



**The U.S. Medicine Institute
For Health Studies**

Edited Transcript — Forum for Decisionmakers

***Taking The Long View:
The Value Of Studies Over Time***

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Executive Summary

Long-term studies help answer specific questions about health risks and consequences over time and often deliver byproducts not originally envisioned but with ongoing, exponential value. Consequently, long-term studies are essential for informed policymaking and provide liberal return on the substantial investment they entail.

These were the views interwoven throughout a forum held on March 4, 2004, by the nonprofit **U.S. Medicine Institute for Health Studies**. The consensus among panelists and



participants was that long-term studies undoubtedly deliver great benefit to society at large, as well as to the specific group or groups targeted in a particular protocol. For example, the 22-year-old Ranch Hand study of agent orange exposure in Vietnam offers a trove of longitudinal data on the aging process in men — with much of this data yet to be tapped.

Forum deliberations found long-term studies of such value in answering questions relating to public health that they should become a byproduct of how “we normally do business” in healthcare — especially as digital patient records make collection and analysis of data amenable to routine analysis.

These edited proceedings present the remarks of panelists at the forum and the ensuing discussion among participants. Observations presented during the group’s deliberations include:

- Long-term studies are essential for the understanding of disease and, consequently, for disease management. They give policymakers the data and findings needed to make rational determinations about eligibility for compensation relating to occupational exposures.
- As long-term studies are done in future, they should be accompanied by “clear” business case analyses, “so that there really is a clear understanding of the rewards that come from the ... investment in conducting these studies.”
- As disease patterns among Americans shift away from the acute toward chronic, multiple conditions, long-term studies will assume a greater role, because they allow examination of particular populations and pick up a “different set of information” about risk factors than short-term clinical trials can. Decades-long studies such as the Framingham Study of risk factors in heart disease and the Harvard Nurses Study of risk factors for major chronic diseases in women are well-known examples of the importance that long-term investigations can have in shaping health practices and policies.
- Long-term studies conducted by federal agencies need the stability afforded by designated funding, rather than having their funds come through basic agency appropriations.
- The Veterans Affairs and Defense departments use long-term studies to help answer questions about potential

deleterious health effects in troops from exposures during deployments — questions now anticipated for every deployment: Who was exposed; are those exposed showing unusual disease; are those exposed dying at unusual rates or from unusual causes, or has their health changed over time; do those exposed show higher incidence of cancer(s); do the children of those exposed exhibit higher rates of birth defects?

- A classic longitudinal study is the Air Force Ranch Hand Study, initiated in 1982, which has seen the collection of 74,000 biological specimens and 19,000 x-rays and has involved more than 13,000 physical exams, more than 20,000 questionnaires and thousands of records on conception and birth. In addition, more than 2,800 death records have been obtained.

This study is scheduled to terminate in 2006, but that directive has met with controversy on grounds there is much information yet to be mined. To resolve whether the study should be continued, Congress has asked the Institute of Medicine to examine the scientific merit of retaining and maintaining the medical records, specimens and other data collected for the study; the potential value of extending the study; and the advisability and costs of making study specimens available to independent researchers.

- An important longitudinal study that is just beginning in the military is the Millennium Cohort Study, which involves an initial study group of 10,000,

with 20,000 more to be added this year and another 20,000 to be added in 2007. The study will examine employment exposures and post-deployment consequences in a group exposed in Kosovo or Southwest Asia, compared to a nonexposed cohort.

Study participants will be followed every three years by postal surveys; demographic and health information will be obtained and correlated over a 22-year period.

- The Veterans Affairs Department regularly turns to the Institute of Medicine for objective, independent literature reviews of the long-term effects of exposure on troops — for Vietnam, for the first Gulf war and for the current Iraq conflict, for example. Results are used to help set compensation policy.
- Tri-service longitudinal studies might best be centralized and coordinated through the Uniformed Services University of the Health Sciences, which encompasses all service branches as well as the U.S. Public Health Service.
- Doing longitudinal studies often is difficult in the academic setting, where there is pressure for immediate pay-off. At the same time, studies produced by federal researchers all too often are rejected by regular scientific journals as being of limited interest because they focus on military or veteran populations.

Forum Proceedings

Moderator — Susan H. Mather, MD, MPH

We're here to look at the value of long-term studies. That title presupposes that there might be some controversy about the value of long-term studies, and I have to say in full disclosure that I am biased to the view that long-term studies are not only worth their very considerable expense, but absolutely essential to policymakers. I've been in a policymaking role almost 25 years now; without long-term studies, we would have no hope of answering the very important questions that our stakeholders want to know and need to know the answers to — whether you're talking about the natural history of AIDS, whether you're talking about the value of hormone replacement therapy for women and the risk-benefit analysis — that is something that we are only just beginning to understand, as the result of a long-term study — whether you're talking about natural risk factors or risk factors for heart disease, the risk of high blood pressure, for which we've had ongoing studies now for many years, or whether you are talking about the narrower focused area of occupational exposures.

The healthcare industry is a very dangerous industry, with a higher incidence of violence than the Post Office — something that comes as a surprise to many people who just read the popular press. There are also a lot of dangerous chemicals in the healthcare industry, a lot of activities that cause problems that are long-term in the way of ergonomic problems, et cetera.

Of course, you get even more narrowly focused if you look at specific exposures: Agent Orange in the Vietnam War; the multiple exposures that were present in the last Gulf war. And, just the question of what is the long-term effect of having participated in combat or having participated in numerous deployments on the health of individuals? We have to ask, in modern times, in 2004, is that effect different for men than it is for women? Women now play a very important role in the defense of this nation. We probably could not defend it without them, even if the draft were reinstated.

So, I'm not *at all* anti-long-term study. In fact, one of the hopes that I would have for this symposium is that we come away with more ammunition to support long-term studies and to help people understand their value, because they are very expensive. There is no doubt about that. I don't pretend they are cheap. But, well-designed long-term studies, in my opinion, are worth it.

Panel 1: How do long-term studies demonstrate their value?

Mark Brown, PhD — *Director, Environmental Agents Service, Veterans Health Administration*

Michael Stoto, PhD — *RAND Corp., Chairman, Ranch Hand Advisory Committee*

David Tornberg, MD, MPH — *Deputy Assistant Secretary of Defense for Clinical Programs and Policy*

Mark Brown:

VA sponsors a lot of long-term health studies — studies that Congress has made us do in the interest of trying to figure out what's going on with veterans, and also quite a few studies that we've done under our authority to answer questions we think we need to have information on about veterans' health issues. I hesitate to come up with a number, because it's so big, but we must spend many millions of dollars each year on these studies. So, it's a reasonable question, what do these studies over time tell us — how do they inform our policies towards veterans?

I think that the answer is really very simple. Based on our experience dealing with veterans from the 1991 Gulf war, for example, and before that, veterans from the Vietnam war, it became obvious to us that we are going to get a lot of questions from veterans, from their families, from Congress about what their health status is, and we're going to have to have answers to those questions. We're going to be asked if they are dying at unusual rates — Vietnam veterans or veterans from the first Gulf war, for example. Is their reproductive health normal; are they having unusual birth defects among their offspring, among their children; has their health changed over time since they've returned from their combat mission?

