

ORPP&E Webinar

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Session: Review and Approval of Non-Veterans in VA Research

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Dr. Molly Klote: Hi, good afternoon, everybody. Or morning, for you West Coasters. Thank you, Erica, for the intro, and we can go to the next slide.

So we understand this is a topic that you all have had a lot of interest in and it's taken us a little while with the COVID happening to come back around to sort out some of the bread and butter topics that everybody is really interested in hearing about. And this has been actually, it has come up and become an important topic during COVID as well. So we're glad to host this today. So here's what we're going to be looking at today. You know, we're going to be reviewing the definition of research, we're going to go back over what the R&D Committee's responsibilities are when it comes to considering non-Veterans in research studies, looking at how they are recruited into studies, responsibilities for the cost of subject injury, and then things for the R&D Committee to consider, when it's looking at requests, to include non-Veterans. Next slide, please.

So VA research, right? This is important because we get—there's two different angles that come into this, and it's why the topic gets a little complicated. One, is pretty straightforward: It's research that's conducted by VA investigators, who they can be, on VA time or on VA property. And the research may be funded by the VA or other people, right? And that, in order for it to be considered VA research, it has to be approved by a VA Research and Development Committee, before you can get started. I think everybody knows that. That's a requirement out of 1200.01. But we also find a reference to the R&D Committee in another statutory document. Next slide, please.

Which is 38 CFR 17.85. Which talks about the fact that when you enroll people into VA research studies, in order for them to be covered for the potential of a research-related injury, this study also has to be approved by a VA Research and Development Committee. So this is the other place you find this statutory requirement that the VA have Research and Development Committees. Okay? Next slide.

So there's lots of things that the Research and Development Committee is responsible for. And here's a whole bunch of them, and I think there's an animation with this. What we're talking

about today is the relevance of the research to the VAs mission—that's what we're going to touch on, first—and the care of Veterans. Next slide.

So, of course, our mission. You know, President Lincoln's famous quotation that starts the VA for us: "To care for him who shall have borne the battle." Of course, today, we would say him or her who shall have borne the battle. And that's the mission of the Veterans Healthcare Administration. And the second part of that: "...and for his widow and his orphan," gets us into the Veterans Benefits Administration, right? Benefits that go out not only to the Veteran but to the Veteran's family and children. Then of course, we have the National Cemetery Administration, you know, putting our Veterans to final rest, and then our VA Fourth Mission. And this has come up during COVID. This is where this has become important, because as we've seen in New York and with the Navajo Indians in Arizona, we have taken in non-Veterans into our VA Medical Centers, to care for them, from an overflow perspective and all sorts of things, and it is our fourth mission to do this, to support the rest of the nation when the nation needs additional care. Next slide, please.

So a lot of people have brought up the question: So why is this happening under the R&D Committee instead of the IRB? Because historically, we used to have the IRB do these requirements, or do these requests, and review these requests and make these approvals. And when we put out the new 1200.01, we shifted that responsibility to the Research and Development Committee. And it's for a really important reason. Because including non-Veterans in our research studies, is really, it has the most impact. Not on considerations for human subjects protection, which is the IRBs job. It has considerations for the institution regarding potential liability and cost of subject injury. And that's why it's really important that we put this into the R&D Committee's realm, for them to take a look at. Because they can look and see, you know, how is this study fitting in with the overall research program at the hospital, and how is it positioned in terms of risk portfolio for the institution? Next slide, please. I think we're having a lag in our slides.

There we go. So we have to first dig into this definition of research. And as much as you'd think a definition can be straightforward, there are a couple of nuances that go along with this. So you define the definition of a Veteran as being a person who served in the active military, right? Who was discharged or released under conditions other than dishonorable. So they have to be honorably discharged, essentially from the military, in order to be considered a Veteran. So then you have, then who's not a Veteran, right? You have the caregivers, their family members, providers that work in the hospital who have never served on active duty. But you also have people who served on active duty who were dishonorably discharged would be considered non-Veterans. Next slide.

