leg/hip pain, shoulder/neck pain, and headache/migraine. Had all pain categories been combined in one group, pain would have been the second highest ranked condition of interest overall. Back pain was the top-ranking condition of interest overall for all study groups, and it ranked sixth for all studies overall. Chronic pain was among the top 20 conditions of interest for the groups with all and many service members (17th and 14th respectively). Acute pain was among the top 20 conditions only in the group with many service members, and was not in the top 20 overall.

3.3. Trends by study start year

Fig. 2 depicts study start dates by year over the 10-year period from 2005 to 2014. The number of studies by study start year peaked in 2011 for all included studies combined (n = 70), for the group with many service members (n = 35), and for the group with all service members (n = 19). For these groups, there was a decline in the number of studies started each year from 2012 to 2014. For the group with few military, 2014 was the year the greatest number of studies started (n = 31).

3.4. Study type

Overall, most studies were interventional (n = 405, 79.1%) and fewer were observational (n = 107, 20.9%). This distribution did not differ significantly from the excluded studies comparison group (p = 0.433). The greatest difference between interventional and observational studies occurred in the group with many service members, with 84.6% (n = 154) interventional studies compared to 15.4% (n = 28) observational (Table 5). There was a higher proportion of interventional studies in the many service member group than in the group with few service members (n = 160, 76.2%, p = 0.042), and in the group with all service members (n = 91, 75.8%, p = 0.071).

3.5. Estimated enrollment

Investigators often sought to enroll large numbers of participants (Table 5). Significantly more studies among the included studies sought 500 or more participants compared to the excluded studies comparison group (n = 69, 13.5% vs. n = 45, 8.8%, p = 0.022). Among studies exclusive to military service members, 25% (n = 30)
had a goal of 500 or more participants. This was a significantly higher proportion than for the groups with few service members and (n = 32, 15.2%, p = 0.040) and many service members (n = 7, 3.8%, p < 0.001) and for the excluded studies comparison group (p < 0.001).

Similarly, significantly more studies among the included studies sought 2000 or more participants compared to the excluded studies comparison group (n = 21, 4.1% vs. n = 7, 1.4%, p = 0.011). Among studies exclusive to military service members, 13 (10.8%) had a goal of 2000 or more participants. This was a significantly higher proportion than for the groups with few service members (n = 6, 2.9%, p = 0.005) and many service members (n = 2, 1.1%, p < 0.001) and for the excluded studies comparison group (p < 0.001).

Overall, more than half (n = 272, 53.1%) of the included studies had a goal of 100 or more participants, significantly more than in the comparison group (n = 218, 42.6%, p < 0.001). The group exclusive to service members had the highest proportion of studies seeking 100 or more participants (n = 83, 69.2%), while the group with many service members had the lowest proportion (n = 66, 36.3%). The group with many service members had significantly more studies enrolling less than 100 participants than both the groups with few and all service members (p < 0.001). However, the group with many service members did not differ significantly from the excluded studies comparison group in the number of studies enrolling less than 100 participants (p = 0.160).

4. Discussion

A systematic review of ClinicalTrials.gov identified studies with U.S. military service member participants from 2005 to 2014 to identify and report the trends in and extent of their research participation. This study is unique among reviews of
ClinicalTrials.gov in that it is the first of which we are aware that focuses on research on military service members of any nationality. Additionally, the research question could not be answered through a straightforward search of ClinicalTrials.gov and thus reports a unique approach to searching the ClinicalTrials.gov clinical trial registry to identify and categorize research trends within a specific population of research participants.

4.1. Consistency of studies’ top conditions of interest with priority clinical needs

Nearly a quarter (22.5%) of the studies with exclusively military participants and over one-third (36.8%) of the studies in the group with many military participants had PTSD as a condition of interest. Overall, PTSD was the highest ranked condition of interest, accounting for 19.5% of all included studies. TBI was the only condition of interest represented in the top five conditions of interest across study groups, regardless of the proportion of service members included.

The top conditions of interest in the studies included in this review are consistent with many of the top health needs of service members given the wars and conflicts since the early 2000s. More than 52,000 U.S. service members have been wounded in action between 2001 and mid-2015; over 177,000 U.S. service members have been diagnosed with PTSD since 2000; there have been more than 327,000 cases of TBI among U.S. forces since 2000; and over 1600 U.S. service members have suffered major limb amputations from battle injuries since 2001 [26]. Based on this review, investigators are clearly making efforts to help address these priority clinical areas.

4.2. Trends in numbers of studies started with service member participants

From 2012 to 2014, there was a trend of decreasing numbers of studies started each year in the groups with many and all service member participants. This trend is inconsistent with other sources that have anticipated a continued increase in research relevant to and including military service members during this timeframe. For example, Executive Order No. 13625, “Improving Access to Mental Health Services for Veterans, Service Members, and Military Families,” [27] in 2012 called for the establishment of a National Research Action Plan (NRAP) to address needed research and development in the areas of TBI, PTSD, other mental health conditions, and suicide prevention. The NRAP is a wide-reaching collaboration developed by the U.S. Departments of Defense, Veterans Affairs, Health and Human Services, and Education [28]. The NRAP would lead one to anticipate an increase in the number of studies in these priority clinical areas following 2012, rather than the decrease identified in this review.