We're going to get sometimes very pointed questions about is this particular group of veterans' showing higher rates of cancer than they should be. Finally, probably the key question we're going to be asked, should a particular group of veterans receive disability compensation, special disability compensation at higher rates, because of something that happened to them during their particular combat deployment? We know from our experience that we're going to have to have solid, reliable, scientifically sound answers to these very highly charged questions.

I want to talk about the magnitude of VA's mission to serve veterans. There is a lot of money involved. There are a lot of veterans, a lot of Americans involved in our programs. I want to give you the sense of the scope and magnitude of our charge and why we have to have these answers. In a nutshell, the VA is responsible for providing federal benefits to veterans and their dependents. It's the second largest of all Cabinet-level departments, and it operates a nationwide program for healthcare, financial assistance, burial, and other benefits for veterans. It's an enormous mission.

About a quarter of all Americans, about 70 million people, are at least potentially eligible for VA benefits and services because they are themselves either veterans or they are dependents of veterans or survivors of veterans. Probably for most people, the most visible of VA benefits and services is the healthcare program that we operate. VA's healthcare system includes about 163 hospitals spread out all across the country. Just to give you the scope of the medical care that we offer for this group of Americans, more than 4-1/2 million people received care in VA healthcare facilities in 2002. VA's outpatient clinics registered approximately 46.5 million visits. That's a lot of healthcare.

VA's compensation and pension benefits are equally important for veterans. In fiscal year 2002, VA spent \$25 billion in disability compensation, death compensation, and pensions. About 2.7 million veterans receive disability compensation from VA each year. VA disability compensation — what does that technically mean? It means these are monetary benefits that we pay to veterans based on their disability from an injury or an illness that was either incurred while they were on active duty or was exacerbated somehow; it was made worse by their military service.

So, VA functions as a kind of workmen's compensation for our military population. If you are disabled to some degree, to a small degree or a large degree, the VA will compensate you for your lost ability to work, as a veteran. That means that the disability compensation has to be related to your deployment. It has to be for something that happened to you while you were on active duty. The amount of the disability compensation is based on amount of disability. A person with a greater disability would receive a bigger check each month and a person with lesser disability that they incurred while they were on active duty would receive less money. It's a workmen's compensation program.

It's an easy program to implement conceptually if the injury is something obvious like a shrapnel wound or hearing loss that occurred as a result of some activity during active duty, firing a cannon or something like that. Hearing loss is a common disability that VA compensates for among veterans. On the other hand, it's not so straightforward if the disability is related to a chronic illness that is of perhaps unknown etiology. The classic example that we face is a veteran, 30 or 40 years after he got out of military service, who puts in a claim for some type of cancer that he or she argues was caused by an environmental exposure that occurred many decades in the past. It's very difficult to evaluate that and to make the connection with their military service.

Disability for chronic illnesses is a little harder for us. Evaluating disability claims for chronic disabilities based on military environmental exposures has become a big issue for VA. That issue has fueled many VA-sponsored studies on long-term health effects. I think from our prospective, the answer to the question of how do long-term studies demonstrate their value is, how well do those studies help us to understand the health status of any group of deployed veterans, and how well do they inform VA healthcare and compensation policies?

I'd like to turn to a couple of examples. The granddaddy issue for VA that should come immediately to mind is, of course, the Vietnam experience. As veterans started returning from service in Vietnam in the '60s and early '70s, many of them had growing concerns about how their health may have been affected by exposure to herbicides during that conflict. Many veterans who were returning, as they started developing health problems, attributed them to exposure to herbicides, and started asking for healthcare and disability compensation based on those concerns. This included issues such as birth defects among the offspring of these returning veterans that they attributed to herbicide exposure. I think it's fair to say the VA had a lot of difficulty in trying to respond to that issue, in part, at least, because at that time the literature, our scientific understanding of health effects of dioxins in particular, was really in its infancy. Our appreciation that dioxins could cause health effects was really just growing. It was just coming into fruition.

What VA tried — this is ancient history now for us — but what VA tried to do initially is I think very logical. We tried to establish a VA scientific advisory group that would review the literature on dioxin and herbicide health effects and try to help us through this and try to think about how we could compensate. That seemed like a very logical approach, but it turned out not to be completely satisfactory, because basically VA was perceived by many veterans and veterans advocacy groups as having a conflict of interest — the same agency that was reviewing the scientific literature on health effects from dioxins and herbicides was also the agency that was responsible for doling out benefits. That was perceived as a conflict of interest; one group had conflicting responsibilities.

So, what to do? Congress thought about this, and VA thought about this. The answer was, we turned to the National Academy of Sciences' Institute of Medicine and established a process which is still ongoing today. That IoM process has been so successful that we've transformed it now and use in a variety of other areas to answer similar questions. But basically, in response to concerns about Agent Orange health effects, Congress asked VA to turn to the IoM for help. In 1982, VA requested the IoM to conduct an independent review of the available scientific and medical literature on human health effects from exposure to herbicides used in Vietnam. The first IoM report was released in '93, followed by four major updates, special reports in '96, '98, 2000, and the most recent report we received is 2002.

Each 600-page biannual report costs us about a million dollars. Because of the enormous amount of literature — essentially all literature that could be pertinent is reviewed — it requires about two years to complete. The original and biannually updated reviews are unique in that they literally examine all published scientific studies that are pertinent, that are relevant to the human health effects from exposure to herbicides and contaminants like dioxins, regardless of whether the particular study was looking at veterans or some other group. If you look at these studies, look at the analyzed health effects from herbicides, most of the human studies involve occupational studies of workers, civilian workers in factories where these chemicals are manufactured, or survivors of accidents, particularly civilians who are at the scene of an industrial accident and were exposed to very large amounts of these chemicals and therefore become reasonable subjects.

Few of the studies — some, but not many of them — actually involve Vietnam veterans. Based upon these IoM reviews, the VA has made some policy calls to presumptively recognize about a dozen diseases for service connection for Vietnam veterans — mostly cancers, and one birth defect for children.

To summarize this approach, I think this deliberative process has been very helpful in allowing VA to establish compensation policies for veterans exposed to herbicides which are widely seen to be both fair and scientifically grounded. The strengths of the program are its breadth and thoroughness and the independence and prestige of the scientific review body that conducts this for VA. In fact, the process has been considered such a successful approach that it has been adopted by VA in a number of other areas where we've had similar environmental health and environmental exposure questions. A good example of how VA has generalized the IoM process is the reviews that we've sought on health effects in veterans of the first Gulf war, the 1991 Gulf war. It had some parallels to the situation with the Vietnam war and Agent Orange, and basically, in response to growing concerns about how environmental hazards encountered during the 1991 Gulf war may have affected the health of U.S. servicemembers, Congress requested VA to contract with the IoM to conduct reviews of the scientific and medical literature on long-term health effects from exposures to Gulf war environmental hazards.

