Establishing a Human Research Protection Program in a Combatant Command

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Extensive United States combat operations commenced for the first time in over decade in 2003. Early in 2004 there was no human research protection regulatory review and approval mechanism based in a deployed military combatant command. The absence of such a system presented a critical impediment to implementation of the time-honored tradition of a robust combat casualty care research effort. A coalition of concerned military medical personnel from the US Army proposed a novel mechanism to meet Department of Defense (DOD) requirements for the human research protection oversight of studies conducted in the combat theater of operations. In 2005, the Commander of Task Force 44 Medical Command (44th MEDCOM), who was serving as the Multi-National Corps Iraq (MNC-I) Surgeon, was charged with negotiating a DOD Assurance and implementing a new system of research review and protections. He deployed an Army Medical Department Medical Corps officer to assist in this endeavor and operationalize the plan. On March 19, 2005, the Multi-National Corps Iraq Commander signed a historic agreement with the US Army Surgeon General who developed a regulatory support and oversight mechanism to conduct research in theater. This innovative system not only honored the Army's commitment to human research protections, but also provided much needed support in the form of scientific and ethical review and compliance oversight to those deployed medical personnel with the vision to conduct healthcare studies in the combat environment. On July 20, 2005, the first DOD Assurance of Compliance for the Protection of Human Research Subjects was approved for MNC-I. This assurance allows the conduct of human subjects research in full compliance with all Federal, DOD, and Army regulatory requirements. This article describes that unique process.

Key Words: **Nuremberg Code, Belmont Report, 32 CFR Part 219, Assurance of compliance, Human research protection.**

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Systematic analyses of data collected regarding the processes and outcomes of patient care delivered in a wartime setting is a time-honored responsibility of military medical personnel.[1,2] Traditionally, great advances in healthcare, especially in the field of trauma, accompany the cauldron of combat casualty care. Medical personnel supporting Operation Iraqi Freedom and Operation Enduring Freedom recognized the importance of conducting research to answer important patient care questions. They also understood their responsibility to conduct these studies in a manner that both ensured scientific rigor and simultaneously protected the rights and welfare of the subjects involved. This report describes the events that transpired in the development of a military Human Research Protection Program (HRPP) and first ever approval of a Department of Defense (DOD) Assurance of Compliance for the Protection of Human Research Subjects for a Combatant Command in Iraq.

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BACKGROUND

Operation Iraqi Freedom began in March 2003. By early 2004 there was an abundance of patient data from diverse clinical combat experiences requiring analyses and generating multiple research questions that demanded answers. Although casualty care data were analyzed for utilization management and performance improvement purposes, there was no combat theater-based human research regulatory review and approval mechanism.

The DOD's commitment to the highest ethical standards in the conduct of human research is reflected in the DOD Directive (DODD) 3216.02 that states ". . . the rights and welfare of human subjects in research supported or conducted by DOD Components shall be protected."[3] This protection encompasses adherence to the Belmont Principles of a basic respect for persons, beneficence, and justice in the selection of subjects. The directive mandates that DOD Components conducting or supporting research ensure that the investigators are familiar with the Nuremberg Code, 1946, the Belmont Report (Ethical Principles and Guidelines for the Protection of Human Subjects of Research, 18 April 1979), 32 CFR Part 219 (Protection of Human Subjects, 18 June 1991 [also called the Federal Policy or the Common Rule]), the DODD, and other key regulatory documents. Of particular note is the requirement in DODD 3216.02 that human subject research performed at DOD

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facilities and supported by the DOD is conducted under a DOD Assurance of Compliance.

An Assurance of Compliance for the Protection of Human Research Subjects is a written document that codifies a DOD institution's acknowledgment and acceptance of its responsibilities for protecting the rights and welfare of human research subjects. An official who represents the institution's leadership signs the assurance and commits the institution to the conduct of research that complies with the "Common Rule" (32 CFR 219) for the Protection of Human Subjects, Title 10 United States Code Section 980 (Limitation on Use of Humans as Experimental Subjects), the Service Component regulation (e.g., Army Regulation 70-25, Use of Volunteers as Subjects of Research), when applicable, the Food and Drug Administration (FDA) rules governing human research and the Common Rule subparts B, C, and D (45 CFR 46; Protection of Human Subjects, Subpart B: Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research; Subpart C: Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects; and Subpart D: Additional Protections for Children Involved as Subjects in Research) governing research involving the vulnerable populations of pregnant women, fetuses, neonates, prisoners, and children.

