RESEARCH PROTECTIONS UPDATE

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

Volume 10, Number 3 *September 2020*

Commentary

Protocol Deviations and Opportunities for Growth

By Kathleen Osei

Protocol deviation monitoring and reporting in human subject research is utilized to keep research subjects safe, research sound, and regulatory bodies and sponsors aware of the status of ongoing research. IRB monitoring of protocol deviations in general provides a means for institutions to track and mitigate instances in which deviations could lead to harm and increased risk to subjects. While some researchers may view the task of self-reporting deviations from IRB approved protocols as punitive, it can be argued that reporting protocol deviations can be of benefit to the research itself.

Definitions for protocol deviations vary across research institutions as neither DoD, Navy nor other federal regulations specifically address protocol deviations. However, some institutions' policies and procedures may include definitions and reporting requirements for protocol deviations. This could be because protocol deviations may also result in unanticipated problems involving increased risk to subject or others (UPIRTSOs), or serious and/or continuing non-compliance for which there are federal, DoD and Navy reporting requirements. The Secretary's Advisory Committee on Human Research Protections (SACHRP), Recommendations on Protocol Deviations [1] addresses the following types of deviations that may provide opportunities for improvement:

- Intentional: "Deviations that occur because an investigator, research staff or other party involved in the conduct of research intentionally decides to

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Spotlight

Mobile Apps in Research & Considerations for IRB Review

By Chidima Ioanou

The COVID-19 global pandemic has led to unprecedented challenges in various aspects of our lives including how we conduct our business of human subject research. In the foreground, we face challenges such as travel restrictions, social distancing requirements, and interruptions in supply of investigational products, all of which limit traditional in-person engagement with research subjects. Meanwhile in the background, we face other challenges such as maintaining the accuracy and validity of subject data still being collected, and ensuring optimal subject safety monitoring. These challenges have affected operations of ongoing pre-pandemic studies as well as newly initiated research. We are now confronted with navigating the increased complexities of ensuring the safety of subjects and researcher personnel, while striving to maintain the integrity of the research itself. However, in the midst of this all, adaptation and innovation in the way we conduct business has allowed for continuity of operations and unrelenting work in our mission.

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deviate from the approved protocol."
- Identified before Occurrence: "Deviations from the protocol that are identified before they occur, but cannot be prevented."
- Discovered after Occurrence: "Deviations from the protocol that are discovered after they occur."

While not all protocol deviations fall under purview of regulatory reporting requirements, a best practice would be to document and report to the IRB and Sponsor per specified timelines. Additionally, deviations can be documented and reviewed regularly by the study team for protocol improvement. This can be done as a part of DoDI 3216.02 required post-approval compliance monitoring programs or plans. Per the DoDI 3216.02, post-approval compliance monitoring is the "Formal and systematic monitoring of research to confirm that HSR is being conducted in accordance with IRB approval or other HRPP regulatory determinations, institutional HRPP policy and procedures, applicable federal laws and regulations, and DoD policy[2]."

"Documentation and routine analyses of protocol deviations can highlight trends leading to process improvement and targeted training."

Documentation and routine analyses of protocol deviations can highlight trends leading to process improvement and targeted training. For example, a protocol may include an IRB approved schedule of subject assessments that incorporates periodic blood draws. If that protocol has repeated deviations in which research associates continually miss the same blood draw, it may be worth examining if any other factors are actively making this time point easy to forget. If it is practical and worthwhile, it may be an opportunity to amend the protocol to make procedures more clear. It may also be an opportunity to ensure study staff are well trained on the protocol procedures. SECNAVINST 3900.39E CH-1, Enclosure (3), paragraph 15 discusses PI responsibilities which include assuming responsibility for all research conducted under the protocol and documenting training. Non-adherence to the protocol procedures that may affect subject eligibility, recruitment, data collection, treatment dose/ administration schedule, and visit schedules can be opportunities for investigators to amend protocols and to create or update protocol specific training to ensure study staff are aware of study procedures in order to prevent future occurrences.

While this is not an all-inclusive discussion of the trends that may be analyzed and improved through routine review of protocol deviations, keeping track of protocol deviations may assist in meeting the regulatory requirements. This can include reporting, post-approval compliance monitoring, PI oversight of research, subject safety, and improving the quality of research. Framed in this manner, reporting of protocol deviations, can be viewed as a normal and beneficial part of the research process.

