RESEARCH PROTECTIONS UPDATE

News and Comment on the Protection of Human Subjects and Animals in Navy Research

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Comment

Human Research: What's Happening?

The Navy Human Research Protection Program leadership team met in mid-June with officials of the Office of the Director of Defense Research & Engineering (DDR&E) to discuss progress in the program since it stood up in April 2005, as well as direction for the coming year.

The June issue of **RPU** provided a hint of that direction in its coverage of the winners of the Navywide research competition, held at the National Naval Medical Center in May. The finalists and runners-up discussed research projects ranging from development of treatments for specific health problems to policy options for protecting Navy and Veterans Administration patients.

Human subject research has been, and will continue to be, a critical element of Navy medical research. Beyond the medical domain, the Research Protections Division of the Office of Naval Research, which is charged with providing support and expertise to the Navy Surgeon General for human research protections in the Systems Commands, fleet and training commands, and extramural performing institutions, now is surveying the field, looking at commands that conduct research with human subjects.

For example, as we reported in our May issue, human-systems integration (HSI) initiatives now underway at the Navy's surface warfare laboratories aim at adapting ship systems to the physical dimensions and sensory responses of human operators.

While some of that work is defined as systems engineering or test and evaluation, much of it requires participation of human subjects, and an Assurance to conduct human research, as defined in precise terms by the new SECNAVINST 3900.30D, now awaiting signature by the Secretary of the Navy.

The challenge for the DON HRPP arises not in policing commands and commanders who have not yet recognized that such work is human research, but in helping them do so. Dr. Tim Singer, acting director for ONR's Research Protections Division within the DON HRPP, stresses that the Division's mission is to ensure that commands comply with the law, not to interfere with the performance of operational missions.

If the new HSI efforts seek to ensure that human operators complement advanced Navy systems by conducting research with human subjects, the HRPP role is to support them. The HRPP team does so by providing expert counsel on the intricacies of Navy, DoD, and federal law; on DON requirements for documentation, training, and organization of Institutional Review Boards; on completion of Assurance applications—and then standing by to assist them in any way.

Early indications are that the DON HRPP vision, mission, and program are attracting serious attention throughout the Navy and DoD. Commands are emailing and calling, asking for help in understanding their responsibilities for protecting human subjects, in fleet and laboratory settings, and in the Navy medical community. Keep the calls coming. The DON HRPP team will be ready with answers.

Also in this Issue:

Spotlight on Technology

QuikClot: Saving Lives in Combat

The Warfighter Performance Department of the Office of Naval Research (ONR) has funded an evaluation by the Naval Medical Research Center (NMRC) of prototypes of an advanced wound dressing that represents an improved version of the QuikClot dressing now carried by Marine Corps infantrymen in Iraq.

The original QuikClot is an innovative product, developed and tested with ONR funding, that when used to treat a bleeding wound, stops the blood flow almost instantly.

QuikClot, produced by Z-Medica of Wallingford, Conn., also is used by Air Force personnel and members of the Army's 101st Airborne Division serving in Iraq. The product has been credited with saving the lives of more than 150 military and civilian personnel in Iraq.

The prototypes being tested at NMRC were produced by Z-Medica based on research carried out at the University of California-Santa Barbara (UCSB).

In 2002, the Marine Corps asked ONR to evaluate the effectiveness of several products for control of moderate-to-severe hemorrhage.

The Casualty Care & Management program of ONR's Warfighter Performance Department funded the design of a large animal model (a representation of human battlefield injuries). The research was carried out by the Uniformed Services University of the Health Sciences (USUHS). Of three products looked at, only QuikClot stopped bleeding in 100 percent of wounds to which it was applied; all the animals treated with QuikClot survived.

Following the USUHS tests, the Food and Drug Administration in May 2002 approved the product for external use.

