RESEARCH PROTECTIONS UPDATE

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

Volume 9 Number 2 *Summer 2019*

Spotlight

The Belmont Report is 40 Years Old! It's Enduring Legacy On Current Regulation *By Chidima Ioanou*

The Belmont Report was born in the wake of a series of exposed unethical research involving human subjects. These unethical research practices resulted in a national outcry, especially following the expose on the Tuskegee Syphilis study, a natural history study in which African American men were enrolled and deliberately left untreated for syphilis. In an effort to prevent the repeat of such atrocities, Congress passed the National Research Act of 1974 which led to the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This Commission was charged with identifying basic ethical principles to guide the conduct of human subjects research. After years of deliberations, the Commission released the Belmont Report on April 18, 1979.

In this landmark report, three basic ethical principles guiding research on human subjects were identified. These basic ethical principles subsequently became the foundation of our current federal regulations governing research involving human subjects. In addition, the report also provided guidelines for application of these principles[1]. The Belmont Report is a staple in human subjects research training and most of us are very familiar with the three basic ethical principles identified; respect for

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Commentary

Top Five Tips for Preparing for an FDA Inspection

By Kersten Wheeler & Elizabeth Dayag
Clinical Investigation Department
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On an ordinary day, your HRPP world may feel like it's turned upside down when you receive notification that your program is going to be audited by the FDA. If you're like me, you probably "know" that the FDA doesn't inspect DoD facilities. Well, we are both wrong. Apparently, the FDA does conduct routine audits of DoD IRB programs. Typically they are conducted every five years (according to their website) but the last one conducted at NMCP was 19 years ago!
From someone who has survived, here is how to prepare for the FDA's arrival. First things first. Don't panic! You've got this!! Now here's what to expect when you are expecting…the FDA.

1. **No black tie:** Don't expect the same formality that you are used to when it comes to audits or inspections. You may only receive

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Also in this Issue:

A Message from RDML Via, the Special Assistant to the Surgeon General of the Navy for Human Research Protections

RDML Darin K. Via

As the Special Assistant to the Surgeon General of the Navy for Human Research Protections, I want to take this opportunity to thank the Human Research Protection Community. Each and every one of you have been doing tremendous work at a time when significant changes have been implemented to regulations guiding the protection of human subjects research. On top of that, many of you are becoming intimately aware of changes as BUMED and DHA continue to evolve. As these transformations are occurring, it is essential that we continue to be mission focused and remain knowledgeable of the current revisions and diligent in our roles as protectors of the men and women entrusted to our oversight. It is also important that we are cognizant and responsive to the potential impact of these changes to our respective Institutions, specifically, the Institution's Human Research Protection Program (HRPP). The effective implementation of these revised regulations could not be possible without the dedication and tireless effort of all of you working to ensure human subjects research is conducted in compliance with the federal, state, and institutional policies and procedures. I know that you will all continue your diligent efforts to ensure the protection of human subjects in research all across the Navy. For this, accept my deepest gratitude.

Alert! Your 32 CFR 219 Citation Maybe Incorrect. A table of frequently cited 32 CFR 219 text that has moved from one location to another within the CFR.

Section Title	Old Citation	New Citation
Exempt categories of research	.101	.104
Definition of research	.102(d)	.102(l)
Definition of human subject	.102(f)	.102(e)
Definition of intervention	.102(f)	.102(e)(2)
Definition of interaction	.102(f)	.102(e)(3)
Definition of private information	.102(f)	.102(e)(4)
Definition of identifiable private information	.102(f)	.102(e)(5)
Definition of minimal risk	.102(i)	.102(j)
IRB operations	.103	.108
Basic Elements of Informed Consent	.116(a)	.116(b)
Additional Elements of Informed Consent	.116(b)	.116(c)
General waiver or alteration of consent	.116(d)	.116(f)

The Belmont Report is 40!

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persons, beneficence, and justice. So, in celebration of its 40 year anniversary, a moment to reflect on this pioneering document in relation to our current regulatory changes in the revised Common Rule is truly well deserved.

