Interview

The nursing scientist as a principal investigator (PI) of clinical trials on dementia

— Interview with Associate Professor Ruth A. Mulnard —*

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Interview and translation :
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Abstract

This article is an invaluable record of an interview with Prof. Ruth Mulnard, who is a nursing scientist as well as a clinician in United States, who has especially focused on the area of dementia and has extensive experience of working as a principal investigator (PI) of 20 to 30 protocols of clinical trials. There seems to be no other nurse who has such experience. This became possible not only because she herself has the ability to formulate research questions and design protocols, but also because there are physicians on her team to work with her taking responsibility as physicians to prescribe drugs, overseeing medical care, controlling adverse events, etc. Her experience of working a long time as a chairperson of an ethics committee is extremely important. In this regard, she presents a model for other researchers to use in order to conduct highly ethical research just as she has required of other applicant researchers, as chair of the committee.

She also has experience to lead activities to revise the California law on informed consent for research participation to benefit cognitive impaired patients; to develop guidelines for gathering brain tissue and banking it at Alzheimer's centers across the country, funded by the National Institute on Aging. She also introduced her success in the debate to conclude that, in case any incidental findings not related to the research questions are found during the research, the researcher should give the patients-subjects appropriate referral and introduce them to a medical facility where they can be properly cared for. Several kinds of rare, significant experience have led her to become an outstanding characteristic role model of a contemporary nursing scientist and clinician.

Key words
principal investigator (PI), nursing science, research ethics, informed consent, dementia

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1. On becoming a nurse-principal investigator

Interviewer Thank you so much for your acceptance of our interview. When we found that you are coming to Sapporo to offer on lectures at the 30th Academic Conference of Japan Academy of Nursing Science, we also found that you are the first author of the report of clinical trial on estrogen replacement therapy for treatment of mild to moderate Alzheimer Disease [1], which is very important and widely known. We regard the research finding is also important as it is "negative result".

When you replied our e-mail, you informed that you worked as a Principal Investigator (PI) of this clinical trial. It is fantastic to take on assignment of a PI! That is great and encouraging to nurses working for clinical trials. In Japan, the role of research nurse is regarded to help doctor-investigators. In the case of research question is nursing care, nurse-initiated clinical researches are commonly conducted but I think it is very rare that a nurse plays a role of PI of clinical trial to prove efficacy and/or safety of a drug, for which physician has a right of prescription. So we would like to know the background story how you came to play such role, and how such thing came to be possible.

Mulnard In the United States (US), most of the time, nurses are clinical research coordinators; the same as in Japan. They assist the physician and the rest of the team with making the research happen, taking care of the patients, collecting data, helping in that way. When I got my master's degree in nursing, I worked at Johns Hopkins and I was the clinical research coordinator for all of the clinical research that was happening in the Department of Neurosurgery at Johns Hopkins. My focus has always been in the neurosciences. But after years of doing that and then getting my doctoral degree, obviously at the doctoral level we always want to work at a team in doing our research, but we're much more capable then of generating the idea and making the idea happen, leading the team; being the scientists, not just data collector and helping.

With that being said however, I must be very clear that in getting a doctoral degree that doesn't change my basic license as a Registered Nurse (RN), and what I'm allowed to do is only within the scope of that RN license. So I can't be a PI of clinical trials without having physicians on my team. That has worked out very well however, and I have a team of physicians that I work with, all of whom are neurologists who aren't interested in being the PI. Those individuals aren't conceptualizing the idea. They didn't create the study and make it happen. But they want to be a part, and they're able to be on the team with their medical license. They oversee the safety of what's going on in the trial through the regular medical oversight that is needed for the trial, and they're very much a partner with me. I have 2 physicians on my team right now. Both have been with me for more than 10 years.

So I have probably 6 to 8 clinical trials going on right now, and these 2 physicians are on every one of those. We understand each other's roles very clearly. When a patient has any kind of an adverse reaction, small or big, the physician is right there to provide the care, to provide the analysis of what's happening, and to recommend what we should do with the patients.