QuikClot is made from zeolite, an inorganic material. When used to treat an open wound, the zeolite acts like a "molecular sieve" that absorbs water molecules from the blood. The platelet and clotting-factors remain in the wound, permitting rapid clotting of blood. However, the zeolite becomes hot when exposed to water or blood. The NMRC testing will evaluate a cooler version of zeolite developed by USCB that retains the blood-clotting ability.

The original QuikClot product was a loose granular material. While this form conforms to the wound it is poured into, it could be dislodged by helicopter rotor wash, and cannot be applied if a casualty is trapped in a vehicle. ONR and USUHS devised a solution that contains the loose granules inside a "tea-bag" for application to the wound.

Further testing by Z-Medica and ONR resulted in a new product called the Advanced Clotting Sponge (ACS), which received FDA approval in 2005.

In June, the U.S. Army took delivery of 140,000 units of QuikClot ACS.

ONR officials say that Z-Medica products are approved for external use only; acceptance for hospital use will require a definitive clinical trial that will require testing with human subjects.

QuikClot now is used by law enforcement, fire safety, and other public safety agencies. The Department of Homeland Security has qualified QuikClot for purchase by state government security departments with grants from the Department. The product also has been adopted for use by Canada, the European Union, and several Asian countries

DDR&E Review

DDR&E Inspects Navy Human Research Protection Program

Senior staff members of the Office of the Director, Defense Research & Engineering (DDR&E) visited the DON HRPP in mid-June to evaluate the program's achievements of the past year.

Vice Adm. Donald C. Arthur, Surgeon General of the Navy, who is the single authority for execution and oversight of the DON HRPP, hosted the meeting with Dr. Robert Foster, Director, Biosystems Directorate, DDR&E, and Patricia Decot, Assistant Director for Regulatory Affairs and International Programs of the DDR&E Biosystems Directorate.

The DDR&E staff visit looked at the DON HRPP's successes in establishing policy guidance and setting up procedures for protecting human subjects in Navy research.

DDR&E oversees the Defense Department's human research protection programs. In early 2004, DDR&E directed the military services and other Defense Department components to update their policies governing the protection of human subjects in research.

In coming weeks, the DDR&E staff plans to visit the human research protection programs of all the services and DoD agencies to evaluate their progress. DDR&E then will release reports to each component on its findings.

Capt. Eileen Villasante, DON HRPP Director, Dr. Tim Singer, Acting Director of the Research Protections Division of the Office of Naval Research, Singer's deputy, Lt. Cdr. William Deniston, and DON HRPP staff member Marianne Elliott briefed the DDR&E representatives on the completion of actions for a number of areas cited by DDR&E as requiring special attention.

The DON HRPP team briefed Foster and Decot on the drafting of a new Navy instruction on human research protections (SECNAVINST 3900.39D), now awaiting signature by the Secretary of the Navy. The instruction will supersede SECNAVINST 3900.39C, which has been in effect since 2002.

The team reported to DDR&E the completion of a new Assurance application and application instructions, as well as a Command Checklist that enables commands and facilities seeking new Assurances and/or renewals to ensure they have the policies and procedures to support the assurance application.

The team also has completed a Navy Addendum to the Federalwide Assurance, a Joint Research Review Agreement, and Review Guide for headquarters-level review of research protocols. Villasante and Singer briefed Decot on the DON HRPP's site visits to the Navy Experimental Diving Unit in November 2005 and to the National Naval Medical Center in March of this year. The visits included exhaustive inspections of

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USN hospital ship Mercy *anchored off Tawi-Tawi, Philippines* (USN Photo)

DDR&E

DON HRPP Seeks Changes in DoD Human Research Protection Policy

In mid-June, the DON HRPP completed six Issue Papers that provide recommendations for revisions to the Defense Department's primary instruction on human subject protection, DoDD 3216.2.

DON HRPP director Capt. Eileen Villasante submitted the Issue Papers to the Office of the Director of Defense Research & Engineering (DDR&E), which may incorporate the recommendations into new DoD human research protection policy guidance.