References:

1. Department of Health and Human Services (DHHS). "Attachment C: Recommendation on Protocol Deviations." HHS.gov, 26 Apr. 2016, www.hhs.gov/ohrp/sachrp-committee/recommendations/2012-march-30-letter-attachment-c/index.html.
2. Office of the Under Secretary of Defense for Research and Engineering. DoD Instruction 3216.02. "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and Supported Research." Glossary, 15 Apr. 2020.

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DIRECTOR'S CORNER

Every year the President issues proclamations calling on the people of the United States to honor, with appropriate ceremonies and activities, groups from the rich mosaic of our country. These observances provide a perfect opportunity to reflect on both the successes and the challenges that those groups have faced in their history, and the history of America. In this edition of our newsletter, we take note of Women's Equality Day, 26 August, and National Hispanic Heritage Month, 15 September-10 October.

Viewing human research subjects' protection history through the combined lens of these two observances forces us to acknowledge the fact that sometimes medical progress has been made at the expense of human autonomy, health, and even lives. For example, during the 1950's, in what was touted as a step toward women's liberation and freedom, birth control pills were tested on Hispanic women without granting them the dignity and freedom of informed choice. According to Ray Quintanilla, "participants weren't told they were guinea pigs in testing the world's first birth-control pill, a tablet with three times as much hormones as today's version" (2004). Theresa Vargas notes, "as many as 1,500 women took the drug over several years" (2017). Side effects, including blood-clotting complications, were left out of the picture in the promise that taking this "magic pill" would enable women's control of their reproductive future. Participants were chosen explicitly for their convenience to the researchers and they were solicited without being afforded the knowledge that they would be taking part in a drug trial and that "little was known about the drug's effects…" (Vargas, 2017).

It is clear that women and Hispanic individuals have persevered through many challenges to make countless great contributions to the American society (see the observance features above and below). The navigation of ethically questionable research participation should never have been, nor should it ever be in the future, one of those challenges. As we honor the past, we must remember the role that human subjects' research protection plays in facilitating ethical treatment of participants in human subject research. Future generations of women and Hispanic individuals deserve no less than the non-negotiable preservation of their complete rights and welfare, not only commeasurable with their celebrated contribution to our country, but, first and foremost, consistent with the infinite dignity and worth due to them as human beings.

-CDR Leedjia Svec

References

- *Guinea or pioneers? How Puerto Rican Women were used to test the birth control pill,* Theresa Vargas, The Washington Post, May 9, 2017.
- *Puerto Ricans recall being guinea pigs for 'magic pill,'* Ray Quintanilla, Tribune Newspapers: The Orlando Sentinel, April 11, 2004.

For more ways to celebrate diversity, please see observance materials provided by the Defense Equal Opportunity Management Institute at https://www.defenseculture.mil/

Also, in this issue of our newsletter, we mark Women's Equality Day, and National Hispanic Heritage Month, by celebrating these remarkable women in science featured below! We celebrate their accomplishments and acknowledge the adversities they faced in making these achievements.

(Image credit: public domain)

Dr. Ellen Ochoa (born May 10, 1958) an engineer, was an astronaut and the 11th director of the Johnson Space Center (JSC). She was the JSC's first Hispanic director, and the second female director. Ochoa joined NASA in 1988 and became the first female Hispanic astronaut to go to space in 1993. She served on the nine-day mission aboard the space shuttle Discovery and went on to serve in other space missions, logging in nearly 1,000 hours in orbit. As a research engineer, Ochoa investigated optical systems for performing information processing. She is the co-inventor on three patents and author of several technical papers. Among many other recognitions, Ochoa has been recognized with NASA's highest award, the Distinguished Service Medal, and the Presidential Rank Award for senior executives in federal government. Dr. Ochoa's service and achievements are an inspiration to all.

https://www.nasa.gov/centers/johnson/about/people/orgs/bios/ochoa.html

(Image credit: public domain)

Rear Admiral Grace Hopper (December 9, 1906- January 1, 1992) was a pioneer in computer programming. She invented computer programs that converted English to machine code. She worked on the Mark I computer during World War II and, subsequently worked on Mark II and Mark III computers. Hopper's many years of service in the Navy began in WWII when she joined the Navy Reserves. Following retirement from the Navy Reserves at the age of 60, with the rank of commander, she was recalled and continued to serve until she was 79 years old. She retired as a rear admiral and was the oldest commissioned officer in the United States Navy. She was buried in the Arlington National Cemetery following her passing on January 1, 1992. Hopper was awarded the Defense Distinguished Service Medal and the U.S Navy guided-missile destroyer USS Hopper is named after her. Rear Admiral Hopper's contribution to the Navy's computing infrastructure remains invaluable.