I also have a nurse practitioner; a registered nurse who actually has broader scope of practice as a nurse than I do. She's not the investigator but she's part of the safety oversight team and working with the physicians to make sure that the patients are taken care of and everything is done safely. So again it's an unusual role. This study in particular, the one in JAMA [1], was supported by the National

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Academic Distinctions

- 2008 – Appointed by Governor Arnold Schwarzenegger as a founding member of the Public Health Advisory Committee, California Department of Public Health, State of California
- 2002 – Honored with Certificate of Appreciation from California Department of Health Services, for involvement in changing the California state law concerning informed consent for research (AB2328)
- 1988 – Honored with induction into Sigma Theta Tau International Nursing Honor Society: Iota Lambda Chapter, University of Southern California, Charter member

Research Abstract

As a clinical researcher, she has built a program of research that provides a translational bridge between the basic and clinical sciences. Her current research portfolio addresses each of the strategies as follows: 1) Strategy 1 – integrating biology and behavior through clinical trials and biomarker studies; 2) Strategy 2 – designing and using new technology through a home-based assessment study; 3) Strategy 3 – developing new tools through participation in many instrument development studies in clinical trials.

Additional research efforts include collaborative studies on elder abuse in demented persons and another collaborative project that investigates the benefit of a passive exercise regimen on the bone development and growth of premature infants. This latter project benefited from her clinical trial design expertise, and ongoing oversight of the data and safety monitoring board for this study.

Her clinical work with the cognitively impaired population led her to develop a deep interest in the area of impaired decision-making capacity. The pursuit of this area of interest was complimented by her robust regulatory knowledge, gained through long-term service on the university's Institutional Review Boards and active participation as an AAHRPP site visitor. Combining these areas of expertise supported her impact on state wide health policy to lead a state-wide initiative to modify the California Health and Safety Code.
(This profile is extracted from : http://www.faculty.uci.edu/profile.cfm?faculty_id=5454)

Institute on Aging (NIA), and I work with the group within the NIA called the ADCS (Alzheimer's Disease Cooperative Study). That group is still funded.

The ADCS is still doing many clinical trials. And I'm the only nurse-scientist of 83 sites that participate with that group. I'm the only nurse who's leading any of the sites. Even in the US it's unusual, but it's accepted. And yet, when I work outside of this group, when I work with private pharma companies who have the ideas, and I want to be one of the sites in their study, several of them, and I've only run across 2 in all my years of doing research, 2 who have said I can't be the PI because I'm a nurse; that they would only allow a physician to be the PI. So it happens that sometimes I am denied that access because of not having an MD credential. It's not common. Most of the time, they simply want to see our track record; how well we have done in previous studies; how many patients are we able to recruit; how well characterized. I work with an Alzheimer's Center at our university that was state-funded and federally-funded. So we have a very well characterized group of patients

that are ideal, and they come to us because they want the cutting-edge research opportunities to treat their disease or to possibly treat their disease. So again, only 2 companies have ever said, "That's not good enough. You must be an MD, rather than an RN." So it's not been a very big obstacle along the way.

The other thing that is I think different about my role is that I'm also, at our university, the chairperson of one of our ethics committees. We have three ethics committees and I'm the chair of one of those three. I have had that role for more than 10 years now. Again it's unusual. Usually nurses don't lead those ethics committees; although that's certainly done at some other universities as well. But again it puts me in a position which, to do clinical research, people think that I bring a higher level of ethics to the research, a higher scrutiny, oversight, making sure that, you know, since I'm in a leadership role with the ethics committee, that my research will be done very well because I want to be the model. So I try to practice that way.

So it's just another piece. It is part of what led me to be involved in the whole informed consent issue with the dementia patients, and the restrictive law that we have in the State of California which I worked on many years ago. It's all part of building the credentials to be a very good clinical researcher and to be a desirable clinical researcher for more studies because we've done well. We have a good oversight. We have good teamwork between the different clinicians. It all sets a very good pattern for us.

Interviewer　We understand very well about the collaborative work of nurse-PI and physicians. So, in the case of clinical trial, the responsibility for prescription is on the part of the physicians?

Mulnard　That's correct, right.

Interviewer　In US, is there any qualification or certification for PI?

