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Performance of Ethical Military Research is Possible: On and Off the Battlefield

John McManus · Annette McClinton · Robert Gerhardt · Michael Morris

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Abstract Many of the same fundamental principles and regulations that govern civilian biomedical research also apply to research conducted by the US Military. Despite these similarities, the conduct of research by the US Military has additional requirements designed to preserve service members' informed consent rights, ethical standards and information that may be deemed classified. Furthermore, there are also additional rules and regulations associated with potential research to be done in a combat setting. Before conducting battlefield research, many unique circumstances must be considered to include: (1) the current legal and regulatory requirements for advanced informed consent (2) the tactical situations, and the ability to adequately document in the "austere" environment (3) the need to provide improved drugs and devices for combat casualty care and (4) the special nature of the superior-subordinate relationship. This paper discusses historical background, regulatory oversight, ethical implications and release of information as it pertains to research conducted by the US Military.

Keywords Military research · Combat · Consent · Ethics · Informed consent

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J. McManus (✉) · A. McClinton
US Army Institute of Surgical Research, 3400 Rawley E. Chambers Ave B, Fort Sam Houston, TX 78234-6513, USA
e-mail: john.mcmanus@amedd.army.mil

R. Gerhardt · M. Morris
Brooke Army Medical Center, Fort Sam Houston, TX 78234-6513, USA

Introduction

Investigators in both the civilian sector and military-related research environments hold an ethical obligation to allow potential participants input into actions that affect them. We summarize these motivations as being among those that ethicists call the principle of "respect for persons" which is essentially the acknowledgment of individual autonomy and protection of those with diminished autonomy [1]. "Respect" is one of the three basic ethical principles (beneficence and justice being the others) defined by the Belmont Report [2]. Prior to the publication of this report, there was great controversy surrounding human patient-oriented research and consent practices in both the civilian and military communities in the United States.

Much of the previous medically related research conducted by the military has been surrounded by controversy. History is fraught with examples of "research" conducted in military settings with questionable ethical principles. Some notable examples include: (1) The Continental (subsequently United States) Army's use of compulsory variolation (exposing uninfected individuals to matter from smallpox lesions) on troops in an attempt to prevent the spread of smallpox during the American Revolution; (2) the use of an experimental cholera vaccine on non-consenting prisoners located in the American-occupied Philippines during the Spanish American War, which resulted in 13 deaths, [3] (3) the infamous Tuskegee Syphilis Study , in which subjects were denied treatment and were misled even more after a diagnosis of secondary syphilis, [4] and (5) Axis powers (Nazi Germany and Imperial Japan) war experiments conducted during the Second World War [5].

While these and other past military-sponsored research practices produced distrust toward federal medical institutions and the government in general, these events have become some of the most influential in shaping public perceptions of research and fostering the government's role in human subject's protection. Furthermore, these military experiments and subjects' experiences helped guide future regulations and rules that now serve to protect human subjects, both in the armed forces as well as in the civilian sector. In fact, at the conclusion of World War II, the Nuremberg Medical Trial became "the most important historical forum for questioning the permissible limits of human experimentation"[6]. As a result the Nuremberg Code was established based on ten points describing required elements for conducting research on humans [7]. The Nuremberg Code was the first international standard for the conduct of research on human subjects and was affirmed in 1954 in the United States when the Army Surgeon General's Office issued a memorandum for human subject protection during research, becoming one of the first official documents to guide the conduct of human experimentation by military researchers [8]. Currently, there exist stringent regulations that must be followed to conduct research on Soldiers and civilians on the battlefield.

Rules and Regulations for Conducting DoD Research

The foundation for the Department of Defense (DoD) rules and regulations governing the conduct of human subjects' research is primarily based on the

