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

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ABSTRACT

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.

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

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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 ICMJE 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 fields, 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 elimination or inclusion 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
Search strategy.

Item	Specification
Search type	Advanced
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.