

Informed Consent and Ethical Issues in Military Medical Research

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Abstract

Informed consent in military research shares many of the same fundamental principles and regulations that govern civilian biomedical research. In fact, much of modern research ethics is grounded in events that occurred in the context of war or government-sponsored research. Despite these similarities and common origins, research in the military has additional requirements designed to preserve service members' informed consent rights. The special nature of the superior-subordinate relationship in the military necessitates careful protections to avoid perceptions of coercion or undue influence on a military subject. Additionally, current legal and regulatory requirements for advanced informed consent significantly restrict the flexibility of the military to conduct research using waiver of consent. This has

implications on the ability of the nation to develop effective medical treatments for the global war on terrorism. Nevertheless, work is under way to realign defense research policy with the norms of civilian biomedical practice. Future directions include the adoption of waivers for military emergency research, and the cautious introduction of human subject studies on the battlefield. This paper discusses historical background, regulatory differences, and concerns and challenges of some of these regulatory differences for research personnel that apply to informed consent and waiver of said informed consent for emergency research conducted by the U.S. military. **Key words:** ethics; informed consent; military; research; waiver of consent; Department of Defense. *ACADEMIC EMERGENCY MEDICINE* 2005; 12:1120-1126.

Every dose of medicine given is an experiment as it is impossible in every instance to predict what the result may be.

—William Osler, 1907

Informed consent in the military and civilian environment is a fundamental right for all subjects who participate in clinical research. However, progress in emergency care and trauma research will require that some research be performed on patients who are unable to grant prior informed consent. Inherent to the nature of the disease process, trauma and critical care patients are unable to provide informed consent prior to research participation. Indeed, treatment of this group of patients is often rendered without consent, and is frequently initiated under conditions of "implied consent." This category of patients must

be considered vulnerable, and, in fact, military patients in combat may be arguably the most vulnerable research patient population. Because of past experiences and the vulnerability of the military population, rules and regulations involving informed consent are more stringent for some of the Department of Defense (DoD) agencies who conduct or sponsor research.

HISTORICAL BACKGROUND

A person's desire to have information about medical decisions and input into actions that affect his or her life carries with it an ethical obligation of the investigator. 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 This principle, respect, is one of the three basic ethical principles (beneficence and justice are the other two) of the Belmont Report that underlie all human subject research, but were not identified and described until 1979.² The National Research Act in 1974 established the "National Commission for Protection of Human Subjects of Biomedical and Behavioral Research," which published the Belmont Report, and laid the foundation for the ethical principles of the report. Unfortunately, prior to the Belmont Report there was much controversy surrounding research and consent practices in both the civilian and military communities in the United States.

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Many such controversies arose from questions regarding true autonomy for service members and citizens over their choices to voluntarily participate or receive therapy in research. As early as the 1700s, General George Washington used forced variolation (exposing uninfected individuals to matter from smallpox lesions) to stop the spread of a smallpox epidemic in his troops. In 1900, Major Walter Reed and his colleagues used American soldiers and Spanish volunteers in Havana to document the mode of transmission of yellow fever, which had plagued American interests in the Caribbean.³ Unprecedented for his era, Reed drew up a written contract, in English and Spanish, identifying the risks and benefits in the yellow fever study. Although research on humans had been conducted for years, it was not routine, or even required, to get written consent. Reed and the Yellow Fever Commission were regarded as the first research group to use consent forms in their research.³

However, other government-sponsored research in the past century was not as successful, and did not exemplify the same ethical standards set by the Yellow Fever Commission. In 1906, an American researcher named Richard Strong was the first to use prisoners for U.S. medical research in Bilibid prison located in the American-occupied Philippines.³ After the prisoners were inoculated with an experimental cholera vaccine, 13 out of 24 inmates died. In retrospect, the disaster at the Bilibid prison in Manila presents an epitome of the problems surrounding the use of prisoner-subjects without authorization and without their voluntary consent. The Bilibid episode remains, however, as a cautionary tale for those engaged in clinical research.⁴ Unethical behavior in government-sponsored research also occurred in the continental United States. In 1932, the Public Health Service initiated the Tuskegee Syphilis Study. In the longest running nontherapeutic research study in American history, more than 400 African American men who were diagnosed as having secondary syphilis were actively misled about the nature of their participation in the project, as well as denied new and effective treatment with the discovery of penicillin.³ While the study at Tuskegee cast a shadow of distrust over the country's medical institutions and government, especially where research is involved, it remains among the most influential in shaping public perceptions of research and fostering the government's role in the protection of human subjects.