Then you get into Veterans, right? Now we're talking about Veterans. So people who served and were honorably discharged, then you get down into Veterans who are eligible for care at the VHAs and people, and Veterans who are not eligible for VHA care. And this is a really important distinction. It's actually the Veterans Benefits Administration who reviews the medical records and service history of Veterans when they leave the service, if the Veteran so

chooses to submit that paperwork to the VBA, and the VBA makes a service determination about eligibility for care. And so where you can start coming to the VHA for care is when you have a 30% or greater disability rating. And so, and this is a complicated topic. I am not a Benefits Administration Specialist. This is sort of the high level to give you a sense. So then we do have Veterans who are not eligible to come to the VHA for care. And that's somebody who has less than a 30% disability as determined by VBA. So when you're bringing in people who are Veterans and considering them even for enrollment in studies, you've got to look at that eligibility of the Veteran, right? Because this will become important when we talk about research-related injury and how this works and how our appropriations work. Okay? These eligibility determinations by VBA can be long processes. It could be three to six months, historically, they've been much longer than that, depending on the backlog that's occurring at VBA. It can take a while to get these done. So this isn't something where a Veteran shows up on your doorstep, they say—Hey, I'd like to participate in this study. And you say—Well, are you eligible for VHA care? You're not going to answer that question, necessarily, that day. And if they've never applied for benefits before, this is going to be a long-term process. Next slide, please.

Okay. So last year, because of the rise in suicide and the concern over suicide across the nation, really, there was a mental health care exception. So in case anybody comes to you and brings this up and says—Wait a minute, we do have these even dishonorably discharged service members, who can get care at VHA. And that's true. There is a one-year free mental health care provision that has been written into the VA laws for care, for people regardless of the status in which they left the military. But for our considerations, this does not make them a Veteran. Just because they are eligible for this specific mental health care for this year, it doesn't put them into the category of a Veteran. And for the purposes of research, you would still, if you wanted to include them in a mental health type study, you would include them as a non-Veteran. Next slide.

So what are the responsibilities here, when we look at making this determination, right? You have two parties. You have the investigator, who must justify why he or she is including non-Veterans in the study. And then you've got the R&D Committee, who has to review that justification and provide a specific approval. So when we say specific approval, what we're really saying is it's got to be documented somewhere that they have specifically approved the inclusion of non-Veterans into this particular study. Next slide.

Okay. And then can the R&D Committee use the Designated Review Process? Of course, in 1200.01, we have this ability to do designated review, and as long as the rest of the protocol fits into one of the categories that allows it to be done under designated review, then the review of the non-Veteran provision can be done in that same designated pathway. Next slide.

Okay. So there's two ways that you can justify putting Veterans, or asking non-Veterans, I should say, into a study or adding them into a recruitment plan. And that one way is that there aren't enough Veterans that are suitable to meet the needs of the study and so you've got to go to a non-Veteran population in order to try to increase your numbers and make your

recruitment goals. So that's one reason that it happens. The other reason, Option B on this slide, is they can be recruited when the study will generally benefit the Veterans, but the Veterans aren't the target of the study, right? So if you are doing a caregiver study or a family member study, or you're looking at the children of Veterans. In those cases, you could also justify enrolling non-Veterans into the study. What you can't do is say—We're going to put non-Veterans into this study because they happen to be available. So we have a bunch of medical students that come through the VAs each year, doing rotations, they would be an easy access pool. But what's the point of the study? If it's not about training to care for Veterans, and it's some other kind of a study, you'd really have to look at why are you targeting this population for a study conducted by the VA? And that's again, getting back to our mission. What's our mission? Our mission is about caring for Veterans. So what is your study about and how is that advancing or supporting the care of our Veterans? Next slide, please.

So the Fourth Mission. We talked about this a little bit before. We can include people who are brought into our facilities for treatment, Fourth Mission people, into our research studies. We absolutely can. And in fact, we did it, on a number of occasions, during COVID. And when we talked to the Office of General Counsel about this, you know, when we said—Look, we're going to have a Veteran in one bed and a Fourth Mission person who has been brought in, in the bed next to them, you know, can we offer a clinical trial to the Veteran and not offer it to the non-Veteran, you know, and we talked to ethics and we talked to a lot of people and the idea was, if they are admitted into our facility under our care and we're offering enrollment into a particular therapeutic protocol for our Veterans that it behooves us to make that same offer to the Fourth Mission people who are there. And so we did, in fact, offer enrollment in those cases and assume that liability then, for the issues of research-related injury. When you do that under a Fourth Mission, do you still have to get R&D Committee approval for including non-Veterans? Absolutely, you do. Next slide.

