RESEARCH PROTECTIONS UPDATE

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

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Spotlight

Ms. Sophea Sout: HRPP Administrator Working to Deliver Culturally Appropriate Ethics Training for NAMRU-2's Extramural Collaborators *By Derek Englis*

Ms. Sophea Sout has been working at the U.S. Naval Medical Research Unit-2 (NAMRU-2) Phnom Penh, Cambodia laboratory, as the Human Research Protection Program (HRPP) Administrator, since 2009. She is responsible for ensuring that all human research studies conducted or funded by NAMRU-2 are in compliance with U.S. Department of Health and Human Services (HHS), Department of Defense (DoD), Department of Navy (DON), and Cambodian government regulations. She currently oversees 30 projects/ protocols being executed in six (6) different countries in Southeast Asia. On a day-to-day basis, she interacts with extramural partners, directors of institutions, Ministry officials, and Navy Medical Research Center (NMRC) IRB staff, in carrying out her duties. During her time at NAMRU-2, Ms. Sout has worked to improve the HRPP processes, developing HRPP standard operating procedures (SOPs) and checklists that help NAMRU-2 researchers meet HRPP requirements. She has also worked to improve the human subjects research (HSR) training for NAMRU-2's Southeast Asia collaborators.

One of the challenges Ms. Sout has faced in carrying out her duties, is how to deliver meaningful training related to U.S.-based HSR regulations for NAMRU-2 collaborators in Southeast Asia. Basic HSR training for researchers and HRPPs in the U.S. is typically done online. U.S. Navy researchers and HRPP staff members follow the U.S. model, certi-

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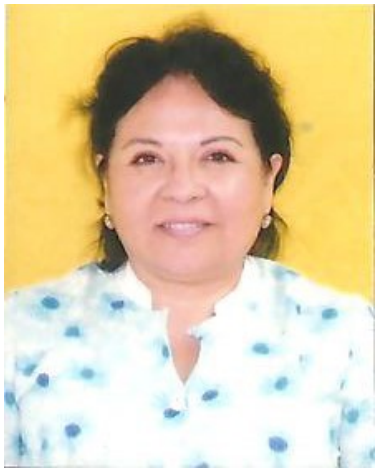
Commentary

U.S. Institutional Review Boards on an International Stage: An Interview with Roxana Lescano of NAMRU-6 IRB

By Chidima Ioanou



Roxana Lescano JD, Head Research Administration Program NAMRU-6

Conducting human subject research that must follow U.S. human subject regulation outside the U.S. comes with many challenges. U.S. Navy conducted or supported research in a foreign country is impacted by numerous variables such as language, culture, local laws and customs, host country regulations (possibly conflicting), local socio-economic resources etc. Each international setting has its own unique set of challenges. Therefore, it is imperative that careful consideration is made during protocol planning and development, Institutional Review Board (IRB) review, and protocol implementation.

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Also in this Issue:

Flashback

Major Walter Reed; 1900 Yellow Fever Trial and Unprecedented Implementation of English and Translated Informed Consent Forms *By Chidima Ioanou*

Major Walter Reed is most famously known for leading breakthrough research in yellow fever. However, some details in the execution of his research may not be as well known. In 1900, Major Walter Reed, a pathologist and bacteriologist, was appointed chairman of the U.S. Army Yellow Fever Commission in Cuba. During his tenure in Cuba, Major Reed and his team conducted rigorous (and fatal) human subject research that proved yellow fever was transmitted by mosquitoes. During an era when human subject protections of vulnerable populations were frequently violated, in an unprecedented act, Major Reed implemented informed consent forms not only in English but translated in Spanish as well, to obtain consent from subjects.