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."⁵ In an effort to reduce the number of Jews in Europe, but still maintain a labor force, the Nazis were determined to use those fit to work, while at the same time rendering them incapable of reproducing. Men and women were sterilized without their permission or even their knowledge by x-rays, injection of an irritating solution, or surgical

procedures.⁵ Although hundreds of physicians were involved in the many unethical experimentations conducted by the Nazis, only 23 were tried, and only 15 of those tried were convicted for "crimes against humanity" at Nuremberg. Included in the legal judgment and sentences handed down at the culmination of the trial were ten points describing required elements for conducting research on humans, resulting in the Nuremberg Code.⁶ 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. This memorandum became one of the first official documents to guide the conduct of human experimentation by U.S. military researchers.⁷

The Nazis' atrocities clearly demonstrated that their research practices involving humans were not ethical; and this indirectly helped focus what might be regarded as ethical by comparison. This motivated the U.S. DoD to increase ethical standards for future research conduct, and development of products against nuclear, biological, and chemical agents during the Cold War. Between 1954 and 1973, more than 2,300 Seventh Day Adventists (SDAs), with the encouragement of the church leaders, served as volunteer subjects in 137 protocols in defensive biological weapons testing.³ In light of the religious objections against bearing arms, the SDAs participated in studies directed at developing and testing vaccines and therapeutic drugs against Q fever, tularemia, various viral encephalitides, Rift Valley fever, sand fly fever, and plague. Conscious of the Nuremberg Code, information that was exchanged between investigators and research volunteers at Fort Detrick effectively implemented the "process" of informed consent, and respect for the principles of the Nuremberg Code. The SDAs received a detailed briefing by the commanding officer as to the purpose of the study, the risks involved, and the role of each volunteer, and were allowed to ask questions before deciding whether to sign a consent form for participation in the experiment. Human subject research conducted at Fort Detrick for the past 49 years has resulted in only one claim of disability, and no death.⁶ However, during the same period, several other human studies on military personnel were conducted without subject consent and/or knowledge. Examples of some of these studies include radiation exposure,⁸ mustard gas experiments,⁹ and lysergic acid diethylamide (LSD) testing in nonvolunteer human subjects.¹ Why one group was allowed to give written consent, while consent was not sought from others, is not clear. Speculation might be that the SDAs were represented by an organization that had worked out an agreement with the military; whereas the subjects in the radiation, mustard gas, and LSD experiments were individually approached for participation in these experiments.

Although some of the above research practices were considered unethical and involved human research without consent, these military experiments and subjects' experiences helped guide future regulations and rules that now serve to protect human subjects in the armed forces. Despite these past examples of poor ethical research practices, the U.S. military has also successfully conducted several ethical and landmark experiments during the last century that have advanced science in both the civilian and military settings. The DoD continues to conduct and sponsor numerous studies and grants for both in-house and civilian institution-based research. The Army alone manages nearly \$1 billion annually in medical research and development funding, with a portion earmarked for universities and other research institutions. Some of the more active DoD agencies include the Army Medical Research and Materiel Command's Medical Research Institutes of Infectious Disease, Chemical Defense, and Environmental Medicine, Walter Reed Army Institute of Research, and Institute of Surgical Research; the Navy Bureau of Medicine and Surgery's Naval Health and Medical Research Centers; the Air Force Research Labs Human Effectiveness Directorate; and the Defense Advanced Research Projects Agency.¹⁰⁻¹³

REGULATIONS FOR CONDUCTING DEPARTMENT OF DEFENSE RESEARCH

The foundation for regulations protecting human subject research can be traced back to 1966 when the U.S. Surgeon General mandated that research funded by the Public Health Service should have oversight and enforcement of the Nuremberg Code principles.¹⁴ In 1974, two events occurred due to perceived abuses, including the Tuskegee case. First, the National Research Act in 1974 established the "National Commission for Protection of Human Subjects of Biomedical and Behavioral Research," which published the Belmont Report (*Ethical Principles and Guidelines for the Protection of Human Subjects of Research*) in 1979 and laid the foundation for the primary research principles of beneficence, justice, and respect for persons. The second event that year was the first publication of 45 Code of Federal Regulations (CFR) 46 by the Department of Health and Human Services (DHHS), later revised in 1979, and then finally adopted by numerous federal agencies in 1991 to include subparts A (The Common Rule), B (Pregnancy), C (Prisoners), and D (Children).