If you look at the legislative language in that bill, it looks exactly like the legislative language that set up the Agent Orange process. Somebody just copied it and crossed out Agent Orange and put in Gulf war risk factors. Literally, that's what it looks like. The first two-year IoM review was released in 2000, and it examined long-term health effects of sarin, depleted uranium, certain vaccines, pyridostigmine bromide. There is a second and third review; the last review will come out in 2004, and it's looking at fuels and combustion products. I would just say that from a policy standpoint to date, VA has not established any presumptive service connections to any specific health effects among Gulf war veterans related to any of these exposures, based on the information provided to us in these reports by the Institute of Medicine.

Now, I want to talk about Project SHAD. While it may be obscure to many of you, to us at VA it has become a major issue. It's a recent example where we again turned to the IoM for assistance. Project SHAD is short for Shipwork Hazard and Defense. It was a series of tests conducted by the Department of Defense during the 1960s, apparently to determine the vulnerability of U.S. warships and attack ships to attacks with chemical and biological warfare agents. The tests involved live chemical and biological warfare agents as well as simulants for these agents. The tests were originally classified, but we know that about 5,000 servicemembers were involved.

When the story broke a couple years ago, the reaction of many veterans was that they were outraged. In their eyes, they were the victims of secret chemical experiments that were done without their permission — at least that's how some of them saw it, as unwitting subjects of secret experiments. Secondly, many veterans and their families were concerned that maybe their health had been affected somehow by these exposures that would have occurred 30, 40 years ago.

Faced with this controversial issue, how was VA to evaluate claims that might be coming in relative to these types of exposures, to these SHAD participants, mostly Navy, a few Army people? To help address this issue, we turned to the IoM, we asked them to conduct a retrospective epidemiological study to evaluate the long-term health consequences of participation in these tests. Subjects are the entire cohort of 5,000 SHAD veterans, so you could say it's truly population-based. They will be compared to a control group of comparable servicemembers who were not involved in SHAD, and we expect the results in 2005. The results are going to serve VA a couple of important purposes. The most obvious is that it may affect our disability compensation policies for these veterans, depending on what we find. But of course, also, it will answer some of the concerns that veterans have about how their health may have been affected. We think that's very worthwhile.

VA also conducts its own epidemiological studies, carried out by our own researchers. For example, we are conducting an ongoing mortality study and some limited morbidity studies of Vietnam veterans, and these also have proven quite valuable. We did a mortality study of U.S. Army and Marine Corps Vietnam veterans, and basically, we were able to show, looking just strictly at mortality in comparison with a control group of era veterans, that there are statistically significant excesses of death from laryngeal and lung cancer.

As an example of how such studies can have a tremendous effect on VA compensation policy, I want to talk about a study that we completed recently on the health of women Vietnam veterans. There weren't many women Vietnam veterans, but there were some. The VA conducted a study on the long-term health of women Vietnam veterans in comparison with a control group. One of the causative findings was that women Vietnam veterans had greater rates of birth defects among their children compared to controls. This wasn't an Agent Orange study, it's a study about the effect of participation in that war itself, because it considered all women Vietnam veterans. Based upon that study's findings, VA asked Congress for, and got, the authority to provide compensation and rehabilitation benefits, as well as other benefits for the children of women Vietnam veterans. So that study and that analysis of what was going on with that population had a tremendously significant effect on our compensation policies for that particular group of individuals.

Interestingly, there is no ongoing general population-based longitudinal "epi" study on the long-term health status of Vietnam veterans, so we don't really know too much about what's going on with them exactly. I think the focus has been on Agent Orange; we put a bright spotlight on Agent Orange, as if somehow all health problems of Vietnam veterans today are due to Agent Orange. But, if you think about it, there were a number of other risk factors in that war — like regular bullets, for example, or just the experience itself of service in Vietnam.

We're in much better shape, I think, with epidemiological studies on veterans from the first Gulf war, because for some years, VA has been conducting a longitudinal

population-based study to evaluate long-term health status of these particular veterans. Numerous publications have come out of that study. Similarly, one of the more useful categories of studies that VA has been doing on Gulf war veterans is an ongoing mortality study. Mortality studies go until the last veteran breathes his/her last breath. We have a study looking at mortality of Gulf war I veterans, and the results, I think, are very striking. The results of this ongoing study show that veterans of the 1991 Gulf war have essentially the identical mortality and cause-related mortality to era controls. Secondly, match them up to civilians, for age and gender and other demographics, and mortality is about half, less than half actually, than their civilian counterparts. People who tend to join the military tend to be healthier, and that's what I think we're seeing there. That observation has had a profound influence on our thinking about disability in that population.

I'm certain we're going to be asked to do similar studies on veterans now who are in Operation Iraqi Freedom, Operation Enduring Freedom. We're certainly going to be doing mortality and morbidity studies on that population as well.

I'm going to talk just briefly about DoD's Millennium cohort study, which is the military equivalent of the Framingham Study. It's an enormously ambitious study. It's going to be very interesting to both VA and DoD. It's something that VA is very interested in participating and cooperating with.

As I mentioned at the outset of my remarks, VA supports and conducts a great deal of research on long-term health effects of veterans. The value of this research for VA is to help us respond to questions and concerns raised by combat veterans, their families, from Congress, and from the media about possible impact of military service on their health over time. We know at VA that we're going to face health-related questions about every group of servicemembers who are deployed to combat. Currently, and in the future, for every group of soldiers who are deployed we are going to be asked basically the same questions: Are they showing any unusual diseases? Are they dying at unusual rates or from unusual causes? Has their health changed over time? Are they having reproductive health problems, including birth defects? We will certainly be asked, Are they getting cancer at higher rates than they should be?

The point or thrust of these questions really focuses us all on disability compensation. We're going to be asked, for a particular group of veterans, should we be compensating them for specific disabilities based on something that we understand happened to them, an environmental exposure that happened to them during their military service? The wide range of long-term health studies and reviews sponsored by VA will help to give us the solid, scientifically sound information that we'll need to answer these questions in the future.

Michael Stoto:

I have to begin with a bit of a disclaimer. First, it's a bit uncomfortable for a scientist to be talking about somebody else's study. I'll be talking about the Ranch Hand Study, which I'm involved in as the chairman of the advisory committee, but not really as the PI [principal investigator] in any way. I have also been involved for a long time with the studies done at the National Academy of Sciences that Mark Brown mentioned; I was the staffer for the first one. But I can't speak for them today. And I work for RAND, which does a lot of work in military health and has long been associated with the Air Force. But again, this is not a RAND project, so I can't speak for RAND. So, this is really my own opinion that I am giving.

Agent Orange is an issue that has been with us for long time, and I think it will be with us for a long time. Back more than 20 years ago, with direction from both the Congress and the President, the Air Force was directed to conduct a 20-year prospective epidemiological study of herbicide exposure and health mortality and reproductive outcomes in the veterans of Operation Ranch Hand. Operation Ranch Hand was the operation in which fixed-wing aircraft were used to spray herbicides in Vietnam. A number of herbicides were used: Agent Orange was the most common one.