Regarding the definition of PIs, the DON HRPP Paper points out that "the directives of the individual military services are not consistent in defining who may serve as PIs for intramural and extramural DoD-supported research."

The Issue Paper says that the inconsistency among the services "permits the use of different standards, creates confusion, and hinders collaboration." It also may lead to unfair application of policies for contractors hired to conduct research and those hired primarily for clinical care purposes, yet support accredited training programs. The Paper urges the services to "harmonize" policies to define who may serve as a PI in DoD-supported intramural and extramural research.

The other five deal with: (1) defining a member of an Institutional Review Board (IRB) as a federal employee; (2) potential for undue influence; (3) international research; (4) medical monitors for research involving more than minimal risk; and (5) research-related injury.

The DON HRPP Issue Paper on IRB members as federal employees notes that DoDD 3216.2 requires IRB members to be federal workers, employees hired through the Intergovernmental Personnel Act (IPA), or consultants hired in accordance with 5 USC 3109. It argues that these limitations "threaten the spirit and intent of 'non-affiliated' representation on DoD/DON IRBs."

The Paper points out that non-affiliated representation, whether scientific or non-scientific, provides transparency, objectivity, local input, and checks and balances for otherwise institution-based IRBs. The Paper also recommends revising 3216.2 to allow persons who are not federal employees to serve as IRB members. The Paper also calls for simplifying the appointment procedure and specifying liability coverage for IRB service.

The Issue Paper on undue influence notes that 3216.2 attempts to ensure that superiors do not influence subordinates' decisions on participating in research involving more than minimal risk. The Paper points out that the Directive (paragraph 4.4.4) doesn't address other research, when risk may be minimal; it recommends that the prohibition of undue influence be extended to cover all research regardless of the risk level.

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Nurses aboard the hospital ship Mercy *discuss a patient's condition* (USN photo)

DDR&E Inspects Navy Human Research Protection Program

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the human research protection documentation of both commands, as well as interviews with key command staff and IRB chairs and members.

The DON HRPP team also discussed the new Navy HRPP training program, now nearing completion. The training package will consist of training modules derived from the modules offered by the Collaborative Institutional Training Initiative (CITI) program. The DON HRPP team staff completed the training this past spring.

Villasante and Singer cited a number of DON HRPP initiatives, including launch of new websites, one hosted by the DON HRPP office and a second by ONR's Research Protections Division, and introduction of *Research Protections Update*.

The DON HRPP leaders also cited the development of briefings for prospective commanding officers and executive officers of medical commands, outreach efforts to the operational Navy, and support for numerous Navy commands that conduct human-systems research.

An F/A-18 Hornet fighter/attack aircraft swoops in for an arrested landing aboard the carrier John C. Stennis *off the California coas*t (USN photo)

DON HRPP Seeks Changes in DoD Human Research Protection Policy

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For international research, according to the DON HRPP Paper, DoD may approve the substitution of international standards for human research protections that are at least equivalent to the Common Rule and DoD Policy. The Paper points out though that DoD has not exercised this option.

The DON HRPP says that the increasing globalization of research underlines the importance of consistent human research protection standards and policies. The DON HRPP recommends revising 3216.2, or developing new policy guidance to permit acceptance of international standards in countries where DoD has found that protections are at least equal to DoD requirements.

The DON HRPP paper on medical monitoring points out that 3216.2 addresses only monitoring of biomedical research and research involving more than minimal risk. It recommends revising 3216.2 to broaden the concept of monitoring to permit IRBs to determine the type of monitoring required, and who should serve as monitors.

The Issue Paper on research-related injury notes that 3216.2 covers only research greater than minimal risk. It recommends revisions to broaden coverage to protect subjects from expenses of research-related injuries, regardless of risk.