Yellow fever epidemics ravaged cities in the United States around the 1800s. Epidemics were widespread reaching as far north as Boston. The most notable of epidemics were those occurring in Philadelphia in 1793 and in the Mississippi River Valley areas in 1878 with estimated deaths of 5000 and 20,000 respectively[1]. The devastating effects of yellow fever were felt also in battle. On June 22, 1898, U.S. troops landed in Cuba during the Spanish-American War. The United States emerged victorious with Spain surrendering in July, 1898. However, it is reported that more casualties were as a result of yellow fever than combat with less than 25% of the Army arriving in Cuba remaining fit for service.[2] Hence, a commission of a board of research scientists was estab-

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NAMRU-2's Sophea Sout; Delivering Culturally Appropriate Ethics Training *(continued from page 1)*

fying that they have met the minimum HSR training requirements by completing online courses. In using the Navy-sanctioned online HSR training for NAMRU-2's collaborators in Southeast Asia, Ms. Sout realized that the training was not an ideal training method for several reasons. First, the training content had been translated, but the translations did not correctly convey human subjects research concepts. To address this Ms. Sout, many of her NAMRU-2 colleagues and collaborators worked for many hours to make the Khmer (language spoken in Cambodia) and Vietnamese translations understandable to Native speakers. Second, many of NAMRU-2's collaborators in Southeast Asia did not have access to the Internet. Third, Ms. Sout found that even with the updated translations for those who had access to the Internet, the online training methods were not generally helping NAMRU-2's collaborators learn about HSR. Fourth, she noticed that presenting the content from the online training course, in person, was not effective, because it was too much information and not culturally appropriate.

Some of the differences in language and culture between the U.S. and Southeast Asia may account for the difficulties experienced in communicating HSR training. Related to the translation work that Ms. Sout completed, Ms. Sout reported that many English HSR terms could not be translated directly to Khmer. Some words in English relating to HSR required several Khmer words to communicate a similar general concept. Consequently, more text and more explaining was necessary. To add to the complexity of translating, some of the concepts that are em-

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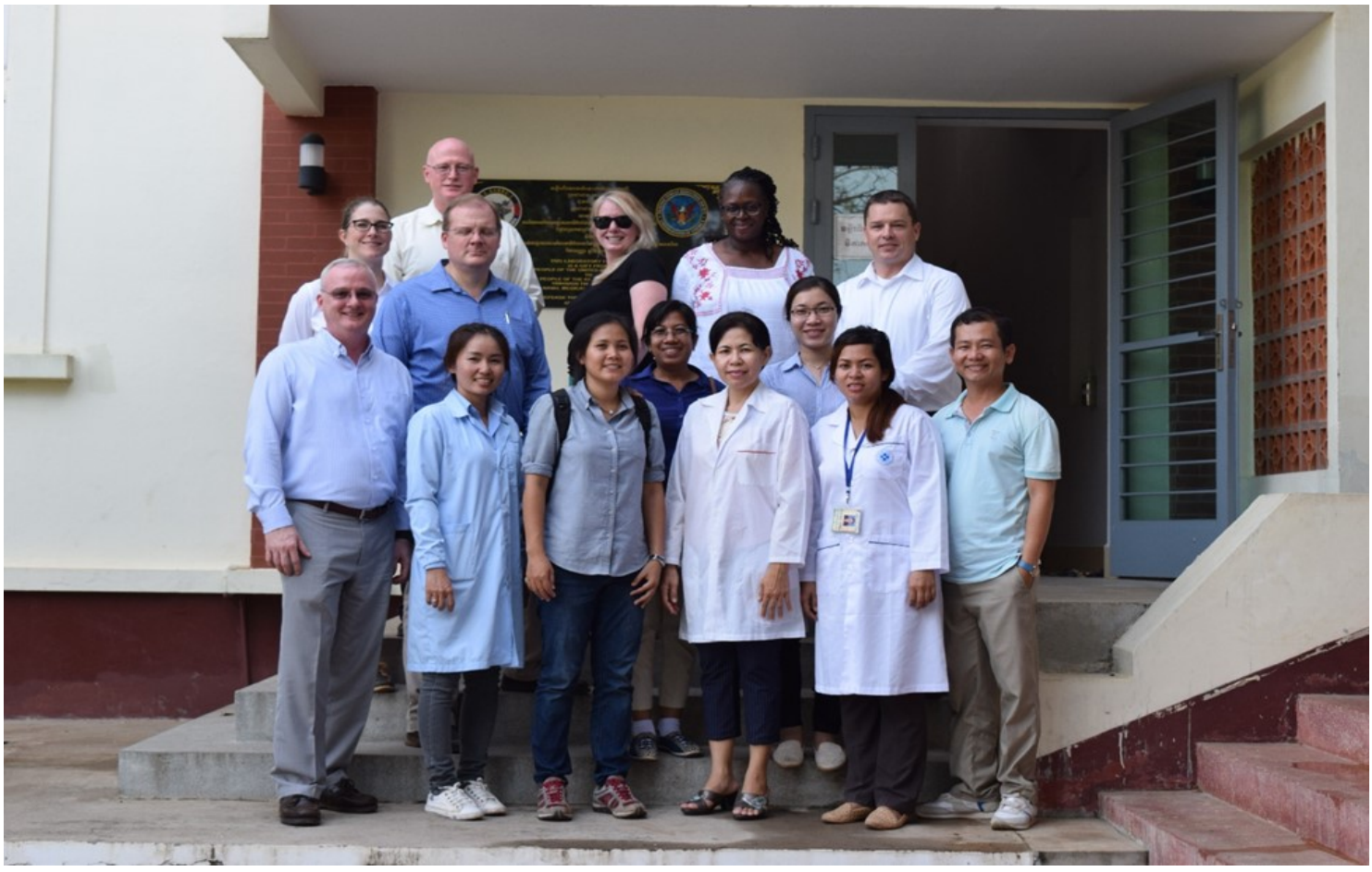
NAMRU-2's Sophea Sout; Delivering Culturally Appropriate Ethics Training (*continued from page 2)*