The Common Rule incorporates the Belmont principles, and requires documentation of advanced informed consent for human subjects participating in research. This limits the ability of researchers to perform research in certain emergency and trauma situations where informed consent cannot be obtained. In November 1996, the DHHS created an exception to

45 CFR 46 and allowed for an "Emergency Research Consent Waiver" that waived the requirement for obtaining informed consent in human subjects in need of emergency treatment, and in whom the medical condition or lack of available legal representative precluded the ability of researchers to obtain advanced consent.¹⁵ In October 1996, the Food and Drug Administration (FDA) published the "Final Rule," which is similar to the DHHS waived consent modification regarding research in emergency circumstances in which the subject lacks capacity to consent. These new strategies by DHHS and the FDA loosen previous constraints placed on emergency research, and have allowed research to be conducted in certain emergent situations using the concept of "community consultation."

For the DoD, the primary regulations that govern research are 45 CFR 46, 21 CFR 50 and 56, Department of Defense Directive (DoDD) 3216.2, and 32 CFR 219 (DoD Common Rule), which was issued in 1991.¹⁶ Under 32 CFR 219, DoD has developed subsidiary policies, and these are implemented by each of the service agencies. Examples of specific service regulations operating under these federal rules include Army Regulation (AR) 40-38, Clinical Investigation Program, and AR 70-25, Use of Volunteers as Subjects of Research. There are also additional general and particular requirements for DoD. Some are more stringent in implementing federal regulations than those of other government agencies. However, for the DoD, other regulations and restrictions are in place that continue to limit research in the context of emergency and intensive care subjects. The primary regulation is United States Code, Section 980 (10 USC 980).¹⁷

The regulation 10 USC 980, "Limitations on Use of Humans as Experimental Subjects," was approved by Congress in 1972 for the protection of human subjects used in research that is performed or sponsored by the DoD. It requires the process of informed consent to be obtained in advance for all DoD-funded research, whether intramural or extramural. Specifically, the regulation states, "Funds appropriated to 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." Published prior to The Common Rule, 10 USC 980 requires that under no circumstances could waiver of informed consent be granted except for those rare instances permitted under the law 21 CFR 50.24.

This constraint has made DoD-sponsored conduct of human trauma and emergency research essentially impossible. DoD research programs have never been granted authority to use deferred consent, implied

consent, or two-tiered consent, despite some use in civilian resuscitation research.¹⁸⁻²⁰ Until 2001, the only circumstance under which a waiver of the advance informed consent was allowed was under the Presidential Directive 13139 for those occasions when an investigational drug might be used in military contingency settings for protection against biological or chemical agents. For investigations using emergency drugs or devices, the using physician is the agent responsible for following the FDA-prescribed requirements, and must comply with all FDA procedural requirements specified in 21 CFR Parts 50, 56, 312, and 812 for emergency use of an investigational drug or device. In December 2001, 10 USC 980 was amended in the 2002 Defense Appropriations Act, allowing 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 under all laws and regulations (i.e., Emergency Research Consent Waiver) including those pertinent to the FDA. Except for these limited waiver circumstances, obtaining informed consent in advance in all human research studies continues to be a requirement for the DoD. Following successful application for the Secretary of Defense approval of the waiver, the military investigator must then seek community consultation and public notification for the conduct of the study within a specific area. To date, no DoD study has received a waiver to perform research without advanced consent.