DON Animal Research Protection Program

Animal Models Aid in Understanding Human Research

By COL Mark Gold

You don't have to be an animal activist to ask why we use animals in medical research. Responsible, well-conceived, and properly conducted animal research forms the foundation of most medical discoveries and developments that help us save and improve the lives and health of people and animals. Without animal research, many of the advances in medical care would not be achieved.

> ***"Responsible, well-conceived, and properly conducted animal research forms the foundation of most medical discoveries."***

Human research is the ultimate arbiter of innovations in medical science, but because of ethical issues, longer life cycles, and logistical concerns, among others, human research should begin only after researchers complete preliminary animal work. This work—more than 90 percent of which is performed with rodents—can test a greater number of hypotheses and provide insight in only a fraction of the time required for human research. For those in pain or dying of incurable illnesses, and those who see others suffer (including pets), these gains far outweigh the costs.

Model selection remains the foundation on which animal research is based. Animals that share a spontaneously induced ailment, those in which such ailments can be experimentally induced, or animals that are resistant to various conditions offer the best models for studying causes of ailments, as well as progression, preventives, and treatments. An animal's physiology doesn't have to match that of the human body in order to be helpful to research. Similarities or differences in physiology, pharmacology, disease susceptibility, and resistance all can help researchers understand ailments and develop treatments. Because we can identify the many conditions that impact an animal's life and discern the subtle differences among species, animals of most species can yield information that can prove valuable in human research.

Animal research often leads to early deliveries of prospective prophylactic and therapeutic alternatives. In areas where test conditions are impractical, such as the development of countermeasures to highly toxic agents, animal research results are accepted by the Food and Drug Administration (FDA) in lieu of human results and can lead to the fielding of potentially life-saving pharmaceuticals. Data derived from both rodent and non-rodent models have reduced the need for research with human subjects and helped alleviate human suffering.

The laboratory animal community is working to find, develop, and employ non-animal models that can reduce or replace animal research, in the same way the use of animal subjects has reduced human research. Whether these alternatives are cell cultures, computer models, or inanimate models, we hope that remaining animal work, alternatives, and human studies will help answer our most important scientific and medical questions.

In recent years animal research has been the target of increased regulatory oversight. As laboratory animal scientists have provided more suitable animal subjects and better-controlled environments, local Institutional Animal Care and Use Committees (IACUCs), funding agencies, the federal government, and accreditation organizations all exercise greater oversight, ensuring humane treatment of animals in research programs. While we expect laboratory animal science to continue its growth in the future, we can be sure that animal-use regulations and oversight will grow along with it to continue to protect animals while we build better models.

Col. Mark Gold, USA, is Director of Veterinary Affairs in the Office of Research Protections at the Bureau of Medicine and Surgery.

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Research Review

The "Other" IRB: Looking Elsewhere for Research Review

By Marianne Elliott

Some Navy researchers are assigned to commands that simply are too small to support permanent Institutional Review Boards (IRBs). To conduct research that involves human subjects, they arrange for IRB review of their research at commands or activities with established IRBs. To do so, the researcher's command must have an approved DoD Assurance, which is a command's "promise" to follow DoD and Navy requirements for human research protection.

The command of the prospective researcher is responsible for (1) reviewing and endorsing research protocols *before* submission to the IRB and (2) monitoring and overseeing the conduct of research protocols *after* IRB review and the approval of the commanding officer of the researcher's command.

The command's Assurance must name an individual, appointed by the CO, who is familiar with the command's research and conversant in human research protections. The individual may be designated the Research Coordinator, Research Director, Human Research Protection Program POC, or something similar.

The CO may wish to have research protocols reviewed by an advisory committee to consider command-unique requirements or the command's ability to support the research. He or she may task a current committee with additional training in human research protections or appoint a separate committee to conduct this review.

The Assurance of the researcher's command requires it to designate the IRB or IRBs on which it will rely for review of the research. The command or commands with the IRBs also must sign the Assurance held by the command that is conducting the research.