It is important to note that the comparison group of excluded studies also experienced a sharp decline in the number of studies started in 2014, after a peak in 2013. For the groups in which the number of studies started in 2014 declined from previous years, it is possible —yet unlikely—that this decline is due to studies not yet being registered in ClinicalTrials.gov: (a) studies are generally registered in advance of the study start date, as previously discussed; (b) this review was conducted in the second half of 2015 to capture any late registries; and (c) the group with few military service members recorded its greatest number of study starts in 2014.

4.3. Trends in research with many service member participants

The group of studies with many service members tended to be interventional studies with fewer participants. This group had significantly more studies with less than 100 participants compared to the groups with few and all service members. Additionally, significantly more studies in the group with many service members were interventional studies compared to the groups with few and all service members. This trend may be helpful for researchers to consider when designing interventional studies that will include mostly service members along with other groups of participants.

4.4. Trends in research with exclusively service member participants

Studies with exclusively service member participants often sought large samples. Significantly more studies exclusive to service members sought to enroll 500 or more participants compared to the groups with few and many service members. When considering even larger studies of 2000 or more participants, the group of studies with all service members remained with significantly more studies compared to the groups with few and many service members. Studies in which service members participate exclusively often seek significantly more participants than do studies with few or many service member participants. This trend may be important for investigators, institutional review boards, and funding agencies to consider when designing and reviewing studies that will include exclusively service member participants.

Research exclusive to Guard and Reserve service members was limited in comparison to the number of studies in which exclusively active duty service members participated. More research may be needed to support the unique needs of these service members, particularly in relation to reintegration and transition to civilian environments following deployment. Guard and Reserve service members may have different challenges in post-deployment reintegration [29,30] and access to care [31] as they may not have the extensive military community support and resources available to active duty service members.

4.5. Limitations

This review provides insight into one publicly available data source regarding research, completed and in progress, in which U.S. military service members participated. This study has several limitations. First, not all studies in which military service members participate are registered in ClinicalTrials.gov, as not all studies are legally required to be registered [9]. This may explain why a smaller proportion of observational studies were identified in this review compared to interventional studies. A second limitation is the inability to determine whether there has been an increase in the overall number of studies in which service members participated or simply an increase in studies registered in ClinicalTrials.gov.

Data collection and study categorization were performed mainly by the primary author, who has nearly 20 years of full-time active military experience in the U.S. Military Health System. This approach provided consistency in the way studies were categorized. The time and attention to detail given to the data collection and organization was significant; it would not have been feasible for multiple authors to perform these tasks and it would not likely have added adequate value and improvement to the study overall to be worthwhile.

5. Conclusions

U.S. military service members participate in biomedical research both in exclusively military studies and along with other groups of participants, such as Veterans, military retirees, military health care beneficiaries, Department of Defense employees, and other civilians. Investigators of studies that exclusively enroll service members often seek large numbers of participants. Research exclusive to
Guard and Reserve service members during this time period was limited. This review identified an overall decline in studies started each year from 2012 to 2014, following a peak in 2011, though the number of studies started in 2012, 2013, and 2014 still remained above the number started each year from 2005 to 2010. It is important to ensure that there is not a prolonged decline in research among this population. The top conditions of interest in the studies identified in this review were consistent with priority clinical needs of service members. U.S. military service members have acute and chronic health needs, often as a result of injuries or exposures during their service, which they experience during their service and long after leaving the military. Military-relevant biomedical research must remain a priority.

This review used a complex search strategy to identify studies in ClinicalTrials.gov pertaining to a specific population of research participants. Although this review was limited to U.S. military service members, the methods described could be used by researchers to identify research trends among military service members of other nations or other populations of research participants. The review provides a search strategy which may be adapted for other ClinicalTrials.gov reviews of specific participant populations for which no straightforward search strategy is available.

Conflicts of interest

The authors do not have any conflicts of interest.

Author contribution

The authors are grateful to Lieutenant Colonel Kristal C. Melvin, Army Nurse Corps, PhD, Chief, Center for Nursing Science & Clinical Inquiry, Brooke Army Medical Center, San Antonio, TX, for her expertise in reviewing this manuscript.

Commander Wendy A. Cook is an active duty member of the U.S. Navy Nurse Corps. The views expressed in this publication are those of the authors and do not necessarily reflect the official policy or position of the Department of the Air Force, Department of the Army, Department of the Navy, Department of Defense, or the United States Government. This work was prepared as part of the author’s official duties. Title 17, USC, §105 provides that ‘Copyright protection under this title is not available for any work of the U.S. Government.’ Title 17, USC, §101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person’s official duties.

Acknowledgments

This research was supported by the National Institute of Nursing Research of the National Institutes of Health under award number K24NR015340.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.conctc.2016.04.006.

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