Despite the recent allowance for limited emergency research, legal interpretation of 10 USC 980 stipulates that institutional review boards (IRB) must determine, in cases where surrogate consent must be obtained (e.g., unconscious persons, children, mentally ill, trauma patients), that the research is intended to give direct benefit to subjects. This has disallowed the use of surrogate consent for those trials that involve a placebo or standard-of-care arm, where participants do not receive any direct benefit. Military or DoD-funded research, especially in trauma, emergency department, and intensive care unit settings, has been severely limited in its scope because of this restriction, which is not paralleled by other government agencies.

SPECIAL CHALLENGES IN MILITARY RESEARCH

Review Process. The review process also offers some challenges involving human subject research in the U.S. military. Exploring some of the differences and challenges between the military and civilian research regulatory practices reveals that first-level ethical review and approval of all human studies in a military environment occur through a local IRB operating under the same CFR with the same processes and

procedure as is required by a civilian IRB. Approval for the conduct of human research in the military system does not differ greatly from the approval for the conduct of human research in civilian institutions, except that the military requires an additional level of review and approval beyond that given by a duly formed and constituted IRB. Local IRBs are charged with the task of first-level review of all research that is conducted, whether the research is extramural or intramural.

In the Army, however, all human research must undergo a second-level review.²¹ Army Regulation 40-38, in 1989, gave the Clinical Investigation Regulatory Office (CIRO) located at Fort Sam Houston, Texas, the responsibility for oversight of clinical investigation activities within Army hospitals, and second-level review authority.²² This regulation also mandated that studies conducted within a military treatment facility, including the emergency department, must have a DoD employee as a principal investigator. Another military oversight office that conducts second-level review in specific cases, such as force protection issues of the active duty soldier, and collaborative research involving civilian institutions, is the Army Surgeon General's Human Subjects Research Review Board (HSRRB) at Fort Detrick, Maryland. These additional review levels were established to ensure compliance with federal regulations governing the protection of DoD human research subjects, and prevent violation of any of the principles of the Belmont Report. The goal is to afford protection to the military subjects; at times, this has become yet another layer in the approval process that may push the normal start time of a study beyond what one would anticipate with a civilian approved study.

Service Members as Research Subjects. Although the magnitude of vulnerability is different throughout populations, service members may also be considered a vulnerable population because of the nature of the military environment. Service members are obligated to obey all lawful orders from superiors, and may feel compelled to respect the orders from senior officials conducting research. To prevent such a possibility, research regulations (e.g., AR 40-38) state that service members' commanders or supervisors may not be in the room during the consent process.²¹ As an additional measure, the IRB may require that an ombudsman be present during the informed consent process. Finally, the nature and location of the service member (e.g., battlefield) contribute to a sense of vulnerability and may also be a source of unintended coercion.¹⁴ The contrast of a service member as both a vulnerable subject who must be protected from a commander's coercion and, simultaneously, a warrior who may at any time be ordered into harm's way is not well explored.

Despite these and other protections afforded in military biomedical research, the ability of service

members and their surrogate (legal representative) to refuse some nonexperimental medical procedures is restricted.²³ In other words, commanders do have the legal right to require service members to undergo certain medical procedures such as vaccinations and periodic medical examinations for fitness of duty. This authority may be misinterpreted by service members, resulting in confusion between mandatory procedures and medical research.

Some of this controversy surrounds the U.S. military's use of vaccinations without consent for certain chemical and biological agents.²⁴⁻²⁷ The question is whether the vaccination is investigational and, if so, whether these vaccinations constitute "treatment" or "research" that would require consent. The DoD immunized service members prior to the Gulf War based on the 1990 interim final regulation that permitted the Commissioner of the FDA to determine that obtaining informed consent from military personnel for the use of an investigational drug or biologic is not feasible in certain situations related to military combat. The DoD could have justifiably and legally immunized service members under the doctrine of command authority alone, but chose to seek waivers with the FDA. Despite the FDA's cooperation, there are concerns and allegations from the public and service members that these mandated immunizations have led to reactions, including injection site hypersensitivity, Guillain-Barré syndrome, multiple sclerosis, anaphylaxis, and Gulf War syndrome. The controversy surrounding the use of these vaccinations without consent has resulted in the following: 1) the FDA revoked its 1990 interim final regulations in 1999; 2) the British and Canadian militaries adopted a voluntary, "recommended" anthrax vaccination policy (more than half of British soldiers refused the anthrax vaccine for the recent war in Iraq),²⁶ and 3) the U.S. District Court for the District of Columbia issued an injunction against the current U.S. Military Anthrax Vaccine Immunization Program (AVIP) halting all anthrax vaccinations.²⁸ Despite such controversy, the DoD continues to maintain an ethical obligation for protecting its service members.