To comply with these regulatory requirements an institution must implement an HRPP, described by the Institute of Medicine [4] as a system composed of interdependent elements that come together to implement policies and practices that ensure appropriate protection of research participants. The Institute of Medicine notes that the exact structure of an HRPP will vary among research organizations. In early 2004, there was no HRPP based in or providing oversight for the combat theater, although a compelling need existed to develop such a system to secure a DOD assurance that would provide a system for the review, approval, and compliance oversight for military medical research in that environment.

Not surprisingly for a combat theater, the greatest research interest, and also the greatest research need were in the areas of trauma management and surgical combat casualty care. Throughout late 2003 and early 2004 the Commander of the US Army Institute of Surgical Research, who is also Trauma Consultant for the US Army Surgeon General, in conjunction with the 31st CSH Research Group, championed the conduct of retrospective research studies to answer critical questions in trauma care. He contacted the US Army Medical Research and Materiel Command's (MRMC's) Office of Research Protections (ORP) and requested that a regulatory support mechanism be developed. Concurrently, military healthcare providers approached the MRMC ORP and the Army Medical Department Center and School's Clinical Investigation Regulatory Office to inquire about the appropriate mechanisms for review and approval of deployed human research protocols. These protocols either involved the retrospective analysis of patient data collected in the combat theater during deployment or prospective studies to be conducted in theater. Simultaneously, the Chiefs of Departments of Clinical Investigations at Army Medical Centers were also being queried as to whether deploying investigators could submit protocols to their local military institutional review boards (IRBs) for approval for study implementation in the combat area of operations. However, the assurances held by local military medical facilities did not extend to the conduct of research in a combatant command. The assurances held by Army medical centers had been signed by their local commanders, and they had no jurisdiction within the command hierarchy of the combat environment. At that time there was no DOD assurance in place for deployed investigators and no mechanisms for scientific review, ethical, or regulatory approval of research studies to be conducted in the combat area of operations.

It was clear that an HRPP and a DOD Assurance were needed to allow the conduct of mission-critical research in the combat theater. During the next several months a coalition of principals from the MRMC ORP, Brooke Army Medical Center Department of Clinical Investigation, the US Army Institute of Surgical Research, and the Health Policy and Services Directorate of the Office of the US Army Surgeon General drafted a Memorandum of Understanding (MOU) that would eventually be signed by the Commander of the Multi-National Corps Iraq (MNC-I) and the US Army Surgeon General (TSG).[5] This MOU established the HRPP that enabled the MNC-I to negotiate an Army-approved DOD Assurance permitting the conduct of human research.[6] The success of this negotiation was caused in large part by the efforts of the MNC-I Surgeon (Task Force 44 Medical Commander) and his vision to deploy an Army Medical Department officer as the director of clinical research in May of 2005.

THE MNC-I ASSURANCE OF COMPLIANCE—KEY ELEMENTS

To conduct human subjects research in the DOD, the institution conducting research must meet the following minimal requirements: (1) operate under an approved DOD Assurance; (2) assure that all human subjects research, not exempt from Federal, DOD, or Army human subjects protection, is reviewed and approved by a duly constituted IRB; (3) investigators are trained in the basic tenets of human subjects protection requirements; and (4) mechanisms exist for ongoing compliance oversight.

In the establishment of an assurance for the combat environment, defining the "institution" was the first decision to be made. Given that Army medical units deployed to Iraq come under the command and control of the MNC-I, that military organization was chosen to be the umbrella institution to implement the DOD Assurance. With the institution defined, the next major decision was who should be the institutional official, the signatory authority who was entrusted with upholding the tenets of the Assurance. It was thought to be important for the Institutional Official to have a medical background, and ideally he would be in the chain

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of command of the medical personnel conducting research in the combat theater. The MNC-I Surgeon (a position at that time held by the Task Force 44 Medical Commander) fulfilled both these criteria and became the ex-officio Institutional Official for the new Assurance.