The study was designed in the late '70s and was put into place in the early 1980s. It involves an index group of veterans of the Ranch Hand operation, about 1,200 of them, essentially all of them. It has a control population of Air Force veterans who served in Southeast Asia at the same time. There are around 19,000 of them. There is a specially selected group of controls that are matched on age, race, and military occupation who are followed more closely than all of the controls. So, we have a study of something like 3,000 men who have now been studied for over 20 years, based on their exposure to herbicides as part of Operation Ranch Hand back in the 1960s and early '70s.

The first exposure index was simply being in the Ranch Hand cohort. Over time, a variety of other measures of exposure were developed, a number of different measures that focused on how much herbicide was used and how much the men might have been exposed to. Then in the 1980s, a method was developed to actually measure dioxin, which was a contaminant of Agent Orange, one thought by many people to perhaps be the primary cause for its negative health consequences. That could be measured in serum. Now of course, by the time the test was invented and applied, more than ten years had passed since the people had served in Vietnam. There's some difficulty in extrapolating back and knowing what the precise measure of exposure was, but it's a biomarker that has a lot going for it. Many of the results that have come out of this study are because of the availability of that biomarker.

The Ranch Hand Study is not a study of Vietnam experience. Everybody in the study, both the cases and the controls, served in Vietnam or Southeast Asia. There have been other studies that have attempted to look at the Vietnam experience, per se. I also want to make the point that beyond the original goal, there are other things that have come about. For example, what we have is a very intense longitudinal study of men aging, with lots of

information gathered, with a variety of information about health risks, health outcomes, and gathered in a longitudinal way. I think there is a lot of value there that has not been fully tapped as of yet.

NIOSH [National Institute for Occupational Safety and Health] has worked on a number of occupational studies, and others around the world who have done occupational studies where the exposure levels are much higher [than in Vietnam ground troops], and there was a factory explosion in Seveso, Italy, where people in the neighborhood were exposed to far higher levels. But in this range of available studies, the Ranch Hand Study is a relatively highly exposed cohort, which makes them valuable for epidemiological studies, because that increases the statistical power, our ability to find things. The study was designed with multiple endpoints, looking at mortality, morbidity and reproductive outcomes, and it was designed to have repeated physical examinations, interviews, mortality assessments and so on. In addition, biological samples of various types were drawn at various times. All of the veterans' medical records were reviewed, and there were very detailed military and civilian employment histories taken.

The study was designed in the late '70s; of course, the men were exposed in the '60s to 1971, and then there were very intensive physical exams every five years, starting in '82. There was an extra one in '84 or '85. And the last one has just recently been finished in 2002. A variety of morbidity endpoints were examined as well as mortality of all causes and specific causes. The results have been published quite extensively in reports put out by the Air Force Health Study every five years that the advisory committee that I chair helps to review. I think maybe even more importantly, a whole long series of publications in the scientific literature has been put together.

I'll mention some of the areas where there have been interesting findings. The one that I would highlight relates to diabetes, where there has been a consistent finding of elevated diabetes and risks for diabetes in the men with higher levels of dioxin and higher level of herbicide exposure. I highlight it because the Ranch Hand Study has been relatively important in the scientific literature on that subject. In many other areas, the Ranch Hand Study contributed to the body of evidence reviewed and then led to VA determinations of service connection.

As you might imagine, when you start with a couple thousand men and follow them intently for more than 20 years, you have lots of information. Let me just highlight some of that. One is, the number of veterans who were examined in the Ranch Hand and the comparison group going back to the first study in '82, and including the latest study in 2002 — roughly 2,000 men per year have gone through a very intense physical exam. As a result of this and the other efforts of the study team, quite a lot of material has been gathered: 74,000 biological specimens, 19,000 x-rays, more than 13,000 physical exams, more than 20,000 questionnaires, records of death in 2,800 cases; information on conceptions in many thousands of cases.

This information has all been gathered, stored at the Ranch Hand study site in San Antonio and is being archived and recorded. A lot of the information is scanned in so it

can be saved digitally. I think it's also important to recognize that there is a lot of human capital involved in the study team. There are people who know where the records are, and they know what the files contain and they know the details of the study. There are people who are civilian and uniformed employees of DoD, and a number of contractors who have worked on this over time.

That is important, because the critical issue that's facing this study is that after more than 20 years, the study is scheduled to come to a conclusion in 2006. Recognizing that that is about to happen, Congress passed a provision last year in the Veterans Benefits Act of 2003 calling for a new study by the National Academy of Sciences to address five issues: The scientific merit of retaining and maintaining the medical records, specimens and the other data; the obstacles to retaining these materials; the advisability of independent oversight for activities involving these; the potential value of extending the study; and the advisability and the costs of making these specimens available to the independent researchers.

I understand this study is moving along and will be starting soon. I think these are really the right questions that need to be asked. There is a potentially very important resource that is available in what's been done in this study up until now. We need to think carefully about how to make sure we don't as a nation squander that resource.

There are obstacles — for instance, simply the logistics of saving all of those biological samples. Is there some way that some information can be gathered from them, rather than saving all of them? How do we deal with the privacy and confidentiality issues of the men who are the subjects? Of good news along this line is that in the last round of examinations, the men were asked whether they gave their consent to use the records and materials in the future. They were asked about further studies about Agent Orange, further studies of Agent Orange and other military health issues. The vast majority of them said yes to Agent Orange and other military health issues. Now, they did not ask about the use of the data and materials for health studies beyond Agent Orange and military health issues. I think maybe even the biggest potential is in that area. So, that might involve going back to the participants to ask for further permission. But, this suggests that quite a number of them are interested in making a contribution in this area.

Now, what is the potential research value? The VA's use of the Ranch Hand Study and other studies have really made it clear that the study already has made quite an important contribution to resolving some of the health effects of Vietnam service, and particularly exposure to Agent Orange. The study has also made an important contribution to our understanding about the health effects of herbicides in general, particularly of dioxin, which was a contaminant of some the herbicides. That's been a very contentious policy issue for years.

In the future, I actually think that the value may go further. We had a lot of information on men and occupational exposures of all sorts that was gathered to study the effect of herbicides, but in fact, there's quite a lot of information there. We also have a study of thousands of men who are in a normal aging process, and there is quite a lot of interest in

that issue these days. So, my sense is that the scientific community, if it knew about this resource, these data that have already been gathered, these samples that have already been gathered, and if this information and these samples could be made available to the scientific community, in occupational health, in aging and in other areas, there actually could be far greater benefits that come out of this study than have been seen to date.

I hope that the panel that the Academy is setting up will consider those issues and to flesh those out and to bring this resource, the potential availability of this resource, to the attention of the scientific community, where I think there could be quite a positive benefit.

David Tornberg:

My role clinically over the years has been primarily a consumer of the product of longitudinal studies. I must say that I feel they are essential; essential to practice of medicine, essential to our understanding of disease, disease management, and without them, we would be really adrift.