So that led us then to the start of the vaccine trials. And we had a number of employees, both Veteran and non-Veteran employees calling our office saying—Hey, can we enroll in these vaccine trials? Well, it doesn't change that they're either Veterans or not Veterans, eligible for VHA care, not eligible for VHA care, all those distinctions still have to be met. What the complicating factor is, when we talk about employees are that employees relationship, potentially, with one of the unions, right? So we spent a good portion of this summer working with labor and management relations and talking to union leadership about how we could offer enrollment to employees into the vaccine trials that were coming, in a way that wouldn't have to take us down the bargaining pathway and all sorts of things. And the truth is that we put out this guidance, it is the best that we could do without going back to bargaining, and ultimately, next slide.

The two big outcomes of this were that the conditions of employment for our employees couldn't change. So that was really the biggest outcome of this, is that the employees would have to volunteer during non-duty hours, and if something came up, like the flu shot, which it is coming up, right? If an employee has to get their flu shot, versus the employee wants to enroll in a vaccine trial, which one takes precedence? Well, we didn't change the conditions of

employment, so the employee must get his or her flu shot if it's required for his or her job, right? So that then complicates, well, then what if, then they can't necessarily participate. Well, almost all these vaccine trials allow for people to get their flu shot, there may be a one-month delay in being able to then participate in a trial after getting a flu shot. I've seen it as low as two weeks to participating in a particular trial, but the point was they still had to meet the requirements of employment. Now, for the study teams, what this meant was if they wanted to open the study up, and it was the choice of the facility based on how much staffing they had at that particular site, if they wanted to open it up to employees, they had to do—you know, early morning hours before employees came to work, late night hours after employees were getting off work, if they wanted to capture those people. And employees had the choice of taking annual leave to come in and enroll and do their study participation if they felt so inclined to do this. So a lot of hoops to jump through to make that available and to clarify all the concerns around it, but it is an option now that is available. Are they still considered non-Veterans if they're non-Veterans? Absolutely. Next slide.

And you have to get the R&D Committee to approve it. So for anybody who is a non-Veteran or is a Veteran who doesn't have a record in CRPS or the Cerner system, now that that's rolling out, a medical record has to be created for anybody that is participating in a trial where there is going to be some sort of clinical interaction, okay? So what's important about this is this isn't normally done by the study team. They don't normally make a medical record. So figuring out within your facility who is going to be impacted by this, you know, if you're going to enroll five non-Veterans, that might not be a big deal. But if you're doing a vaccine study and you're going to try to bring in 400 non-Veterans, that is going to have a significant impact on whatever office is responsible to create records. And what's the turnaround time on that, and how do you build that in, and is there a way to back that up so that maybe you can find out that they're coming in for an appointment, get the medical record made before they show up for the appointment. So there's lots of things to consider when people are thinking about bringing in non-Veterans and having to create that medical record. Next slide.

And with the medical record, for anyone who is a non-Veteran or who has not had care at the VHA before, when they come for what should be, at the first interaction you have with them in a clinical way, they should be provided a copy of VA's Notice of Privacy Practices. And this is in accordance with the VHA Privacy Handbook. And what's required is for the person to sign an acknowledgement. It's called the VA Form 10-0483, and it needs to be signed by the non-Veteran or the Veteran who has never been seen in VHA before. And that, we've heard from a couple different facilities, some say that their privacy teams want that filed, not only in the study record but sent into either the Health Information Management Office or the Medical Services Office, or some office within the hospital. But that has to be looked at and addressed to make sure that everything is being filed properly. There are two versions of the Notice of Privacy Practices. There is one that is a small font and then for your Veterans with sight disorders or your older Veterans, there's also, I've attached here, the large print version of the Notice of Privacy Practices. Now, you don't have to hand them a hard copy version of this. This can be emailed to them, it can be included as part of their consent process, if you're doing electronic consent, this is a document, the 10-0483 can be put through the DocuSign process, if

you're using DocuSign or another electronic consent process, but it's got to be documented. Next slide.

So in order to, or following along with the idea that we are in the midst of our transition to VAIRRS, which is our VA Innovation and Research Review System, where we're looking to standardize and harmonize all of our forms and templates across VHA, we have created a justification form for investigators to complete to submit into their Research and Development Committee. And it starts off very simply with some demographics of the project. Next slide, please.

It goes into those two reasons why you can bring a non-Veteran into a study, right? Is it going to involve either inpatient or outpatient treatment? And if it's not, is it going to generally benefit Veterans and their well-being, but not include Veteran subjects, and if no, you don't have a reason to include them, but if you go back up to—Will the study involve either inpatient or outpatient treatment of non-Veterans? If it's yes, is the reason that there are an insufficient number of Veterans suitable to be entered? If it's no, you need to stop. Because those are the only reasons that we have been given to be able to allow non-Veterans to be able to participate in research studies. Next slide.