The next step of the process was the negotiation of an MOU between TSG and the MNC-I Commander to specify the key elements of the MNC-I HRPP. These provisions included the (1) designation of the MNC-I Surgeon as MNC-I institutional signatory of the DOD Assurance; (2) provision that all medical research protocols conducted within MNC-I required the approval of the Commander of the facility, where the research is to be conducted, and the Commander of the unit(s) to which the volunteers are assigned; (3) requirement for MNC-I Surgeon approval; (4) scientific review of research involving human subjects by the USAISR scientific review committee; (5) IRB review and approval by the IRB at BAMC; and (6) second-level review by Clinical Investigation Regulatory Office. The US Army Institute of Surgical Research scientific review committee was specifically identified by the Assurance because of its significant preexisting expertise in the areas of trauma research and combat casualty care. The Brooke Army Medical Center IRB was already providing oversight for research from the USAISR, and it was therefore chosen to support this assurance because it was the Army IRB with the most experience in the review of trauma research. Second level review by the Clinical Investigation Regulatory Office is an additional regulatory and ethical safety net that was already in place for all research reviewed and approved by the IRB's of Army medical centers. This additional level of oversight was maintained for research conducted under the auspices of the new assurance.

A key element of the DOD assurance was the commitment to ensure investigators were trained in the basic tenets of human subjects' protections. The MOU set the requirement that all investigators conducting human subject research must complete Human Subject Protection Training. Investigators completed the on-line Collaborative IRB Training Initiative Course in the Protection of Human Research Subjects with follow-on evidence of completion provided to the BAMC IRB.

The MOU between TSG and the MNC-I Commander was ratified on March 19, 2005. With this foundation, and with the facilitation of the Task Force 44 Medical Commander, legal counsel from the Task Force 44 Command Judge Advocate and the deployed clinical research director, the first MNC-I DOD Assurance of Compliance for Protection of Humans in Research was approved by the Army Assurance approval authority on 20 July 2005.

Initial Implementation of the DOD Assurance

In the months leading to and after the approval of the DOD Assurance, the TF 44 MEDCOM clinical research director set up the process for researchers at the 86th Combat Support Hospital and other military medical facilities in the combat theater to have their protocols reviewed. She worked closely with deployed investigators to develop and refine research protocols and delivered numerous presentations to educate deployed staff members on DOD human subjects protection requirements. The research director established written policies and procedures as well as an electronic process to catalogue and track protocol submissions, reviews, approvals, and continuing reviews.

Of particular importance in the theater of operations was the consideration for obtaining informed consent of volunteers participating in research and ethical issues posed in the conduct of trauma research. Because the most severely injured trauma casualties are unable to give consent, trauma research in theater largely consists of retrospective research involving medical record reviews. Such research is of minimal risk to participants and, in certain circumstances, can qualify for a waiver of informed consent. Another unique aspect of conducting research in the combat theater was the consideration of the detainee status of participants. Military facilities in the combat theater are actively engaged in the care of civilians, security forces, and also detainees. Because DOD regulations specifically prohibit the conduct of research involving prisoners of war, it was necessary to take special precautions to ensure that information from all detainee personnel were excluded from research databases.

Since the implementation of the initial DOD Assurance MNC-I institutional officials have changed, requiring negotiation of new Assurances, and the initial MOU has been updated. The process described herein facilitated the deployment of a six-person research team to the Ibn Sina Combat Support Hospital. This team was charged with both performing and facilitating research activities across the Iraq theater. To date, a total of 44 research protocols have been implemented under the MNC-I Assurance. These protocols were reviewed for scientific merit and compliance with federal, DOD, and Army human subjects protection regulatory requirements and conducted with compliance monitoring and continuing IRB review. Today research proposals continue to be reviewed and approved by the military chain of command in Iraq, and receive scientific and ethical review by USAISR and the BAMC IRB, respectively. Joint service efforts are underway to expand the capability to conduct research involving human subjects to other areas of operations (Afghanistan and Kuwait) within the combatant command and place additional dedicated research teams in the theater of operations.

CONCLUSION

It is possible to develop an HRPP and obtain a DOD Assurance of Compliance for the Protection of Human Research Subjects in a Combatant Command. The DOD's commitment to conduct research to learn from the lessons of wartime care, and to conduct such research in a way that protects the rights and welfare of research participants, was evident in the development and implementation of the MNC-I HRPP and DOD Assurance. The success of this program is

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attributable to both the dedicated Army Medical Department officers who exercised imagination and unfailing determination to develop an HRPP, and to those who remain committed to continue conduct wartime research studies that provide mission critical answers to the caregivers.