https://www.history.navy.mil/research/histories/biographies-list/bios-h/hopper-grace.html

Mobile Apps in Research & Considerations for IRB Review *(continued from page 1)*

For research involving human subjects during the COVID-19 pandemic, adapting from traditional in-person interactions to virtual methods has been a means of permitting research to continue. Virtual methods typically used include remote data collection via mobile applications "apps", wearable devices, and telehealth. Wearable devices that can collect subjects' physiological data (such as temperature) and transmit the data remotely, or mobile apps on a subject's smart phone through which a subject can self-report symptoms, or complete research questionnaires have become invaluable means of data collection. For the purposes of narrowing down this discussion, in this article, I will focus on the use of mobile applications in human subject research.

In recent years, mobile apps have been increasingly used in healthcare management and delivery[1]. This increase may be attributable to the portable nature of mobile platforms such as smartphones and tablets, and the user-friendly nature of many apps. The COVID-19 pandemic may further drive (if not catapult!) the use of mobile apps in research as it proves to be an efficient method of data collection and subject safety monitoring that can be employed at a distance. While using mobile apps in human subject research may soon be the norm, along with the new opportunities mobile apps may provide, there are also associated risks. Therefore, careful considerations should be made for human subjects research employing mobile apps. In this article, I will highlight questions IRBs may consider in order to assess risk and to assist in ensuring the criteria for IRB approval for studies using mobile apps is met, per 32 CFR 219.111.

"The COVID-19 pandemic may further drive (if not catapult!) the use of mobile apps in research as it proves to be an efficient method of data collection and subject safety monitoring that can be employed at a distance."

While I do not claim to be an expert in information technology, as an informed consumer of mobile apps, with over a decade of experience in human subject protections, I will share my thoughts on the use of mobile apps in human subjects research. In recent years, there have been numerous incidents that have raised concerns about commercial mobile apps with regard to misuse of data, and data privacy[2]. For example, a commercial mobile app tracked consumers' location without consent, while purporting deceptive privacy claims[3]. Another example, an app that allowed a third-party to collect personal information about the consumer from text message content and real-time location[4]. While, there are many examples of nefarious mobile apps, to avoid digressing too much into such examples, let's take a look at definitions. FDA Guidance titled "Policy for Device Software Functions and Mobile Medical Applications" defines a mobile app as "a software application that can be executed (run) on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or web-based software application that is tailored to a mobile platform but is executed on a server." Mobile apps have a broad range of functions which has led to their expanded use in research. For instance, mobile apps may be used as a tool to assist healthcare providers in the delivery of care, assist individuals to manage their own health, collect health information, or as a tool to access health records. Mobile apps may also be used to transform a mobile platform into a regulated medical device such as a mobile app that manages delivery of pain medication through a pump. In cases such as these, the mobile app may be a mobile medical app[5].

Now that we've got definitions out of the way, let's consider what could be potential risks to subjects and other issues related to using mobile apps in human subject research. When using mobile apps in research, concerns for human subject protection can be grouped into 4 main categories; data privacy and security, technology, regulatory, and informed consent[6]. The IRB is responsible for assessing and ensuring risks are minimized, ensuring appropriate consent has been obtained, and ensuring that there are adequate provisions in place to protect the privacy and confidentiality of subjects. Some questions that could be used to facilitate an in-depth discussion of the risks during IRB review of such studies are:

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Mobile Apps in Research & Considerations for IRB Review *(continued from page 5)*

Data privacy and security

- Does the mobile app require access to the subject's microphone or camera?
- Does the mobile app collect incidental data such as subject location?
- Does the mobile app require a strong password?
- Does the mobile app require authentication to verify the identity of the user?
- Is the subject's IP address associated with the data collected?
- Who owns the app, and ultimately, who owns the data?
- Are third party cloud services used to store the data?
- Is data transmission from the mobile platform to the host server or cloud encrypted and/or coded?
- Is the mobile app up-to-date on the device?
- Are the other applications on the device up to date?
- Is the operating system on the mobile device up to date to the most secure version?
- Are there future plans for commercial resale of data?
- Is the device connected to a secure WiFi network?

Technology

- Upon completion of study participation, how is the app deleted? Can the app be deleted remotely by the study team? Will the participant be instructed to delete the app upon end of participation? Will specific instructions be provided to delete the app from cloud space?
- Who owns the mobile device? Is it the user or the organization conducting the study?
- Is the mobile app restricted to only one type of mobile platform (tablets vs smartphones) or one type of mobile software (Apple vs Android)?
- Who provides technical support to subjects? The research team or a third party support team?
- Will health data be securely deleted from device after study? This might be considered if device will be reused.