A unique aspect of military research involves obtaining informed consent in the combat environment. In addition to overcoming the obvious hazards of hostile fire and close combat, the researcher must gain the trust and confidence of the service member-subject. Unit cohesion and *esprit de corps* present simultaneously as obstacles and potential advantages to gaining informed consent.²⁹ As a uniformed service member, the military researcher may be able to access close-knit units, and be afforded a level of credibility that civilian researchers cannot easily achieve.

Public Opinion. Some of the past research practices described above serve as examples of a lack of proper ethical oversight, and have led to much criticism and distrust from the public. Only through education of

the public will these past blemishes be erased. Military researchers are ethically bound to observe the same protections for their human subjects as are our civilian counterparts. The DoD has more stringent requirements regarding human subject research and use of "waived consent." Not yet in the public forum are the ethical and national security implications for restricting military research to a greater degree than research in the civilian sector. It is a plausible argument that the greater good of society, and, in particular, the future care of wounded service members, is not well served by limiting research on potentially lifesaving treatments in the military setting. In a similar fashion, civil society is deprived of new techniques that could be developed on the battlefield.

Future Department of Defense Research. After September 11, 2001, the threat of terrorism drastically changed the country's priority in medical research. In 2003, President Bush announced BioShield in his State of the Union Address as a legislative priority for his Administration. The BioShield Bill was designed to: 1) accelerate and streamline government research on countermeasures; 2) create incentives for private companies to develop countermeasures for inclusion in the stockpile of countermeasures; and 3) give the government the ability to make these products widely and quickly available in a public health emergency in order to protect our citizens from an attack using a select agent.³⁰ Considered a critical component to our Homeland Security strategy, the Project BioShield Act was signed by the President on July 21, 2004, as Public Law No: 108-276.³¹ The provisions of this bill are designed to allow research and development of medical countermeasures and diagnostics to move at a quicker pace so that new products can rapidly be made available for emergencies. Further, this bill allows the Health and Human Services Secretary to authorize the emergency use of a drug or medical product without normal FDA approval if there is evidence that the product may be effective and there is no approved alternative. The immediate impact on military biomedical research and informed consent policy is not yet known.³⁰

In modern society's changing face of terrorism and war, it is important for all of us concerned with the rights and welfare of human subjects to recognize the importance of having ethical deliberation, rather than rote application of rules, to determine how new products may be approved so they can be used to protect the public or the military from highly hazardous bioterrorism threats in the event of national emergency. Many state-of-the-art products have been used on today's battlefields in Iraq and Afghanistan. Because of the modification of Federal Regulation 10 USC 980 to allow a waiver of consent by the Secretary of Defense (which was delegated to the Secretary of the Army), the U.S. Army Institute of Surgical

Research has submitted a request for a “waived consent” study. A PolyHeme study has been awaiting this “waiver” under the amendment since August 2004, and could serve as the first DoD study to be approved for “waived consent” with community consultation and public disclosure in the U.S. Army since the passage of 10 USC 980.

CONCLUSIONS

The lessons of the Vietnam War and the development of trauma systems, the “golden hour,” and air medical services provide reminders of the mutual benefits gained by military and civilian practice.^{32,33} Military and civilian emergency medicine researchers should continue to take leadership roles in designing, implementing, and supporting research to save lives and reduce suffering in this now very dangerous world. Waiver of consent for this emergency medical research continues to be a controversial subject that places societal and military needs against subjects’ individual rights. It is imperative that researchers find the right balance between protecting individual rights and fostering research that will create new treatment modalities and decrease pain and suffering, and even death, in both the military and civilian research environments. Ethicists must endeavor to understand the importance of research and advancement of knowledge. As ethical researchers, whether military or civilian sponsored, we strive to protect the rights of our patients while continuing to advocate for removing unnecessary impediments to valuable clinical inquiry. 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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