The two very important studies that I think demonstrate this point are the Framingham Study, a 50-year-old study, that was absolutely critical to our understanding of the risk factors involved — and in fact, developed the term "risk factor" — in cardiovascular disease and a variety of other associated conditions. Similarly, the Harvard Nurses Study, an elegant study currently in progress, has made a significant contribution to women's health in our understanding of heart disease, osteoporosis, breast disease, gastrointestinal disease, and it goes on and on.

The understanding, the illumination, and the treatments that have been a consequence and a benefit to society are a result of these studies. No less to the government is a benefit from the studies that my colleagues have enumerated today, and the very rigorous approach that the federal government adopts in trying to shed some illumination on the consequences of occupational exposure in the military service. This, too, is essential.

What is the threat to long-term studies? We've indicated that there may be a societal change here, and a drift, because of the expense in conducting these studies. I would have to say, from a business standpoint, it's a failure perhaps — or would be a challenge in the future — to demonstrate the return on value that these studies provide. A clear business case analysis and the benefits that have been derived need to be applied as we go forward, so that there really is a clear understanding of the rewards that come from a very modest investment in conducting these studies.

From a scientific point of view, they save us, quite frankly, in my opinion as a consumer and a clinician, from the many, many, many shortcomings that are inherent in a lot of our short-term quick studies, very frequently, the design or the conduct of which suggests that they have been done in a manner to demonstrate the underlying premise at the outset.

That's of great concern. It feeds junk science; it feeds anecdotal thoughts about causation, and in general, undermines the integrity of our scientific body of knowledge, and actually threatens the financial stability of our institutions. That applies broadly, not just to industry, where occupational injury — naturally, prevention, and treatment is a major concern, but so are the downstream disability payments associated with alleged exposures and consequence.

I have been intimately involved in this over the last few years, and it's always astounding to see what spurious causations are drawn. There is significant secondary gain associated with these issues. We can't be blind to it. They certainly affect the federal sector. Many of the issues that VA deals with — hearing loss, for example, is a whipping boy in the industrial world, and not the less with VA. There are many, many causes of hearing loss. Some of it may be occupationally derived, the majority of it is probably boombox and shotgun-related as much as it is occupational exposures. When you study, as I had the opportunity to do, and see the implementation of our hearing loss program at Newport News, it was an elegant program; it served our company well. The documentation was clear, and the information was available to seriously challenge a number of disability claims in this arena.

It's very important as we go forward, there is certainly an equity issue here that can be addressed well by well-conducted longitudinal studies. I would hope that they would always be a very important part of our armamentarium, and that we would be willing on a governmental basis to finance these. The underlying costs, if we turn ordinary diseases of life into disability, will have significant societal impact. I would submit that the charitable and humane approach would be to identify them as ordinary diseases of life and save society the cost burden for underwriting disability payments in some of these arenas, allowing us to divert these important resources to prevention and promotion areas that can actually mitigate these ordinary diseases.

In terms of studies, our longitudinal study, the Millennium Cohort Study, which DoD is engaged in, I think has the potential for providing major contributions to understanding the impact of employment exposures in our population and the post-deployment consequences, with their impacts on health. The study involves 100,000 initial members, and this year and in 2007 we will be adding 20,000 more members to the study. It's a cross-sectional study of these 140,000 servicemembers. The base is composed of 30,000 who have received exposure in Bosnia, in Kosovo, in Southwest Asia, and will be compared to a non-exposed group.

They are going to be followed longitudinally every three years by postal surveys, and demographic and health information will be obtain and correlated over a 22-year period. It has many, many opportunities, and that combined with our serum repository provide DoD with a wealth of opportunity for investigation, and also for the opportunity for a number of potentially nested smaller studies. The investigators themselves include scientists from the Army, the Navy, and the Air Force. The Scientific Steering and Advisory Committee includes five distinguished external scientists and three representatives of the largest veterans service organizations. Naturally, we are very

closely engaged in this study with our colleagues at the VA, for whom there will be significant impact in the information and outcome of this study. Again, it will involve 140,000 veterans and it will go until 2022. We look forward to it.

Discussion:

Susan Mather: Military health, even though a large portion of Americans have served in the military, is considered a very specialized field of inquiry. Where does the responsibility lie and how do you balance the perceived conflicts of interest in funding such long-term studies? I don't think anybody questioned funding the Nurses Study, and the Framingham is well-established, but when you talk about specific military populations, where does the responsibility for both planning and funding these studies come in?

David Tornberg: I think we have an essential interest, and, more importantly, a responsibility to conduct these studies. We have an obligation at the outset to provide for the safety and protect the safety and welfare of our troops, the fighting men and women. We as a society ask quite a bit, and we must give a good bit as well. I think the concerns raised by veterans — we certainly have heard them as very vocal expression since Vietnam, and I've been struck by the impact that it's had on my patient population as well, as they migrate into the civilian sector, and continually relate many concerns that they've had to their service exposure.

I think it's essential that we engage in these studies. From an economic standpoint, it's important that we do so, simply to have an equitable disability system, as executed by both the services and the VA. There is a fairly large dollar amount associated with this, and I don't see any way that we can conduct that in a reasonable fashion if it's not science-based, evidenced-based determinations. So, it's critical to have that information. The studies are critical, and they have to be understood as such. It would appear, from a governmental standpoint, that Congress perceives it that way as well. I think that's where the funding needs to come from; it can't come the Defense Health Plan, and it can't come from, I feel, the basic DoD appropriations.

Susan Mather: In other words, designated funding.

David Tornberg: Designated funding.

Michael Stoto: It's a fascinating and very important question. I want to remind everybody that I am speaking for myself, not for any of these organizations that I might have been associated with. I think there are really two issues here. One is the credibility of the work, and the other one is the interest in seeing that the study is carried through and used appropriately.

In terms of credibility, I believe there was a report by the National Academy of Sciences long ago on the first round, basically on the plan for the Ranch Hand Study, that suggested it should not be done by the government for reasons of credibility. The committee that I chair was set up, I believe, as a response to that, to try to give it some credibility. My sense is that the staff has done a fine job and deserves credibility, but of course, you can't guarantee it when you're talking about a study many years into the future. I think that kind of advisory committee is a step in the right direction, but an imperfect one, in part because, as a way to distance the committee from the Department of Defense, it was set up under the Department of Health and Human Services. I guess it was even HEW at the time. And their interest in it has not always been as high as some people would like in carrying this through.

Of course, probably the Department of Veterans Affairs has a bigger interest in these than either HHS or DoD. It's no surprise that this legislation for the study that I mentioned came out of the Veterans Committee between the House and the Senate. I think the question of how to get these different agencies to pay attention is a tricky one.

Susan Mather: What about NIH? Should there be an institute of military medicine or military health in the National Institutes of Health in Bethesda?

Mark Brown: The comments that I'm going to make are quite personal. I can't tell you how many times I have tried to get articles published in medical or scientific journals about veteran or military health, and you get the answer back from the editors saying, "Well this is not of interest to our doctors or our readers, because this is about military health." I think that that's an extremely shortsighted viewpoint about it. If you look at, for example, the environmental exposures that were of concern during in the first Gulf war, some of them were more or less specific to military life, but the vast majority of them weren't. I mean, oil well fire smoke for instance. That's something anybody could be exposed to. Even uranium is something that we have a large, significant civilian population who are exposed to.