Basic Ethical Principle #1, Respect for Persons

This principle incorporates two ethical convictions: 1) individuals should be treated as autonomous agents, and 2) persons with diminished autonomy are entitled to protection. To respect a person's autonomy means to acknowledge that said individual is capable of deliberation and processing of information to make decisions. The primary application of this ethical principle is via informed consent. According to the Belmont Report, informed consent is comprised of information, comprehension, and voluntariness. Looking into the revised Common Rule, an example of a new requirement founded in the Belmont Report's application of "Respect for Persons" is the requirement to begin informed consent with concise and focused presentation of key information to facilitate a better understanding of the reasons one might or might not want to participate in research. According to the preamble to the revised Common Rule, the goal of this new requirement is to present subjects with important and meaningful information before presenting other information, in order to facilitate decision making[2]. Another example is the new option of broad consent for secondary research use of identifiable private information and identifiable biospecimens. Existing data (information or biospecimens) collected for other purposes is an important and efficient resource for investigators, so secondary research has become a widely used research practice. Broad consent is a new pathway in which a subject can make an informed decision on whether to allow or disallow his or her identifiable information or identifiable biospecimens to be used in secondary research. Previous regulatory pathways for conducting secondary research on information or biospecimens (such as stripping off all identifiers, or obtaining a waiver of informed consent) still remains in effect, but for investigators utilizing this new option of broad consent, subjects are provided an opportunity to say no to such future secondary research. Also, keeping true to the spirit of "Respect for Persons," for subjects that have declined broad consent, the revised Common Rule does not permit an Institutional Review Board (IRB) to grant a waiver of informed consent. It is interesting to note that almost 20 percent of the preamble is dedicated to explaining the changes relating to informed consent requirements[3]. This emphasizes the importance of this foundational ethical principle. The changes to informed consent requirements honor subjects' autonomy and is focused on increasing information and comprehension relative to the current landscape of research.

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Belmont Report Ethical Principle #2 Beneficence

This ethical principle is applied by following two general rules: 1) do not harm, and 2) maximize possible benefits and minimize possible risks. The systematic assessment of risks and

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benefits is generally the responsibility of the investigator and the IRB. Appropriate research design, safety procedures, and sound scientific principles are among the ways investigators and IRBs assess favorable risk-to-benefit ratio. The preamble describes the objectives of the revisions as an effort to "modernize, simplify and enhance regulatory oversight." Multiple changes in requirements help achieve these objectives by reducing regulatory tasks for investigators and IRBs. A few examples include: 1) removal of the continuing review requirement for research that meets certain conditions, 2) establishment of new IRB exemption categories of research, and 3) inclusion of a list of activities deemed not research. For investigators and IRBs, reducing regulatory burden associated with low risk research, allows for more time to evaluate greater than minimal risk research activities on human subjects. This relief in regulatory burden allows for enhanced and more meaningful oversight for studies with increased risk.

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Belmont Report Ethical Principle #3, Justice

The ethical principle of justice relates to the fair selection of subjects and the fair distribution of the burdens and benefits of research. There is one revision to the Common Rule, the definition of legally authorized representative, which may be viewed as a change relating to the application of justice. The definition of Legally Authorized Representative (LAR) has been modified to address jurisdictions in which there exists no law allowing an LAR to provide consent on behalf of a prospective subject. The definition is now expanded to include an individual recognized by institutional policy as acceptable for providing consent in the non-research context. According to the preamble, the expanded definition of an LAR may be viewed as an application of justice in that individuals with impaired decision-making deserve the same opportunities to participate in research and should not be excluded from research due to living in a jurisdiction where no affirmative law regarding LARs exists.

"*The expanded definition of a LAR can be viewed as an application of justice in that individuals with impaired decision-making deserve the same opportunities to participate in research and should not be excluded from research due to living in a jurisdiction where no affirmative law regarding LARs exists.*"

The changes that are implemented in the revised Common Rule holds their foundation in the Belmont Report. Although the Belmont Report is mentioned only three times in the final revised Common Rule, it is noteworthy to share that it was mentioned 13 times in the Advance Notice of Proposed Rulemaking (ANPRM) and 18 times in the preamble to the final Rule. The creation of the Belmont Report was a pivotal moment in human subjects research as evident in its 40 year enduring legacy and its impact on the current regulatory requirements governing the ethical conduct of research involving human subjects.

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Tips for Navigating FDA-Regulated Studies Under the Revised Common Rule

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an e-mail communication or phone call from the FDA in advance of the visit. You will not receive a formal agenda or a list of items to be reviewed. You will be given, a likely handwritten, FDA 482 Notice of Inspection on the first day of the visit along with a flash of the auditors' official badges. They will not ask to meet with command leadership, investigators, or the IRB members. You should still notify your command evaluation office and directorate about the visit. Don't offer the auditor anything other than water as they are not allowed to accept anything of value, not even a cup of coffee or yesterday's bagel.