regulations that govern all federally funded research. DoD regulations apply whether research is conducted on the battlefield, in a foreign theater of operations or within medical treatment facilities in the United States. The first governmental regulations and policies were borne out of previous abuses of research initially dating back to World War II and the abuses of prisoners by Nazi doctors as previously described. The Nuremburg Code laid the foundation for research principles of informed consent, scientific merit, and minimizing risks to research participants [5]. The DoD, under Secretary of Defense Charles Wilson, adopted the Nuremburg Code in 1953 as its official policy for research. Further guidance on the conduct of research was provided by the 1964 Declaration of Helsinki which addressed new research issues on research with therapeutic intent, diminished competence, and formal oversight of research [9]. However, due to continued abuses that were exemplified by the US Public Health Service Tuskegee Natural History Syphilis Study, the federal government eventually took ownership of research protections [4]. In 1974, the Department and Health and Human Services (DHHS) drafted the 45 Code of Federal Regulations (CFR) Part 46, Protection of Human Subjects, which governed human research protection. This policy was revised to include specific protections for pregnant women and fetuses (Subpart B), prisoners (Subpart C), and children (Subpart D). It was finally adopted by other 17 federal agencies to include Department of Defense in 1991 and became known as "The Common Rule" [10]. The Common Rule incorporates the Belmont principles of beneficence, justice and respect and requires that all human subject research be approved by an Institutional Review Board before implementation of the study.

Despite the directive to the contrary, the DoD was also responsible for several flagrant research abuses such as administration of lysergic acid diethylamide (LSD) to Soldiers and exposing unconsenting populations to radiation. In 1972, prior to the establishment of 45 CFR § 46, Congress inserted into appropriation bills the 10 USC § 980 requirement for the DoD entitled "Limitations on Use of Humans as Experimental Subjects." This code required the process of informed consent to be obtained in advance for all DoD funded research. 10 USC § 980 states:

> "Funds appropriated by the DoD may not be used for research involving a human being as an experimental subject unless (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance" [11].

Amended three times by 1985, the most current version was amended in the 2002 Defense Appropriations Act to allow for an exceptional waiver by the Secretary of Defense of the advance informed consent process if a research project would (1) directly benefit subjects, (2) advance the development of a medical product necessary to the military, and (3) be carried out per all laws and regulations including those pertinent to the Food and Drug Administration (FDA). This change allowed the conduct of specific emergency research to be carried out under the provisions of the Emergency Research Consent Waiver, 61 Federal Register 51531–51533 [12]. Legal interpretation of 10 USC § 980 stipulates that, in cases where surrogate consent must be obtained, the IRB must determine if the research is

intended to benefit all subjects. This interpretation has limited DoD participation in placebo-controlled studies or those that involve a standard-of-care arm, where surrogate consent is required and participants may not receive any direct benefit.

Human subjects' research by DoD agencies is also impacted by FDA regulations that govern investigational drugs and devices. 21 CFR §56 governs the function and responsibilities of the IRB reviewing and approving human studies including those involving investigational drugs, while 21 CFR §50 specifically addresses the requirements and elements of the informed consent process. DoD Directive 6200.2, "Use of Investigational New Drugs for Force Health Protection," establishes policy and assigns responsibility for compliance for the use of investigational new drugs for force health protection and designates the Secretary of the Army as the DoD Executive Agent [13]. Likewise, there are more specific regulations and directives that govern DoD research that delineate unique issues to the DoD than the more general Office of Human Research Protections regulations. 32 CFR § 219, "Protection of Human Subjects" is the DoD version of the "Common Rule." DoD Directive 3216.2, "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research" was updated in December 2002 and provides updated changes from other federal regulations [14]. DoD Directive 6000.8, "Funding and Administration of Clinical Investigation Programs," updates DoD policy and responsibilities regarding the administration and funding of clinical investigation programs in military medical and dental treatment facilities and the Uniformed Services University of the Health Sciences [15].

Within each branch of the military there are more service-specific regulations that govern different types of human subjects' research. The conduct of research within the Army Medical Research and Materiel Command (MRMC) is also governed by Army Regulation 70–25, "Use of Volunteers as Subjects of Research." This provides more specific restrictions on the recruitment, consent, and payment of volunteers to which the investigator must adhere during the conduct of the study [16]. The conduct of research at any US Army medical treatment facility is specifically governed by Army Regulation 40–38, "Clinical Investigation Program" that adheres to DoD, FDA, and OHRP federal regulations [17].