So there are then some text boxes you can fill out about why do you need them in this study, how many do you think you're going to need, how are you going to change recruitment to try to get non-Veterans into the study, and what do you think the probability of research-related injury is, with your study? So if you're doing a single blood draw, you know, type study, probably very low that anything bad is going to happen. If you're doing a, let's say a cancer trial and you're going to give an investigational drug, there may be a high chance that there could be a research-related injury and so not only do you try to predict what that research-related injury risk is going to be, but then you're going to justify how you made your assessment. Next slide, please.

And then we get into compensation, or reimbursement. Who is responsible to reimburse VA for these research-related injury costs? And we're going to talk in a minute about what those different categories are, but the choices are, you know, that there isn't anybody, and so the medical center is ultimately going to be responsible. Whether this is an ORD-funded study and ORD has given permission to allow the inclusion of non-Veterans, or you've got an industry-sponsored study and you've got a CRADA in place, or there's some other way that you're going to reimburse VHA for research-related injury care. And then the investigator signs this request. Next slide.

So let's talk about money, since we just brought it up. In 38 CFR 17.85, where we get that line from the beginning of the presentation where it talks about a Research and Development Committee, in order to pay for research-related injuries, you had to have a Research and Development Committee approve the study, it goes on to say that it's the Medical Center Directors. It doesn't say Big VHA. It doesn't say the executive in charge. It says the Medical Center Director has a responsibility to care for or arrange for the care for any subject injured

from participating in a study that has been approved by a VA Research and Development Committee. However, okay, so you've done the care, or you've arranged for the care, but that doesn't mean it stops there, right? What we want to do is get reimbursed for that care. And especially if you have a sponsor from outside the VHA, in particular. But in order to do that, you have to have that contractual agreement with the study sponsor, before the study starts, right? If you don't have that in place, you can't go back to the sponsor later and say—Hey, we didn't anticipate there were going to be research-related injuries, and now there are. These things have to be thought through prior to the start of the study. Now, our Office of General Counsel in our standard CRADA agreement, when we do a CRADA with an industry partner, has already templated language about cost of subject injury reimbursement and so when we have a CRADA that's been reviewed by OGC, that language is in there. Unless it's been removed for some reason, which it shouldn't be. Next slide.

So let's talk then, about why you want to do this reimbursement. So our—so there's two appropriations within VA or within VHA. We have our medical appropriation, which is our dollars for care, and then we have our research appropriation, which is for research, for all of the infrastructure of research, those sort of things. There's actually a third appropriation, which is for IT, but we're not going to go into that today. So the medical appropriation can be used for an eligible Veteran, so this is that person who has a 30% or greater disability who served honorably—and was discharged honorably, right? So we can use our medical appropriation to pay for research-related injuries for those. But not for non-VHA eligible Veterans, so people with less than 30% disability, and not for non-Veterans. These are cases where we need to get reimbursed. So research appropriation can actually reimburse in all three of those cases. However, ORD does not have funds set aside to reimburse medical centers for the cost of research-related injuries, and it's why ORD, for ORD-funded studies, requires that some sort of a waiver be signed off on, to bring in non-Veterans. You know, we're putting the ORD budget at risk when we include non-Veterans, who potentially could get hurt, into ORD-funded studies. Next slide, please.

So here are just three big categories. You have industry funded and some information, federally funded, and then ORD-funded. I'm just going to point out a couple of things, which I've already touched on. For the industry-funded, you want to make sure that you've got a CRADA in place and that it says we're going to get reimbursed. For federally funded, it's sort of a mixed bag because the medical center, you know, nine out of 10 times is going to end up being responsible for the cost. Because we don't have, and it's not NIH or DoD's policy to reimburse sister agencies for research-related injuries, okay? Now for DoD studies, if you've got active duty service members that happen to be in our VA studies, you might be able to work out and negotiate in an MOU or an interagency agreement that the injuries would be cared for at a DoD facility. You're probably not going to get that same deal with NIH, because NIH is a research institution, it's not technically a care facility for normal medical care. It's really for only research studies. And then you have ORD-funded, as we've just talked about, and that for ORD-funded, you have to get approval from the funding service prior to submitting the request to your R&D Committee to include non-Veterans. So for our funding services, CSR&D actually has a process, it's on their website, of how you can actually request to do this. From what we heard from CSP,

it's almost always a no. There has been one waiver applied for that ultimately did not go through, but pretty much for the most part, CSP studies are going to be a no. Next slide, please.