Mulnard　Well, PI has to be qualified as far as the FDA is concerned. All that they say is that my CV (Curriculum Vitae) must be robust enough that it supports my role. It's usually done at the level of the sponsor. And all the necessary process is described in the Code of Federal Regulations, 21CFR, the FDA regulations. So if the sponsor is the private pharmaceutical company, they want to make sure that when they choose principal investigators, that if the FDA should come in and audit

Ruth Mulnard and interviewers (left: Saio, right: Kurihara)

them, it will all pass. In a couple of instances they're concerned that if I were listed, it wouldn't be okay. But it's been okay for many, many studies. So they're just being, I think, overly cautious. But that's their right to be overly conservative.

Interviewer Aren't there any other nurses who play a role of PI? You said that there are very few, and it's very rare.

Mulnard I don't know of them.

Interviewer You're the only one?

Mulnard Well, specifically in clinical trials that involved investigational medications, I don't know any others. At least in this large federal group that I work with, there are none. Every site either has an MD which is hard to get, or a couple of them actually have Ph.D. basic scientists who are in charge of it. Obviously, they're kind of the same model that I am except, I think, I'm a higher model because I have a license of some sort. They have no license. They just have physicians on their team who do their role; who are very capable. But at least I have a medical-type of license as an RN where I am a clinician. They're not even a clinician. But I don't know of any other nurses.

Interviewer That's great.

Mulnard It's unusual. It wasn't accepted by everyone. When I was running this study, some people questioned, "Was this okay?" Fortunately, the National Institute on Aging, who was funding this and many other studies, did not see it as a problem. They were at the table all the time when we have meetings; and on the phone when we have meetings, saying "No, Dr. Mulnard is doing a fine job. She is very capable. She's got a lot of experience. She can do this."

Interviewer How many projects do you have in which you play the role of PI?

Mulnard I think I have 8 right now.

Interviewer 8, right now? What is the number in your experience?

Mulnard Totally, 25 or 30.

Interviewer That's so many. So you're only one, and you play the role of PI in so many of these studies. It's surprising!

2. Changing California law on informed consent

Interviewer Now I would like to ask you about another issue of your work, that is, to change the California law on Informed Consent. You wrote in your CV that the law was very strict to enable participation in trials, and so it was revised.

Mulnard In the US research conducted in the institutes which are federally funded is under the federal regulations 45CFR46, and clinical trials are regulated by FDA under 21CFR. In the Federal Law there is a clause called "legally authorized representative." And yet the federal government never defined that. It basically said that if a person cannot give their own informed consent, a legally authorized representative can give consent. So most states in the US made their own interpretation of that, but never wrote it down. It's all just in everybody's mind. But they've decided pretty much anybody, mostly a spouse, could give informed consent. Anybody who comes with the patient could give informed consent for the patient.

But California is very stubborn. California interpreted "legally authorized representative" to not include spouse and family. It means someone has to be appointed by the court for you. So it's a whole legal, long, expensive transaction. Even our patients with Alzheimer's disease, they don't have that. Then they become too impaired along the way to know that they needed that person put in place.

California's law was more restrictive than the federal law. But many centers in California were still allowing spouse, family members, children, to consent for their parents to be in research. That

really was not legal. It was illegal. So we realized this. Basically, we presented this to the University of California, Office of the President. There are 5 medical campuses in the University of California, and obviously that's a very big environment in which we do research. So we went into the Office of the President that governs all of the UC-system and said, "You need to help us change this because we're not practicing consistently, and we're not practicing according to the law."

So we spent two years working with the legislature in California. The Office of the President of the UC-System became the sponsor. Then we finally got the law changed. We modeled the revised law after the law for treatment, because the law had always been very specific about treatment.

If you went to an emergency room and you need an emergency treatment and you could not give your own consent because you were in a coma let's say, the law was very specific about who could consent for your treatment. So we used that same model to say, "This should be the model for research." It was easy to get that approved (although it took a long time) because everyone understood the model for treatment, and said, "Yes, that makes sense. If your spouse can give consent for you to be treated, then your spouse should be able to give consent for you to be in research." Then there had to be a lot of little changes along the way because we ended up having to differentiate between people that want to be in research where it's not an emergency.