These are general public health issues, and I think my perception is that there's some kind of disconnect between military health — it's like military people are some other species — and civilian health. When we try to work with our colleagues, for example, in the civilian sector, in CDC or HHS, their parent agency, sometimes it's hard to get them to see military health issues as something that they should be interested in. They tend to be biased toward the civilian, and they just see it as a firewall. There's civilian health, and military health is somehow something completely unrelated. I think that's unfortunate, because it prevents certain collaborations which otherwise might be quite beneficial.

But, in a practical sense, ultimately DoD and VA are going to end up being responsible for funding research. For example, the very large, somewhat expensive mortality studies that VA carries out on Vietnam veterans or Gulf war veterans — it's unlikely that anybody but VA is going to do something like that, because of our connection with it. That's just the way things have been falling out, I think.

Al Buck: I'm with Martin Associates. It would be helpful to me to hear a comment or two about — and this may sound a little bit basic — what makes a long-term study a long-term study. I think I'm hearing money, time, and congressional imprimatur.

But I'm also thinking I'm hearing that there really is no — and I think I hear this — that there really is no established process that identifies these projects, develops these projects, manages these projects, reports these projects, et cetera. I'm wondering if that in itself isn't a major obstacle. By the way, I'm one of the choir, because I think we should be moving in this direction; it has enormous value. But I'm wondering if some of the very basic stuff is in the consensus pool in the general mind.

Mark Brown: This is a fascinating question, and I'm going to put my academic hat on for a moment. When you think about this from the perspective of an academic, it's hard to imagine that there are ever any long-term studies, because academics have to get payoff in terms of results, soon. Putting things together that are not going to pay off for years is a pretty low payoff activity.

The head of the Nurses Health Study at Harvard is a friend of mine, and I've seen what comes out of that. But I also wonder how they ever made the commitment to that years ago. The Framingham study is another example. I think the answer is that there needs to be something beyond — we can't rely on the normal peer review investigator-initiated process. I do think obviously time and money [are needed], but also something like congressional or government interest. I have in mind the National Children's Study, which is a major longitudinal study that's about to begin that will involve approximately 100,000 children from before the time they are born — from shortly after their mothers conceived them, maybe even before that. It took a congressional mandate to get that off of the ground. I think that probably is something that is going to pay off a lot, and I don't imagine that it would ever have happened without a congressional mandate.

Tee Guidotti: I'm a professor and Chair of the Department of Environmental Occupational Health at GW [George Washington University]. I remember that my mentor in medical school was the first medical director of the Framingham Study. He got things going, established everything, went off, became a dean, had a completely different career, and about 25 or 30 years later, went back to the Framingham Study to be the director and finished out his career. So there is a longitudinal career in a longitudinal study.

I want to make a couple of observations. One of them has to do with the value of longitudinal studies in the private sector, which was briefly mentioned by Dr. Tornberg. I think that just as contemporary biotechnology and genomics is solidly based on federally funded biomedical research and would never have happened without that, one could say that the future of health services, especially reform and profitability of managed care organizations, and the benchmarking, appropriate care, and so forth, is also solidly grounded on largely federally funded research that has to do with developing new approaches to drugs, efficacy studies, and outcome studies. So, I think that the private

sector very much has a stake in longitudinal studies, and I think that there should be cost-sharing, although I'm not very optimistic that that will occur. I think that there is a case to be made that the private sector benefits from this area of research just as much as basic biomedical research.

I think the real issue here is actually the cost-effectiveness of the way that longitudinal studies are conducted. They are expensive, and that causes a great problem, particularly on the front end in terms of who is going to bear the costs. I've personally given some thought to this in other contexts. I think that there may be other ways to put together different types of longitudinal studies; for example, data repositories that look at what happened much later, particularly if unanticipated issues arise, to go back to the original contact information and subject information.

There are HIPAA issues here. I think that going back and looking at HIPAA and trying to distinguish congressional intent between the commercial use of this information and research use of this information is going to be very important. Otherwise, longitudinal research will kind of be choked off by HIPAA over time.

We can maximize the utilization of data from rather expensive studies by enhancing them and incorporating other elements of design and information that we gather. I think that there are some areas for getting some limited additional value from public health surveillance activities that can lend themselves to a little bit of an enhancement to get longitudinal data from them.

David Tornberg: I think those comments are excellent; you have really identified a number of the sticky wickets, if you will, in the process. I will say that, regarding your concept of corporate sharing, one could submit that it already exists in terms of corporate taxes, to the extent that corporations are paying their fair share of the way in addressing society's needs. So, I do think that the economics of it, the manner in which it's conducted, on a broad sense confronting the government — it's important that it be rigorously done in a businesslike, yet scientific fashion, where the outcomes aren't compromised exclusively by the efficiencies introduced from the business standpoint.

In terms of the issue of military studies and the opportunity to consolidate these, in reference to the National Capital Area, I think we have an excellent opportunity and submit that the Uniformed Services University would represent a very important component in going forward in such a construct. It's tri-service. It involves the Public Health Service as well, and it has the very best interest of our servicemen and women at heart. So I would submit that if we were looking for an organization to centralize these studies, I would certainly recommend the Uniformed Services University.

Mark Brown: I would just make a point that occurred to me during your remarks, and it's obvious to me, but maybe it doesn't come across as obvious. Some of the studies that VA does on mortality and morbidity of veterans, we do because we have special resources about veterans. And when it comes to, for example, looking at mortality of any group of veterans, we already have an enormous database. We have to watch when

veterans die. So we have internal resources — there is a reason why VA conducts certain mortality and morbidity studies. We have the resources and access to certain types of data that nobody in the private sector or in the academic world has. So I think that's a good thing, maybe because it means we can do things more efficiently.

Our mortality studies are actually relatively inexpensive to do because we already have access to that data.

Susan Mather: Dr. Zimble, since you are here, would you like to comment on the possible role USUHS might play in this?

James Zimble: [President, Uniformed Services University of the Health Sciences] I very much appreciate the unsolicited testimonial. We are an academic organization and we cater not only to the three services, but we also have a relationship with the VA, and a relationship with Public Health Service. So I think we're in a good position to at least be able to collect and mine data. That would be appropriate for long-term studies.

Bob Schlesinger: I'm Senior Vice President with SAIC. I'd be interested in the panel's comments regarding the Ranch Hand Study, which is currently scheduled to end in two years unless some overt action is taken. Has the study just outlived itself, or is it something that's worthy of being extended, and what might that take?

Michael Stoto: I think that it's almost surely the case that there is value in the information already collected that will remain after the study closes down. So, just shutting it off and turning off those freezers and throwing away the data would be a real shame. I think there is no question about that

Now, when you say should the study continue, sometimes that means to continue to monitor the men, the subjects, do another exam or something else; I think that is a debatable question. And that is one of the topics the Academy panel is going to look at, as the Congress requests. Whether these particular men should be examined again, we need to look at it carefully. But in terms of the question, should we throw away the data? The answer is no.