Okay. So let's talk some practical aspects of this, okay? What can we do? All right, so let's back up a second and say—So a study starts, and they're not expecting to have non-Veterans enrolled in the study, but three-quarters of the way through the study, they realize they are not going to hit their recruitment target, and they panic and they say: You know what, we've got to open this up to non-Veterans. And they want to go through the process for that. What's really important, especially if it falls under the IRB, because under 1200.05, not all amendments have to go to the Research and Development Committee, right? But this is an amendment that actually impacts the facility. So it should be an amendment that goes to a research and development committee. But how do you get that fail-safe in place? How do you make sure that the investigator knows if this changes, that everybody in the IRB staff knows, and we think the best way to do that is including a statement in the original Research and Development Committee approval letter that says specifically, if at some point in the study the PI needs to expand the study to include non-Veterans, the PI must inform the research and development committee. Right? So this would send a signal through your whole system and anybody looking at the original R&DC would know that this is a requirement and it would just raise awareness. Because this is not a rare event that people get toward the end of their study and then look to amend their study to add a non-Veteran population. Next slide.

So another practical consideration is how does this impact the IRB, so the IRB gets this, this amendment comes through, they want to do this, what does this change for what the IRB has to do? And the answer is: Nothing. Right? There's no change to the IRB's core mission, because this isn't, as we started this conversation off, it's not really—the IRB is concerned about a human subject. They're not necessarily concerned with a Veteran or non-Veteran subject, they are concerned with a human subject. So there's nothing specifically different. They would use the same ethical principles they would use to look at the amendment, look at the recruitment plan, the recruitment materials, they would look at any changes that would be needed to the informed consent form, they would look to why are you changing the study sample size, potentially, and ask those sort of questions. But there's nothing really different that the IRB has to do. Next slide.

So then the next question relates to, and this is another one of those tricky subjects, but it relates to the idea of copays and people's insurance, and the question really is: When the IRB is looking at the informed consent form and there's language in there, and this happens sometimes from industry studies that come into VHA where it says, if you get injured, your insurance—we'll go to your insurance company first and if your insurance company doesn't pay for it, then the sponsor would pay for it. Well, we're not going to be billing people's insurance companies. So we remove that language when we're dealing with a VA study. Now, if there are copays for usual care during the course of the study that would normally be collected, that all needs to be addressed within the informed consent form, and copays are fair game. But when you come to research related injury, we're not going to people's insurance companies for that, we're going back to the sponsor. Next slide.

So with that, I'm going to stop in a second for questions. I'm going to just let you know that you can start typing your questions in. Wait, wait, wait. Put the slides back up, please. You can start—sorry, you can start typing in, but there's some really important slides at the end that I just want to touch on. Are you able to put the slides back up? Let's see. I'm challenging them.

Erica: Here we go, I got it now.

Dr. Molly Klote: Okay. And these are some new things that have happened, since I have 349 of you on the phone right now. Next slide, please.

So we now have the searchable FAQs. Right? We've got a little more than 200 published frequently asked questions that we have put together over the past couple of years. We now have them on a platform that you can access, the link is right there, and I'm just asking everybody. And I sent this out to the Field Research Advisory Committee yesterday. We are asking people, before you email anybody on the ORPP&E staff about a question to please use this resource first. See if the answer to your question is in this resource. If you can't find the answer to your question among these 200 FAQs, then please feel free to write to the ORPP&E mailbox. Please do not write to Dr. Jeans directly. Please send all communications through the ORPP&E mailbox so that we can respond to them and capture the questions that are being asked from the field that aren't currently captured in our FAQs, because that's how we decide on our FAQs. We look at what comes in to the ORPP&E mailbox, we answer those questions, and we turn around and create an FAQ about it. So we want to keep adding to this database, so please send questions to the ORPP&E mailbox. Please don't forget that we do have our own policy and guidance webpage. Next slide. This seems a little slow today. Next slide's not coming. Not happy. I can't remember what the next slide is. More good stuff, though.

There we go. So please remember, we've got sample templates for applications, reviewer forms, we now have the ORPP&E toolkits that are published. Right now we've got the exempt research and the R&D Committee Review, and then of course our ORD regulatory mailbox. So this is the mailbox that I'd like you to write to if you have questions and again, not to Dr. Jeans, but send questions into our regulatory mailbox. Next slide. I think this is the last one.

This is the upcoming committee workshops. Next slide.

And you can have—yep, these are all in there for reference, some just important links.

[END OF AUDIO]