Regulatory Authority:

- Does the study require full IRB review or can it be expedited?
- Is it a mobile medical app?
- Is the mobile medical app a device?
- Is the study subject to FDA oversight?
- If a mobile medical app, is the app within the focus of the FDA's regulatory oversight or is it among a subset of mobile apps for which the FDA intends to exercise enforcement discretion[6]?
- Is mobile app required to comply with HIPPA?

Informed Consent

- Are subjects required to accept terms of agreement typically associated with mobile apps?
- Do the terms of agreement include exculpatory language?
- Should any part of the terms of agreement be included in the informed consent process?
- How much information regarding data privacy risks (for example risks associated with data ownership, cloud storage or data transmission) and mitigation strategies (descriptions of data agreements, cloud design or data encryption strategies) for those risks should be included in the informed consent?

Although mobile apps have been used in human subject research for a number of years, it is still a novel space full of opportunities and risks. The aftermath of the COVID-19 pandemic might lead to an even more increased use of mobile apps in human subject research. So during review of such studies, IRBs should be confident that they have thoroughly assessed the purpose of the mobile app in the study and that all the necessary information has been provided for review and to address the questions identified above (as applicable).

References:

1. https://www.fda.gov/medical-devices/digital-health/device-software-functions-including-mobile-medical-applications
2. https://www.ftc.gov/news-events/media-resources/protecting-consumer-privacy/privacy-security-enforcement
3. https://www.ftc.gov/news-events/press-releases/2016/06/mobile-advertising-network-inmobi-settles-ftc-charges-it-tracked
4. https://www.ftc.gov/news-events/press-releases/2018/04/mobile-phone-maker-blu-reaches-settlement-ftc-over-deceptive
5. FDA Guidance; Policy for Device Software Functions and Mobile Medical Applications, https://www.fda.gov/media/80958/download
6. https://www.advarra.com/resource-library/mobile-apps-considerations-for-use-in-research-involving-human-subjects/

Naval Medical Research Center (NMRC) History Panel 3

This is part of a series of historical Navy medical R&D panels prepared by Mr. André B. Sobocinski, BUMED Historian. The mission of the BUMED History Office is to promote, preserve, and document the history and heritage of the Navy Medical Department, past and present. This mission is accomplished through management of the Navy's commemoration/ historical outreach program, oral history program, command operations report program, reference desk, publication program and archives/ historical collection.

Naval Medical Research Center (NMRC)

Established on 27 October 1942

LABORATORIES

THE FIRST NAMRU

In 1944, the Naval Reserve Laboratory Research Unit at UC Berkeley is re-designated Naval Medical Research Unit (NAMRU) No. 1. The laboratory was originally established in the 1930s to investigate respiratory diseases. It was disestablished in 1974.

THE SAGA OF NAMRU-2

NAMRU-2 was established at the Rockefeller Institute in Manhattan, NY, in January 1944. Originally planned for Guadalcanal, the laboratory was deployed to Guam where it was based until being deactivated in 1947. The lab was reactivated on Taipei, Taiwan in September 1955.

In the ensuing years, NAMRU-2 established field activities in Manila, Da Nang and Jakarta. Owing to ever-shifting geo-political situations, NAMRU-2 headquarters relocated from Taipei to Manila, P.I., in 1979 to Jakarta, Indonesia in 1991 and to Pearl Harbor, Hawaii in 2010.

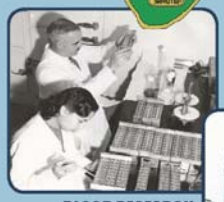
Today, NAMRU-2 is headquarted in Singapore and oversees a field activity in Phnom Penh, Cambodia.

FIELD MEDICAL RESEARCH

Founded in August 1943 through a joint agreement by Bureau of Medicine and Surgery (BUMED) and the Commandant of the Marine Corps, the Naval Medical Field Research Laboratory (NMFRL) in Camp Lejeune, NC, was dedicated to "scientific research, development and testing pertinent and peculiar to the practice of amphibious medicine." The laboratory's proximity to amphibious training under simulated battle conditions allowed for unique "frontline" evaluation of field-level conditions. NMFRL was disestablished in 1974.