So we had to break it into two parts. Emergency and non-emergency, like my Alzheimer's patients. We wrote the law so that no abuse could occur with that group who are very vulnerable, hospitalized (e.g., psychiatric patients). All of these little changes had to be made in the law as it was being enacted. And it went into effect on January 1st of 2003, and has been in effect since then. We got it through the process of being passed in two years. Then we helped basically educate the entire state. We wrote the policy for how to implement the new law for the Office of the President. We went around all the different medical campuses and educated them about how we now consent for research. We called it "surrogate consent" – how will you use surrogate consent when appropriate.

Still for many of my Alzheimer's patients, many of them are still very capable of consenting on their own. We do a decision-making capacity assessment where we test their understanding. It's very brief. We don't rely on their memory very much. But we have a way to make sure that they understand. Each time they come back for a visit, we're reconfirming. Do you understand what's going to happen at this visit? Are you okay with this? So it's not often that we have to use surrogate consent. An example of when it becomes very important, in my mind, is when you're doing a randomized, double-blinded clinical trial, and they're very high functioning at the beginning and they give their own consent. Then maybe they're on placebo, or the drug doesn't work, and by the end of the 2-year or 18 months study, they're very impaired. Now there is an opportunity for them to go into an open-label study of the same drug. If we had followed the previous law, they wouldn't be allowed to go into open-label study because they would be too impaired and they wouldn't have a legal guardian at that point. If you took a chance on being on placebo, then you should definitely have the opportunity to get the real drug if it becomes available in an open-label study. So this way we may not need surrogate in the beginning; but by the time they're ready for an open-label study, surrogate might be needed to put them into that open-label study.

So it's something I'm very proud of, and I think we made a very big impact on the whole state. Other states have now called us and wanted to

understand our process; and wanted to use it as a model for changing the law in their state; although most states have continued to remain silent on the federal definition.

Interviewer Is there any cultural or religious background for why California law was different from other state law?

Mulnard It's kind of the way California is. California does not remain silent on anything. California always makes a statement. On stem cell research, California is against the federal law. California wants to be different than the federal law. The same is true with informed consent. The same is true with abortion; with everything. Everything that's controversial and has ethical implications, California makes a statement, and sometimes is very liberal in that way, but really almost shut the door to research with the previous definition.

Interviewer In Japan the regulations for "surrogate consent" is defined very reasonable. It should be legally defined representative or the person who represents the participant's interest and benefit. The best person should be chosen. In case of emergency, it is also defined that in case of emergency, it is exceptionally allowed to start clinical trial without "informed consent" and also not obtaining even "surrogate consent", if some conditions are satisfied. Rules are defined as such, but there is also some ethics committee member who focused on the risk of participating in research; so they deny the cognitively impaired patients to be included in research. You know, there is a discussion in US, for example "Belmont Report Revisited" [2], it is not a good thing to focus only on the risk of the research. So for the benefit of the participants, it may be sometimes better to give the cognitively impaired patients chances to participate in research.

Mulnard Yes. If the law is so restrictive that they can't get the chance to be in the research, it's taking away a very basic right, I think.

3. Task force for guideline development for Alzheimer's disease centers

Interviewer Your work on guideline development for biospecimen banking is also very interesting. I think that this kind of research to set up a brain bank is very important to gather many specimens. It would be difficult to obtain informed consent from the legal representative of cognitive impaired person to donate their brain tissue after the participant's death. But for the success of research it would be necessary to gather substantial amount of specimens. And I think this kind of policy development will be necessary for the kind of "general consent". So please introduce the discussion or story behind the development of this guideline.