Mark Brown: I would second that. I think the important thing is that we now have the funds to support a \$7 million study that the Institute of Medicine is going to do, reviewing the value of [the Ranch Hand] study. The shorthand title of that IoM study is the Disposition Study, and it means just that. What should we do? It's scheduled to run out in 2006. What's next? I mean, there is an enormous amount of data there. What should we do with it? Who should take responsibility for it? What public health information can be mined out of that information?

I think really the short answer to the question that you asked is, we'll wait and see what this IoM committee tells us. I anticipate that they will do an excellent job in a thorough, fair review and look at these issues, and we'll hear what they say.

Michael Stoto: I'd like to add one more thing. I think it's important to recognize that the potential value goes beyond the original purpose, to study the effects of Agent Orange. And perhaps the values beyond that will be even more important, because we've already learned quite a bit about Agent Orange from this study.

David Tornberg: It's a very focused aging study in a select population of males, and to that end, there has to be some value. It would be interesting to see the results.

William Brew: I have spent most of my adult life working for the Senate Committee on Veterans Affairs. I would like to turn the question, very slightly. In your introduction, you talked about the value of long-term studies, and there was certainly discussion in the panel about the general value of long-term studies. I don't think anyone would disagree. But then you go to the questions of where the money comes from and who controls, and all the rest. Maybe because it's a pointy end of the stick to talk about the Ranch Hand Study, it would seem to me that the question would go — and I'm now speaking from the perspective of the Congress, and the Congress has been the driver in this business, clearly responding to the veterans' concerns.

It would seem that among the consumers of information of these sorts studies are in the first instance the veterans — Tell me, am I at risk? Was I exposed? Am I at risk? What ought I be doing if anything as a consequence of my exposure? So that's one consumer. Second consumer, it's the question of compensation policy. Does anyone believe that the Congress is going to cut back on present compensation decisions on the basis of further science? I will leave that alone.

The third question — a clear consumer of a long-term study ought be the Department of Defense in terms of making policy for future deployments, if we're analogizing this to occupational health studies. An industry wants to find out how not to make its workers sick. Starting with the assumption that the Department of Defense would share that view, I suspect the Department of Defense wouldn't do a Ranch Hand again, probably. We collectively probably wouldn't use herbicides in a combat zone again.

But what out of the first Gulf war did we discover, if anything, before we went back, and what did we do differently, and what would we do differently based on whatever we've learned about present exposures with future exposures? I think that the question. Congress is going to fund these if it's going to be a federal initiative. And I think you start with that.

The question is, who is the consumer of a long-term study of military health, and can you connect that study to that consumer in such a way as to sell it? For instance, I don't think continuing to study the Ranch Hand participants — study, actively study them — can be demonstrated. It's because you're dealing with that cohort. That doesn't have any application. Most Vietnam veterans, there's not an assumption that there was a level of exposure as with the sprayers on the aircrafts. In any event, I think that to take it back around, clearly any informed body would start with the notion that it values a long-term study. But when it comes to specific studies of specific military populations, who is the

consumer or the beneficiary of the study? How do you persuade Congress that it's worth funding it over the long-term?

Susan Mather: I would like to add that there is another consumer, and that's the healthcare professionals who are going to be taking care of what's increasingly become citizen soldiers, more so in this conflict than in any other.

William Brew: I'm a Vietnam veteran. I certainly want to know whether I have any markers of prostate cancer. Right now, under compensation policy, if I get prostate cancer, as somebody who served in Vietnam, I get compensation. That's the law. That's the present law. When I get old enough that my prostate cancer is manifested, I will get compensation. So, I truly don't believe that there's anything that we gain out of studies of the population. In fact, tell me, what do we know now for the general run-of-the-mill — not the Ranch Handers — the general run-of-the-mill folks who served in Vietnam, so if they show up at their primary care provider and they say I was in Vietnam 1968-'69, what can the provider know to do differently about evaluating their health than they would do if they showed up and said I was in Utica '68-'69?

Mark Brown: I can't answer everything you asked. But, the Department of Veterans Affairs runs something called an Agent Orange Registry. The Agent Orange Registry offers basically a free comprehensive health examination to any Vietnam veteran who comes in and asks for it. It's the same as any initial full medical examination that any veteran would get. But another part of it, since it's connected to Vietnam and Agent Orange, is specifically related to Agent Orange health effects; the health effects that we are concerned about, based on our knowledge that we gleaned from this Institute of Medicine study. They would do at least discussions and perhaps some further workup to look for, for example, prostate cancer. They might take a little bit longer, harder look at some of the other health effects — we now particularly might take a harder look at diabetes, for example.

These are illnesses that we presumptively link to service in Vietnam. I think it hasn't revolutionized the way we treat our Vietnam veteran patients, but it has had an impact.

Michael Stoto: Those are tough questions. I won't address all of them, but I do want to say that I think the idea of thinking about who the beneficiaries are is an important one, and to make the point again that there are potentially beneficiaries that no one had in mind when this study was initiated — in things like aging and lots of other areas as well. If we had said those were the points of the study, I suspect that the participation among the Ranch Hand veterans in the controls would not have been nearly as high. We've got to be very careful about changing the goals afterwards, and about what it means to the study's credibility in terms of how it asks for permission to use records and so on. Going beyond that originally clearly stated purpose is a tricky issue, but I think one that needs to be addressed.

Larry Laughlin: [Dean, School of Medicine, USUHS]. I would like to thank Dr. Tornberg for shining the light in our direction. I believe we do have a role.

There are two other points that I would like to make. I would like to come to the defense of academic medicine. At least at the Uniformed Services University, we have a large group of people who are dedicated to population health. We understand, appreciate the fact that to do a three-year prospective study, it takes at least three years. We have tried to interpret that to our promotions committee. And they are beginning to come to grips with the fact that you can have an academic career in an academic discipline that takes a longer period of time.

I came here today to stand in the defense of long-term studies, but it sounds like we are preaching to the choir. Everyone seems to be on the board, so maybe my role is to put a couple of words of caution out there. Doing long-term population studies is very important, but they're very difficult. You have to be unbelievably perseverant, because you do boring sorts of stuff over a very long period of time, and you must be careful. You must have the proper design to start with. If you ask the wrong question, you are going to get the wrong answer. So, you have to make sure that you have asked the right question.

Again, speaking to perseverance, I have no inside information on the Ranch Hand Study, but you worry about the numbers, where the cohort is about 40 percent of what you started with while your control cohort is about 90 percent. Perhaps the reason you have a high percentage of diabetes in your cohort is that the people who dropped out were the people who were well; the ones that come back are the ones worried about the diabetes that you have discovered. I have no doubt that your epidemiologists take that into consideration, but that's an important point, that these are hard, difficult studies — certainly worthwhile, but you have to dedicate yourself to it over a long period of time.

Michael Stoto: Let me just address that one point. You are certainly right that they are hard to do. I think that what you were referring to was the falloff. There was a greater falloff in the Ranch Hand than in the controls. The reason for that is that the Ranch Hands are not replaceable, but the controls are. They make an effort to have the same number of controls every visit, bring new people in after people have fallen off.