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DISCUSSION

Dr. Basil A. Pruitt, Jr. (University of Texas Health Science Center, San Antonio, TX): Colonel Holcomb has just given what is possibly the most important article of this conference. The efforts of Colonel Brosch and her coauthors have permitted the US Army Medical Corps to resume combat casualty research in the theater of operations after an hiatus of 37 years. The HRPP, which Colonel Holcomb has so nicely described, was designed to comply with both federal rules and Army regulations to safeguard those patients being studied. The rules, policies, and regulations cited have been developed in response to the Nuremberg Code (1947), the Declaration of Helsinki (1964), and the 1979 Belmont Report of the National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research. The Belmont Report cites three basic ethical principals that must guide all human studies: respect for persons, i.e., acknowledgment of autonomy and protection of all research subjects, beneficence, and justice. Of great concern are research subjects with diminished or impaired autonomy, e.g., a severely injured hypotensive soldier. When there is a documentable societal need for experimentation on a class of patients with diminished autonomy, special measures must be taken to protect those patients. Those special measures include a waiver of informed consent requirement by a local oversight board, typically the Institutional Review Board. FDA Regulation 21 CFR 50.24 of 1996 exempts emergency research from informed consent when patients are in a life-threatening situation, when obtaining informed consent is not feasible, and when the research could not otherwise be performed. My first question is how many of the 46 research protocols that you cite as having been implemented fall into each of those three categories and was the requirement for informed consent waived for all those studies?

The FDA regulation further requires consultation with community representatives. I assume that your many presentations to various DOD and MNC-I personnel met that requirement, but were other consultations required? The FDA regulation also requires public disclosure to the communities in which the study will occur and the public disclosure of the study results upon completion of the study. Please tell us how you have met or plan to meet those requirements?

In some studies, in the civilian sphere, possible subjects who do not wish to participate are given a bracelet to wear, which will indicate to medical personnel that they are not to be included in the study. Do you have a similar mechanism to exclude troops who do not wish to participate? In the interest of transparency, do you maintain a central research registry, which can be accessed electronically, in which each approved study is listed with a brief abstract of the study and the current status of the project?

Finally, do you think that a majority of the members of the Brooke Army Medical Center, Institutional Review Board, and all other review bodies for combat casualty care research should be non-military to avoid any conflict of interest or even the appearance of a conflict of interest?

Dr. Laura R. Brosch (Office of Research Protections, US Army Medical Research and Materiel Command, Fort Detrick, MD): Dr. Pruitt raises concerns that are of the utmost importance in the review and approval of human research studies conducted in what is largely a trauma care environment. To date no prospective clinical intervention or FDA-regulated studies have been conducted in the combat theatre. Thus, compliance with the emergency research provisions of 21 CFR 50.24 with the requirements for community consultation and opt out provisions have not been applicable. All studies conducted under the Multi-National Corps Iraq Assurance of Compliance have been minimal risk studies and most have involved the systematic extraction of data from existing medical records. Many of these studies sought to describe the magnitude of various phenomena (e.g., face and neck trauma; chest trauma; penetrating injuries to external genitalia) and assess their relationships to patient outcomes (e.g., outcomes of patients receiving blood transfusions). All of the studies involving extraction of medical record data have been approved with waivers of informed consent that meet the requirements of 32 CFR 219 § 116 (d). Several ongoing prospective survey studies are descriptive in nature and conducted with participants providing informed consent.

In response to the question regarding the presence of a central research registry, databases are maintained by the Multi-National Corps Iraq element responsible for overseeing this process, by the US Army Institute of Surgical Research

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responsible for the scientific review of these studies, and by the Brooke Army Medical Center Institutional Review Board.

Finally, each of our Army Institutional Review Boards is constituted in compliance with DOD and federal requirements, and consists of both civilian and military members, with unaffiliated and non-scientist member representation. The Common Rule mandates that IRBs shall be "sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas." (32 CFR §219.107). Inclusion of military members on IRBs that review combat casualty care protocols is critical to ensure that military-unique perspectives are represented and considered. Protection of the rights and welfare of all humans, military, and civilian involved in military research is of paramount importance in the DOD. All Army IRBs that review combat casualty care research include civilians, commissioned officers, and enlisted soldiers in their membership. This diverse composition provides the foundation for a balanced and robust consideration of the ethical issues related to these important studies.

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