NAMRU-3, LEGENDARY INFECTIOUS DISEASE LAB

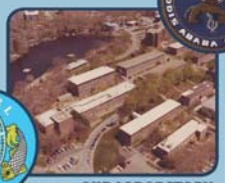
From 1946 to 2019, the Naval Medical Research Unit No. 3 (NAMRU-3) in Cairo, Egypt was the beacon of biomedical research and bio-surveillance overseas and symbolized the very tenets of medical diplomacy and innovation that has marked the history of the NAMRU program. Now based in Signonella, Italy, NAMRU-3 operates field activities in Ghana and Djibouti.



FORGOTTEN NAMRUs

In 1945, BUMED established a rheumatic fever research laboratory at the Naval Hospital Dublin, GA. Later designated as NAMRU-4, the laboratory relocated to Great Lakes in 1948. It was disestablished in 1974.

NAMRU-5 was established as the NAMRU-3 Detachment Addis Ababa, Ethiopia, in December 1965. It closed in April 1977.



BLOOD RESEARCH

The Naval Blood Research Laboratory was established in 1956 at the Naval Hospital Chelsea, MA, to "study techniques and methods for preservation, and transportation of blood." The laboratory relocated to Boston University Medical Center in 1974 and was disestablished in 1979.

SUB LABORATORY

The Naval Submarine Medical Research Laboratory was established as a naval activity at the Submarine Base in New London, CT, on June 1946.

THE NAVAL HEALTH RESEARCH LABORATORY (NHRC)

NHRC was established as the Naval Medical Neuropsychiatric Research Unit on Point Loma, CA, in June 1959. It was renamed NHRC in 1974.

NAMRU-DAYTON

In October 2010, NAMRU-Dayton was activated on Wright-Patterson AFB, Ohio. NAMRU-D is a consolidated command consisting of the Naval Aeromedical Medical Research Laboratory (NAMRL) and the Naval Environmental Health Effects Laboratory (EHEL). The histories of these extend back to the previous decades. NAMRL grew out of the Research Section of the Naval School of Aviation Medicine in Pensacola, FL, and became a seperate command in 1974. EHEL was originally known as the Navy Toxicology Unit No. 1 at Bethesda, MD when it was founded in 1959.

NAMRU-SAN ANTONIO

NAMRU-SA's history goes back to 1947 with the establishment of the Naval Dental Research Unit (NDRU). In January 1967, NDRU became the independent activity, the Naval Dental Research Institute (NDRI). NDRI was redesignated the Naval Institute for Dental and Biomedical Research (NIDBR) in 2002. NIDBR was disestablished in 2009. The reconstituted components of NIDBR relocated to San Antonio in 2010 to become NAMRU-SA.

INFECTIOUS DISEASE LAB IN PERU

NAMRU-6 was originally established in Lima, Peru in January 1983 as the Naval Medical Research Institute Detachment (NAMRID). Its mission was to investigate infectious diseases of "mutual interest" to the host nation and the U.S. Navy. The lab was redesignated as the independent command "NAMRU-6" in February 2011.

DON HRPP News!!

- Congratulations to presenting author Roxana Lescano, Head Research Administration Program (RAP) NAMRU-6 for a successful presentation at the International Working Group (IWG) meeting! The meeting titled "Conducting Human Subjects Research in International Contexts During the Coronavirus Pandemic" was held on 20 August 2020. Presenters discussed challenges and prospects for conducting, or resuming, human subjects research internationally that has been halted or affected by the pandemic.

- Something to look forward to! DON HRPP will provide information related to its Quality Assurance (Q&A) activities in the December 2020 RPU.

- Did you notice the new RPU style with the new BUMED logo? DON HRPP will be updating the style of the RPU, presentations, and other materials with the Navy Surgeon General's new BUMED logo and mission statement.

- Mark your calendars for the DoD Human Research Protections Program Forum on 17-18 November 2020. The DoD Office for Human Research Protections will be sponsoring a forum of presentations and discussions on DoD human research protection programs, the revised Common Rule, and the revised 15 April 2020 DoDI 3216.02. More information to come in the following weeks.

Resources

Please visit the following websites for resources and more information on mobile apps and telehealth in human subject research:

- https://www.fda.gov/medical-devices/device-software-functions-including-mobile-medical-applications/examples-software-functions-which-fda-will-exercise-enforcement-discretion

- https://www.cdc.gov/coronavirus/2019-ncov/hcp/telehealth.html

- https://archive.healthit.gov/providers-professionals/how-can-you-protect-and-secure-health-information-when-using-mobile-device

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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