Research in Combat

Research on the battlefield (whether its basic design is social, behavioral or biomedical) presents a challenge to the entire research community and research process. The aim of medical care on the battlefield is to treat the wounded and either return them to duty or evacuate the severely injured to definitive care. Given the primary focus of military operations upon mission accomplishment, coincidental human subjects' research by necessity is relegated to a subordinate role. Thus, development and implementation of either prospective studies requiring informed consent or retrospective studies of existing data requires a very clear, well defined protocol that can be conducted during the deployment time period but without compromise to the military mission. Concurrently, ethical considerations of conducting such research on the battlefield must be considered, to include the

rights of Soldier-subjects, which are complicated by the traditional commander-subordinate role.

Military subjects on the battlefield should be viewed as members of a vulnerable population and afforded the same protection as other vulnerable populations including minors, prisoners or the economically disadvantaged. Clinical researchers desiring to conduct research in this setting must first develop an appropriate protocol, with the a priori conclusion that such research could not be replicated in a satisfactory manner in a domestic setting. Once such a protocol has been developed and its methodological and ethical validity confirmed by peer review, formal approval should then be sought from the commanders of the units to be impacted by the proposed research, and subsequently from the command element of the theater of operations to be studied. This combat theater command approval ensures that the proposed research can be conducted on the battlefield without jeopardizing the military mission and at the same time ensuring the integrity of the study.

Ensuring that the rights and welfare of Soldier-subjects are protected, no matter where the study is conducted, is still the responsibility of an IRB. The US Army has designated the Brooke Army Medical Center IRB at Fort Sam Houston, Texas as the reviewing authority for all research proposals that will be conducted by US Army personnel in a combat theater. The other services have similar external review constraints and a dedicated IRB to review combat research. Soldier-subjects should be afforded the same research protection as all other civilian research volunteers. Prospective research involving informed consent can only be done when the Soldier-subject is able to provide his or her own written informed consent. The prohibition of 10 USC 980 with its intent to benefit clause does not allow surrogate consent as an alternative to research on the battlefield.

Soldiers as a Vulnerable Population

The performance of patient-oriented clinical research by the US Military also requires investigators to also look at some of the ethical implications and the ability for Soldiers to give informed consent. Because of the structure of the military environment, Soldiers, in some circumstances, may be considered a "vulnerable population." In clinical research a vulnerable population is one that is unable to give informed consent or is susceptible to coercion. The very nature and location of the Soldier in combat (e.g., battlefield) contributes to a sense of "vulnerability" and may also be a source of unintended coercion [18]. At the best of times, during a combat situation, can informed consent be truly obtained? The mere stress of battle or a Soldier's "eagerness to please" may not actually represent the ability of an individual to make a fair, informed decision. However, one could argue that the same concept applies to most trauma patients who are asked to participate in research. Are these patients any more "vulnerable" than Soldiers?

Furthermore, because Soldiers are told to obey all "lawful" orders from officers they may feel compelled to obey "requests" from senior officials conducting research. To assure protection of the rights and welfare of the military research subjects, the IRB

may sometimes require an ombudsman to be present during the informed consent process.

However, the ability of Soldiers and their surrogate (legal representative) to refuse some medical procedures is restricted [19]. This regulation may be misinterpreted by Soldiers and/or surrogates resulting in confusion between a mandatory procedure (e.g. vaccinations etc.) and medical research. The Army has revised the regulations covering medical subjects to prevent unintended coercion. Army regulation 40–38 states that soldier's commanders or supervisors may not be in the room during the consent process [17].

"Informed consent" research can be performed in an ethically legitimate fashion on today's battlefield if investigators can ensure subjects are protected. Despite some controversy, the DoD and its' investigators have an ethical responsibility for protecting its' service members. Following the above policies and procedures as well as using appropriate research ethics will allow military investigators to ensure human subject protection.

Conclusion

The conduct of military medical research has, and will serve as an important contribution to both the civilian and military medical communities. Combat research, when performed properly is rewarding and aids in reducing morbidity and mortality on our battlefield. Furthermore, much of the research done in the past and today in combat has also been utilized in the civilian environment. The lessons of Vietnam and the development of trauma systems, the "golden hour," hemorrhage control products and air medical services provide additional reminders of the mutual benefits gained by military and civilian practice. The role of the military in medical research continues to be diverse, conflicting, and disquieting at times, yet remains a pioneering and crucial part of modern medicine and national defense.

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