bedded in U.S. HSR regulations are based on Western ideas, which do not exist or are different in other cultures. For example, the concept of informed consent is based on the value Western cultures place on individuality. Individuality, is not a ubiquitous value. Some cultures place more value on collectivism, or following group norms. Differing worldviews between groups add to the difficulty of communicating ethical values.

Faced with the remaining challenges mentioned above, Ms. Sout developed supplementary training for NAMRU-2 collaborators. Ms. Sout recounted, "I guide them to get online … training in their local languages (Khmer, Vietnamese, Thai and Laotian)." "I also provide HRPP orientation in addition to [online] training which enables individuals to share human research experiences within the group and get knowledge of basic ethics training concerning procedures and others related [to] the conduct of human research studies." In speaking about her supplementary training, Ms. Sout reports that she takes the time to talk through each basic concept, thoroughly, in a less formal manner, applying humor throughout to keep the learners engaged. She created a presentation that focuses only on the basic HSR concepts (including the informed consent process). Ms. Sout reports that this method enables her to communicate basic HSR concepts to collaborating research staff. As a result, meaningful training happens.

Derek Englis is a compliance analyst (contractor) for DON HRPP. Having lived in Mexico and worked with OCONUS Navy commands, Derek has personal and professional international experience.



Sophea Sout center. Also featured in this photo are members of NAMRU-2's HRPP and members of DON HRPP during a visit to Cambodia.

U.S. IRBs on an International Stage: Interview with Roxana Lescano of NAMRU-6 IRB *(continued from page 1)*

IRBs are the gate keepers for the ethical conduct of human subject research. They are charged with protecting the rights and welfare of human subjects and ensuring that research is conducted in accordance with ethical standards and applicable regulations. United States government IRBs reviewing research in an international setting are thus challenged with ensuring U.S. ethical regulations (founded in the Belmont Report), U.S. government agency specific regulation, host country regulation and a barrage of other local context considerations are being met.

In this article, we will briefly highlight some of these challenges and how these challenges can be overcome by considering the experiences of Ms. Roxana Lescano, JD, Head, Research Administration Program (RAP) at U.S. Naval Medical Research Unit-6 (NAMRU-6), in Peru. Roxana has many years of experience supporting the IRB which reviews research conducted in Peru and other countries in South and Central America. Roxana provided the following responses to our questions related to her experiences:

Question: "In your experience, can you describe some of the challenges of a United States IRB functioning in a foreign country?"