Depending on the type of research to be conducted, a command may rely on multiple IRBs affiliated with other commands. For example, one research protocol may rely on an IRB that is nearby, another on an IRB with specific expertise; and still another on an IRB that is supporting a collaborative research effort.

The command also must execute a Joint Research Review Agreement (JRRA) with commands whose IRBs review its research.

The Assurance templates and directions for completing the Assurance and the JRRA, as well as other information, are available on the DON HRPP websites at http://navymedicine.med.navy.mil/humanresearch/ or http://www.onr.navy.mil/sci_tech/34/343/.

Researchers and command officials with questions about using IRBs at other commands should contact the DON HRPP prior to making arrangements for research. The HRPP staff can provide information on requirements and possible alternatives, review of draft documents, and answers to questions on any aspect of human subject research.

Marianne Elliott, a retired Navy commander, is a member of the DON HRPP staff.

A Navy hospital corpsman conducts a medical examination on an Iraqi child in Fallujah (USN photo)

HRPP Questions and Answers

Education Research, Civilian-Military Teaming

What additional requirements should IRBs consider when reviewing education-oriented research?

The IRB should be aware of additional federal regulations regarding privacy of student records, rights of parents and students, consent procedures, and membership requirements for IRBs that review research supported either by the Department of Education (ED) alone, or by ED in conjunction with DoD. A valuable reference is http://www.ed.gov/about/offices/list/ocfo/humansub.html

This link provides information on Protection of Pupil Rights Amendment (34 CFR Part 98), which is designed to protect the rights of parents and students in programs that receive ED funding.

The link also describes the Family Educational Rights and Privacy Act (34 CFR 99), intended to protect the privacy of education records at all public elementary and secondary schools and virtually all public and private postsecondary institutions.

The excerpts from 34 CFR Part 350 outline the additional IRB membership requirements for certain research projects.

A civilian university investigator has conducted a research protocol about HIV for several years and now wishes to include subjects from a Navy health clinic. A military physician is interested in collaborating in the research. What are the requirements?

The clinic must have its own approved DoD Navy Assurance and the research must be reviewed by the clinic's own IRB or another Navy IRB. A joint research review agreement among the university, the clinic, and the command with the reviewing IRB is needed. The research may start after the Assurance and agreement are signed and the research protocol is approved by the reviewing IRB and the clinic's Commanding Officer or Officer in Charge.

Command Assurances Approved

The Surgeon General has approved an Assurance for Protection of Human Research Subjects for the Marine Corps Air Station, New River, Jacksonville, N.C.

The SG also has renewed Assurances for the U.S. Naval Medical Research Unit 2 in Jakarta, Indonesia; the Naval Health Research Center, San Diego; NHRC's detachment at the Directed Energy Bioeffects Lab, San Antonio, Tex.; and the Naval Undersea Warfare Center, Newport, R.I.

MCAS New River serves as the Marine Corps' primary East Coast helicopter operations base and the principle test site for the Marine Corps' new V-22 Osprey tiltrotor aircraft.

The U.S. Naval Medical Research Unit No. 2, a World Health Organization Collaborating Center for emerging infectious diseases, provides a versatile medical research capability, encompassing virology, microbiology, epidemiology, immunology parasitology, entomology, and clinical medicine, and studies infectious disease that could threaten U.S. military personnel and civilian populations.

Also receiving a renewal is NHRC San Diego, which conducts biomedical and psychological research, development, test, and evaluation to support fleet readiness through close and continuous interaction with operational Navy, Marine Corps, and Special Operations units.

The Naval Health Research Center Detachment, Directed Energy Bioeffects Laboratory, San Antonio, Tex., conducts research on protecting personnel from microwave energy generated by communications and electronic warfare systems.

The Naval Undersea Warfare Center in Newport carries out a wide range of research, development, testing, and evaluation for submarine, unmanned undersea vehicle, and undersea warfare systems.