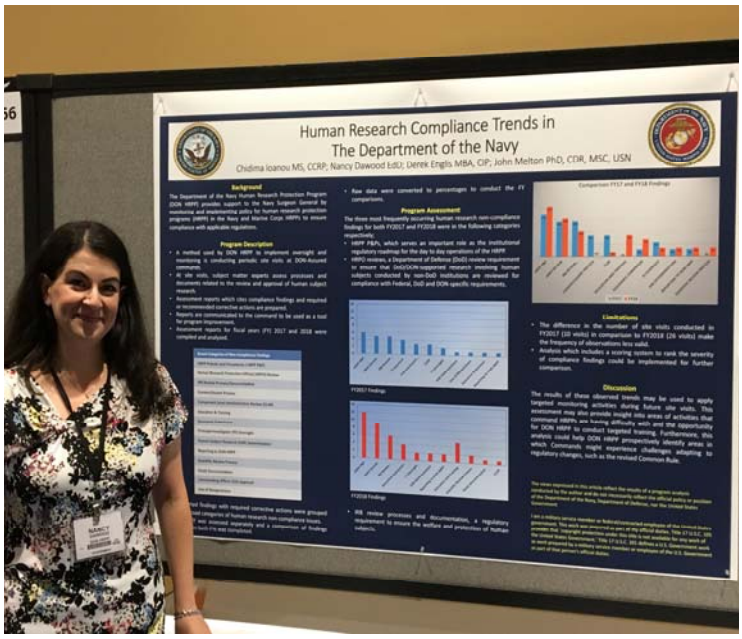
2. **Location, location, location:** In advance of the visit, you will need to reserve a workspace for the auditors and make arrangements for them to get on base. I also recommend preparing a list of the FDA regulated protocols from which the investigator can choose records to review. Depending on the number of protocols, you may want to move the files close to the audit area for convenience.
3. **Who's who:** The auditors will begin by meeting with your key HRPP staff to get a sense of what everyone's roles are and how your program is set-up. The audit will be focused on the HRPP records of FDA regulated studies.
4. **Paper, paper everywhere and not pause to think:** Throughout the three day audit, have HRPP staff available for pulling records and answering questions. The auditors will review protocols, consent/assent forms, corresponding meeting minutes, and IRB member rosters. They will request copies of everything so be sure to have a copier in close proximity. They are allowed to keep copies of any document they want, so I suggest keeping a list of everything you give them for tracking purposes.
5. **The finish line:** At the conclusion of the visit, you will be served the FDA 483 Inspectional Observations form noting any findings. You are not required to respond with corrective actions, but doing so is a best practice. After the visit, we submitted the FDA 483 to command leadership along with our response. Finally, we closed out the visit by submitting our response to the FDA via e-mail and FedEx.

In the end, the audit wasn't any more worrisome than your typical HRPP audit, although the novelty of the visit did ramp the excitement level up to an 11. Hopefully these tips will help you feel prepared when you get that dreaded call.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States Government.

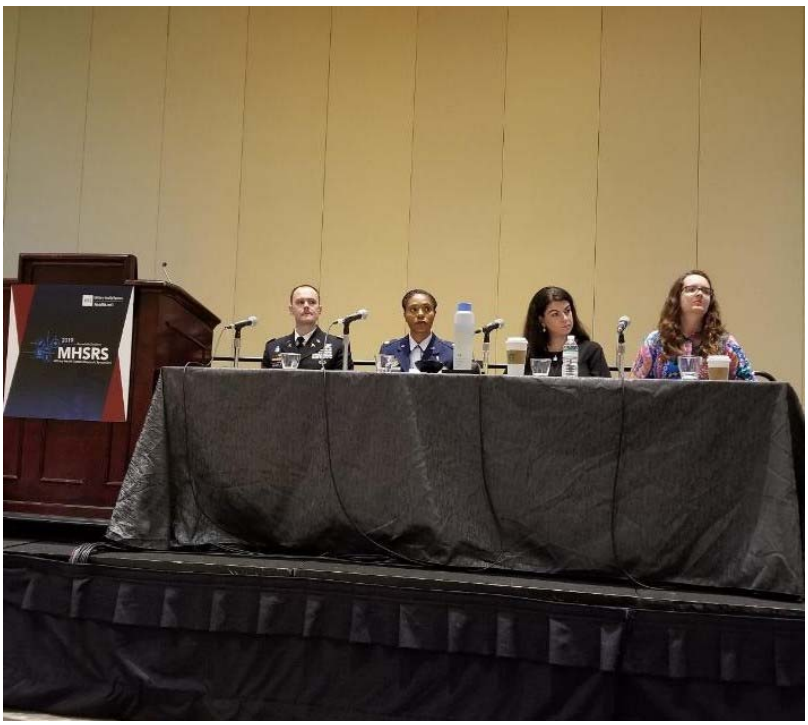
Elizabeth Dayag (left) and Kersten Wheeler (right) of NMCP Research Subjects Protections Division. Kersten Wheeler is the Deputy Director Clinical Investigation Department and Head of the Research Subjects Protection Division at NMCP. Elizabeth Dayag is the Institutional Review Board Administrator and Scientific Review Board Administrator at NMCP.