Roxana: "A U.S. government IRB has challenges that an IRB from a U.S. civilian organization would not have. The most important challenge is meeting the U.S. requirement that IRB members have sufficient knowledge of local culture and community attitudes, and the DoD requirement that IRB board members, even the non-affiliated members, be Federal employees. At NAMRU-6 we have addressed this challenge by including Locally Employed Staff who are from Peru on the NAMRU-6 IRB "

Question: "At NAMRU-6, have local laws and customs had any effect on IRB operations?"

Roxana: "In most developing world countries, there are no local laws for IRBs, so international guidelines are followed, mostly ICH GCP, Declaration of Helsinki, CIOMS and WHO guidelines. Most of these guidelines provide a common ground for IRB operations. The U.S. laws are more specific, but do not, in most of the cases, contradict the international guidelines."

Question: "How about a country's political climate? Has that been an issue in your experience?"

"In addition to mission relevance, the IRB needs to assess issues such as relevance to the local community, provision of results to the community and to the decision makers, cultural appropriateness of informed consent forms, among others".

Roxana: "Not all developing countries have a favorable view of research, and even less of research funded by industrialized countries and conducted in developing countries. In addition to mission relevance, the IRB needs to assess issues such as relevance to the local community, provision of results to the community and to the decision makers, cultural appropriateness of informed consent forms, among others. It is also important to actively participate in the local IRB community, to learn and to share best practices."

Question: "How about religious considerations?"

Roxana: "We have not encountered any issues with religious considerations in our line of work, which is infectious and tropical diseases."

Question: "Translation of research materials for example informed consent forms for IRB review, is that a challenge for NAMRU-6?"

Roxana: "When all your members are bilingual, English and Spanish, review of protocols and consents in either language speeds

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U.S IRBs on an International Stage: Interview with Roxana Lescano of NAMRU-6 IRB *(continued from page 4)*

things up. Translation of consents and CRFs or demographic data forms to Spanish is a burden on the investigator, not on the IRB. Reviewing the accuracy of the translation by a board of bilingual members, without the need for an outside translator or a back-translation, is definitely a plus."

Question: "What are your thoughts on customized institutional training for local research ethical codes and regulations?"

Roxana: "This is an important issue to consider. Establishing a mandatory training program is essential but not everyone we collaborate with has enough funding to pay for example, CITI Program, for their training. So, we need to identify training opportunities, at no additional cost, that are acceptable by DON HRPP and accessible by collaborators in various countries in several languages. One good example is The Global Health Network."

Question: "Are there any local context specific challenges NAMRU-6 has had to overcome?"

Roxana: "It is important for foreign research institutions, like ours, to develop partnerships, within our mission goals, with these local research groups to help develop more local capabilities, to better understand host country values and practices and to share best practices. After a series of negative press releases of a clinical trial in pediatric populations, the president of Peru declared that pediatric trials could not be ap-

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NAMRU-6 IRB

U.S IRBs on an International Stage: Interview with Roxana Lescano of NAMRU-6 IRB *(continued from page 5)*

proved in Peru until a new regulation is implemented. Although the press articles were completely unfounded, the local government response stopped research with children for 2 years. Additionally, it brought along negative repercussions to the research community. That is over now, but from 180 clinical trials approved annually in Peru, we now have about 30 clinical trials. Luckily, observational research remains very frequent, mostly an academic practice and also in Ministry of Health hospitals. Many well-known research groups in Peru continue to be productive, receiving foreign grants, conducting large collaborative studies and publishing in peer-reviewed journals."

Question: "What process does NAMRU-6 have in place for oversight of PIs?"

Roxana: "NAMRU-6 IRB reviews NAMRU-6 funded and/or supported research only, and in addition to this, takes on the responsibility of training and providing oversight of research studies. The latter are conducted by the Head RAP [Research Administration Program]. We have several examples of assist visits, monitoring, site inspections and others, and in many instances, this is done upon request from the PIs. RAP Head informs results to the IRB and to the PI/ Department Head."

Question: "We have discussed several challenges, so now in general, can you comment or provide some tips on how NAMRU-6 overcomes these challenges?"