Mulnard About this guideline [3], this was developed at the request of the National Institute on Aging (NIA) because the NIA funds the Alzheimer's centers across the country. There are currently 28 of them. They asked me to chair this task force which had many qualified people on the committee with me. So as each center is only funded for 5 years; so every 5 years they have to go back in with a new application, compete against existing centers. I think the longest is, 25 years at the moment. But in all of that time, new centers coming on board, some centers being in place for a long time and practices drift, rather than being consistent, there was a need for consistency to make sure they're all doing things according to the same basic guidelines, so that we can share the tissues; and the other thing that happens with these Alzheimer's centers is data that's collected on all of the patients that come through these centers is stored centrally at

the University of Washington in Seattle, where there's a big, big National Alzheimer's Coordinating Center that they call NACC. The only thing that isn't in NACC yet are the specimens. But there's supposed to be a database being built there that will at least be able to look at some quantification of the specimens that exist at every center around the nation. So you could say, I want to get this kind of brain tissue to study this kind of biomarker in the brain tissue, NACC would be able to give you the information about which centers have that much tissue to give you or can provide it for you, or something like that. So that's what the guidelines were for. And they were really for achieving consistency across the centers that are funded by the NIA.

Interviewer It's very important thing. In Japan, importance of developing "brain bank" is recognized, so we learn so much from your experience.

Mulnard Patient may give consent patients for brain autopsy, and we don't care really about the rest of the body. They can still get a general autopsy if they want, but they give consent for brain autopsy as early in the course of the disease as we can. So usually at our first contact with them, where they're perhaps still decisionally capable, we start talking about that at the very first interaction, and get them to sign up if they will as soon as possible.

And they may not die for 10 or 15 or 20 years, but they sign the consent 10, 15, 20 years ago to allow the autopsy. And then when they don't consent, then we ask the family after death if they will give us permission to do the brain autopsy. And every center has a very robust protocol in place for collecting the tissue.

People on call 24 hours a day, 7 days a week, who get a page on their pagers, and go immediately. I mean our average post-mortem time is between 2 and 3 hours. 2 and 3 hours we have gotten to the body, transported the body, taken the brain out, and preserved the tissue. It has to be very, very, very rapid in order for the tissue to have good quality for research as well as for diagnosis. And then we do the diagnosis on the tissue, give that back to the family free of charge. So that's the real benefit, because if we're ever going to know about genetic linkages, that's of great benefit to the family to know what we found.

4. Issues on ancillary care

Interviewer And you're also engaged in PET or MRI imaging research. So we would like to discuss "ancillary care" issue. We had a discussion with Dr. Rieder Lee of the NIH [4]. He is engaged in research ethics issue in NIH (http://www.bioethics.nih.gov/people/lie-bio.shtml). He published a paper with his colleagues about ancillary care issue. For example, they conduct the research in developing country, and they conduct the clinical trial or epidemiological research of an infectious disease. But sometimes they come across other kinds of diseases. So the ancillary care policy said that the investigator should provide some kind of care for the disease that is completely different from the research question. In case of the research using imaging technology, there is a case when the investigator seeking about cognitive impairment and biomarker, can sometimes find some brain cancer in the patient. This is different from the research topic. In such kind of case, the question is whether the investigator should give them information about this. Because it is a matter of course that if the investigator is a physician, they should provide the information, I think, and they should introduce some other facility where the patient can go for treatment. But sometimes, the investigator is a radiological technician. So there is a very difficult discussion on this. They don't have the obligation

to give the patient the diagnosis. So it is very nice that you have a strong relationship and cooperation with physicians. But sometimes the radiological technician conducts the research without such kind of strong collaboration with physicians.

And even where the PI is a physician, sometimes it is a problem because the research question is biomarker of some therapeutic drug or something, the finding of the cancer is not so robust. So there is a problem whether they should provide some diagnosis of the cancer or provide some chance for the patient to go to a cancer hospital by writing a diagnosis of the cancer.

Mulnard That's a very important question, and the same question has come up at our university. Obviously when we're doing research that involves patients, we always get physicians involved. So a physician is always looking at those scans. And anything that came up that looked unusual, even if it's unrelated to the research question, our stance is that we always refer the patient.

We will give them a copy of the scan. It's no different than if we drew labs on someone and we found that they had a blood disorder; something is wrong with their red blood cells. We do a urine specimen; they have a urinary tract infection, right? We still give them those results and send them to their primary doctor. We'll even call their primary doctor and say, "This person is coming in to see you. Here's the results."