Pictured Highlights from the 2019 Military Health System Research Symposium (MHSRS)



Ms. Chidima Ioanou, Training & Education/Compliance Specialist (not pictured), Dr. Nancy Dawood, Deputy Director, Mr. Derek Englis, Program Manager (not pictured), and CDR John Melton Director (not pictured) of DON HRPP, present their poster titled, "Human Research Compliance Trends in The Department of the Navy" at the 2019 MHSRS in Kissimmee, Florida.

From left to right: CAPT Matthew Lim, Acting Assistant Deputy Chief Research and Development, BUMED, CDR John Melton, Director DON HRPP, and RDML Darin Via, Special Assistant to the Surgeon General of the Navy for Human Research Protections, during a poster session at the 2019 MHSRS.



From left to right, the presenters: COL Brett Taylor, MAJ Sundonia Williams, Dr. Nancy Dawood, and Dr. Natalie Klein during the MHSRS panel session titled, "Topics in Research Support, Compliance & Ethics" on 22 August 2019.

Congratulations!

Kudos to Nancy Dawood EdD, Deputy Director DON HRPP, MAJ Sundonia Williams USAF, Office of Human Research Protections, DHA, Natalie Klein PhD, Senior Human Subject Protections Scientist, USAMRDC, and COL Brett Taylor, Director, USAF Research Oversight and Compliance at US Army, for informative presentations and a successful panel discussion at the 2019 Military Health System Research Symposium in Kissimmee, Florida.

The Belmont Report is 40! (*continued from page 4)*

References

1. https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html
2. https://www.federalregister.gov/documents/2017/01/19/2017-01058/federal-policy-for-the-protection-of-human-subjects
3. https://about.citiprogram.org/en/final-rule-resources/

Chidi Ioanou is a Training and Education /Compliance Specialist at DON HRPP. She earned her B.S. in Biology at the George Washington University in Washington, DC and obtained an M.S. in Clinical Research Organization and Management from Drexel University. Prior to joining DON HRPP, she was the Lead Clinical Research Coordinator at a clinical research center for rare genetic metabolic diseases. She joined DON HRPP August, 2017.

DON HRPP News!!

- DON HRPP has updated the Human Research Protection Official (HRPO) sample template and materials in accordance with SECNAVINST 3900.39E CH-1 and the revised Common Rule to support HRPO processes at DON Commands. Please refer to the DON HRPP E-Gram from 7 June 2019 and contact your DON HRPP POC if you have questions or concerns.
- DON HRPP has also updated the Individual Investigator Agreement (IIA) and Institutional Agreement for IRB Review (IAIR) templates and directions to support the conduct of research collaborations at DON Commands. Please refer to the DON HRPP E-Gram from 13 June 2019 and contact your DON HRPP POC if you have questions or concerns.
- Check out OHRP's list of "Companion Q&As about the Revised Common Rule" https://www.hhs.gov/ohrp/education-and-outreach/revised-common-rule/revised-common-rule-q-and-a/index.html
- The 2019 Public Responsibility in Medicine and Research (PRIM&R) Advancing Ethical Research (AER) Conference is scheduled for 18-20 November 2019 in Boston, MA. Please note that Navy authorization is a requirement to attend the PRIM&R Conference.

We Need Your Help!

Get a BZ from RPU

Have a "Good News" story or picture from your Research Protection Program? Don't keep it to yourself! Why not share it with the DON Research Protection community? We're looking for material to publish in the *Research Protections Update* newsletter. Send your research news, success stories, tips, pictures, lessons learned, or other material related to the ethical conduct of human research to usn.ncr.bumedfchva.mbx.don-hrpp@mail.mil.

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