Roxana: "1. Highly trained personnel, not just for the IRB but also for the Research Administration Program. This demonstrates the importance of knowing and following the regulations when conducting IRB activities. There is no external funding for this, however, the time spent by RAP training personnel at Lima and other sites on topics related to human subject research – is essentially funded by management support funding and are supported by the command. Sometimes these are personal initiatives and take on a personal burden but they are important to conducting the job adequately. A third benefit of being well trained is that the local community also acknowledges the level of training and seeks the individual for consultation and to provide training.

2. Supporting local institutions with their training opportunities. Being available to speak at local workshops, as guest lecturer at universities, identifying foreign key note speakers to speak at local courses, collaborating with the host country organizations to bring good courses to the local level to benefit the local community.

3. Becoming well aware of local institutions IRB processes and the differences between theirs and DON HRPP's. This helps identify areas for improvement on both sides, and also helps to guide our NAMRU-6 investigators, as they communicate with their local collaborators.

4. Having a highly supportive Institutional Official with the IRB's decisions.

5. Providing support and guidance to foreign institutions for registering their IRBs or obtaining an FWA.

6. Giving the IRB members the opportunity to be trainers on different topics regarding ethics in research."

Major Walter Reed; 1900 Yellow Fever Trial and Implementation of Informed Consent Forms

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lished to investigate yellow fever and other infectious diseases on the Island of Cuba.

The Yellow Fever Commission led by Major Reed also included 3 army contract doctors; James Carroll, Aristides Agramonte and Jesse Lazear (who died from self-experimentation with an infected mosquito). Grounded on a hypothesis previously purported by Cuban epidemiologist Carlos Finlay, Reed and his team set forth to investigate whether yellow fever was transmitted by mosquitoes. Past attempts to replicate yellow fever in animals had failed, stunting ongoing research. So, Major Reed determined human subject testing was the only effective option. In a letter to then Army Surgeon General George Stenberg, Reed stated "Personally, I feel that only experimentation of human beings serve to clear the field for further effective work."[3] Approval of the research was sought from the Governor General of Cuba and from the Spanish consul.[4] Reed was fully aware of the ethical responsibilities in recruiting volunteers and with support from other members of the Commission, he created the first known modern informed consent form.[5] Major Reed's recruitment consisted of American soldiers and Spanish immigrant volunteers who had not yet contracted yellow fever. Thus, consent forms were created in both English and Spanish, and subject signatures were obtained prior to enrollment. An excerpt from the consent document in English states:

"The undersigned understands perfectly well that in the case of the development of yellow fever in him, that endangers his life to a certain extent but it being entirely impossible for him to avoid the infection during his stay in the island, he prefers to take the chance of contracting it intentionally in the belief that he will receive from the said Commission the greatest care and the most skillful medical service."[6]

Although by current standards the language of the informed consent document is primitive as it does not contain all the elements of informed consent as we know it today, the mere act of implementing such a measure is considered progressive for that time. The informed consent document was essentially a contract between Major Walter Reed (on behalf of the Commission) and the volunteer. The risk of life endangerment was noted in conjunction with the imminent possibility of contracting the disease regardless of participation. Subjects were also informed of access to expert medical care during participation.

While the Yellow Fever Commission human subject research was not without controversy, in this article we focus on this historical milestone in human subject protections; Major Walter Reed and his consideration of human subject protections exemplified by the implementation, translation and documentation of subject informed consent.

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6. Special Order No. 122, Department of the Army, Washington DC, 1900. Otis Historical Archives, National Museum of Health and Medicine, Silver Spring, MD.

DON HRPP News!!

As mentioned in the February 8, 2018 "DON HRPP e-Gram" sent to Commands, SECNAVINST 3900.39 E (Echo) was approved 19 Dec 2017. Per Echo, the Director, DON HRPP is no longer required to endorse Individual Investigator Agreements (IIAs) and Institutional Agreements for IRB Review (IAIRs). These documents will now be reviewed as a part of headquarters-level administrative reviews and during Assist Visits and Site Inspections.

DON HRPP training sessions titled "Review of SECNAVINST 3900.39E (19 DEC 2017)" were held on 13Apr2018 and 23Apr2018 to discuss changes in the revised instruction. Significant changes in responsibilities and procedures were addressed, followed by Q&A sessions. Please continue to contact your DON HRPP POCs if you have any questions.

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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