We don't provide the direct care of it, but we provide the referral and we follow up and make sure the referral happened. In our university, it became a problem in the last couple of years where we had some imaging investigators – imaging investigators who were basic scientists, individuals who study learning and memory; not clinicians, not working with clinicians; no clinicians on their team – and the issue came up of – What if there was, we call them "incidental findings."

And their perspective initially was, it's not our responsibility. But what if this goes on to truly cause this brain tumor? What if it goes on to truly cause this person some problem and they find out that years ago it was there on their research scan. Don't you have an obligation?

They said, "No, I have no obligation." So we tried to fight these basic science investigators with little success until one of them submitted a grant to the NIH (specifically it was an NIMH) and got a wonderful review and it was ready to be funded and the agency said to them – "The only thing that you have to do before we can give you the money is, you have to put in place a procedure for how you're going to handle incidental findings."

They were adding a change in the consent language to say, "If any incidental findings are discovered from review of your scans, we will let you know and may give appropriate referral." But they were angry. They were very angry that the federal government did this. And we were delighted. We were very happy. Because as responsible researchers, we thought this is the right thing to do. You can't ignore this.

Interviewer Just now the idea comes to me – providing emergency care in the case of adverse event is of course a condition of conducting research. So is it the same thing with providing incidental care?

Mulnard We consider it the same.

Interviewer So, you participate in the ADNI (Alzheimer's Disease Neuroimaging Initiative) -1 and ADNI-2 project. ADNI is expanding world-wide, and Japan also participates in. Is it also a policy to provided incidental care, in US ADNI project?

Mulnard Yes.

Interviewer Then I hope that this policy is also expanded world-wide, with the ADNI project.

Mulnard I agree with you.

5. Background story of focusing her special area

Interviewer　For the last, we want to ask you just very briefly about your background story to become a nurse.

Mulnard　My sister was a nurse, and there are 5 children in our family. I'm the youngest. She's the oldest. She's 15 years older than me. So when I was very little, she went away to nursing school, and I just knew that I always wanted to be like my sister. So I grew up thinking I was going to be a nurse. But along the way I also wanted to be a teacher. So my sister said to me, you know, "it's fine for you to become a nurse but you have to make sure that you get the highest degree. Keep going to college. Get the highest degree because if you really want to be a professor, you're going to have to have a higher education than I had." My sister didn't have a college degree. I basically followed her advice. I got my bachelor's and then my master's and then my doctoral degree, and have pursued that path forever.

Interviewer　And they why you chose elderly people psychiatry nursing area? It means nursing related to Alzheimer's disease?

Mulnard　I didn't choose it initially. I got out of my bachelor's program as a brand new nurse not having any idea what I wanted to do. My first job was at Johns Hopkins as a nurse, and I just happened to be placed on the neuro-surgical floor. In caring for those patients as a new nurse, I was reminded that one of my brothers had a very severe head injury when I was just beginning in nursing school in college, and I cared for him.

The people that I was caring for on the neuro-surgery floor were so like him that I felt like this is where I should be. So I stayed there and really developed my neuroscience expertise and then became the research nurse for the neuro-surgery department as I got my master's degree and it just went on from there. Then when I came to California, and when I came to UCI after I finished my doctoral degree, there is a basic scientist on the campus and he was looking for a nurse with a doctoral degree. He's actually the second author on my general paper – Carl Cotman. He's a Ph.D. bio-chemist who had run a very successful basic science program in brain aging and Alzheimer's disease.

Also, he had developed a clinical program. But as he was trying to get more grants funded, he kept getting this criticism that, "you have no one on your grants who can really tie, who can bridge between the clinic and the basic science, who understands both sides." So he said, "I need to hire a nurse with a Ph.D., with a doctoral degree." I came along and he said, "You have a doctoral degree, you're a nurse, you're completely neuroscience focused. That's what I need." And so I started working with him in 1991, and basically have just focused on Alzheimer's disease and aging of the brain ever since then. So several things along the path have led me to where I am today.

Interviewer　We really appreciate your significant story and thank you so much for providing so long of your precious time for our interview. There are many other issues of that we wish to discuss with you about your plentiful and prominent experiences but hope to have next chance. Thank you very much.

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