Dave Roberts: I'm Director of Public Policy for HIMSS. Having worked on the House Appropriations Committee for a number of years, I read a lot of their reports when they come out. In this past year, through the appropriations side of Congress on the Defense side, not the VA's side, they encouraged that the Ranch Hand Study be continued for at least five more years in their report language. I would hope that the Department of Defense takes that into their planning process when they look at this.

My question is, we keep hearing about the side benefits of this 20-year study. Does it make sense after 20 years, when we have all of the folks that have been studied, to just end that project, when probably in 10, 15, 20 more years will really be the greatest benefit out of this study?

Susan Mather: Well, in fact that's what the IoM is going to debate, the value and the cost and whether the numbers are going to be sufficient.

Michael Stoto: Those are tough questions, but I think it's important to recognize that continuing could mean many different things. It could mean another exam five years from now. It could mean just maintaining the information and the samples that currently exist, and the human knowhow — they know where everything is and how to use it.

It might mean as an intermediate thing, following up on this cohort in terms of mortality and doing studies with that, but not doing another physical exam. The men are relatively old now, and that needs to be figured in to the calculations about what are the likely events that might not have already happened.

Mark Brown: I would just add that public health is all about prioritization. I think there is a GAO report that came out a few years ago that said the Air Force has already spent over \$100 million — \$140 million sticks in my mind — on this very expensive study. So, these decisions and these determinations about what do with this very valuable, enormous dataset are not trivial. There is a lot of money at stake in this study. There are not infinite resources to spend on public issues, so some hard decisions are going to have to be thought through.

Panel 2: How can long-term studies help inform healthcare policy?

Robert Graham, MD — Acting Deputy Director, Agency for Healthcare Research and Quality

Rick Erdtmann, MD — Director, Medical Followup Agency, Institute of Medicine

James Peake, MD — Surgeon General, United States Army

Robert Graham:

I will try to address some of the issues related to long-term studies from the perspective of the Agency for Healthcare Research and Quality and our particular interest in terms of healthcare costs, quality, and outcomes. The Agency for Healthcare Research and Quality is a relatively small agency in the U.S. Department of Health and Human Services; it has an annual budget of just a little over \$300 million, and has its roots in the National Center for Health Services Research, which was established in the late 1960s. Classically, it has been an agency that has provided research support for individuals in the general area of health services research. What do we do to make the system work better? How does the system work? Where are the problems? What can we learn about it?

We have more recently started looking at ways that we can move from just that research paradigm, where the emphasis is on discovery and dissemination, to actually taking what is known, whether it is as a result of AHRQ studies or result of other studies, and work towards adoption and assessment of whether or not it brings about a change in the

system. All of you, in one way or the other, are probably facing increasing pressures in terms of both the federal structure, OMB, and external expectations: Just don't tell us what you know; tell us what difference it makes. Tell us what impact it is having. What is improving as a result of it?

AHRQ does not do, does not fund any substantial long-term clinical studies. We do maintain two significant databases: The Medical Expenditure Panel Survey, and the Healthcare Utilization Cost Project, which are longitudinal studies that provide information about patterns of expenditure and resource allocation in the healthcare industry. These are used substantially by individuals who are doing research in that area, but they are not the longitudinal studies at the clinical base that you are talking about here. Part of the barrier for us, in terms of long-term clinical studies, is cost. Being a relatively small agency — a budget of \$300 million now, but for most of the agency's history, the budget has been \$150 to \$200 million — that has not been a possible investment for us.

As for what the value of long-term studies might be as you look at the system — cost, quality, and outcomes — I would be an advocate for the unique niche that longitudinal studies have, and I would use a couple of examples. All of you, I'm sure, are familiar with the Framingham Study. It has been going on now for more than 30 years. It has provided some very basic understandings of the development and pattern of heart disease, stroke, hypertension, and number of others in a given community. More recently, we have seen an example of the unique contribution that longitudinal studies can have, and some of the limitations of longitudinal studies.

Some of you that have may have been following the experience of the NIH with hormone replacement therapy. That set of clinical trials was set in motion by a longitudinal study called the Nurse Study, where the impression from looking at a cohort of nurses who were studied over a long period of time was that those nurses who had used hormone replacement therapy appeared to have better outcomes in terms of cardiovascular and breast cancer. Based upon that, a presumption was made about 10 years ago that we really need to get menopausal women on hormone replacement therapy. That was a clinical conclusion. Of course, we went through the whole process of getting that information out, getting it to the physicians, talking about it as part of continuing medical education, as part of basic medical education. Are you putting your patients on hormone replacement therapy? This is more than just symptom relief. This really has positive health preventive aspects for the future.

At the same time, NIH was undertaking the clinical, classical, double-blind control study to look at these issues to make sure that the impression from the analysis of the long-term study was indeed substantiated. As we have seen over the last 18 months, the result of that clinical study is, no, as a matter of fact, the protective element of HRT is probably not there, and indeed the use of HRT on a routine basis probably carries a risk to women who use it.

That to me does not invalidate the virtue of the long-term Nurse Study, but it does show a balance and a dynamic that we need to keep in mind in terms of long-term studies and more short-term clinical trials. Each of these ways of inquiring about the nature of causality has its own strengths and its limitations. If you look at the pattern of disease that we are going to be dealing with in the United States for the next 20, 30, 40 years, we are seeing the shift from episodic acute to chronic multiple disease. I think in this environment, long-term studies will have a particularly important contribution to make in our understanding of what some of the risk factors or causality may be for chronic conditions.

One of the most vexing clinical circumstances that physicians face today is Alzheimer's disease. We're seeing increased incidence; we're seeing what appears to be an earlier onset. What's that related to? Long-term studies may allow us to have some insight into the chronic disease or other chronic diseases in which the causal agent or the causal experience may not be approximately associated with the onset of the clinical symptomatology. It may be something 10 years, 15, 20 years in the past.

The more and more that we have to deal with chronicity, the more and more that we have to deal with the interface between the environmental and physical and try to understand what the impact is on human health, I think long-term studies may have a very particular contribution to make. They pick up a different set of information over a different time period and allow us to look at populations; whether you are tracking individuals or whether you are tracking community or population groups in a totally different way than you can with a well-designed, classical clinical study.

Rick Erdtmann:

The Medical Follow-up Agency is currently a unit of the Institute of Medicine, but its roots go back more than 50 years. In fact, they go back to the period of time right after World War II, when then-Colonel Michael DeBakey, a very world renowned cardiovascular surgeon, was a member of the Surgeon General's Office. Dr. DeBakey convinced the Surgeon General at the time that because of the tremendous number of records that were available of soldiers and sailors and Marines during World War II, the injuries and illnesses that they had — wouldn't there be an opportunity, maybe the unique opportunity, a once-in-a-lifetime opportunity, to take advantage of those records and learn about disease, learn about effective treatment over time? He convinced the Surgeon General that a research agency ought to be set up to have this capability and work with the Veterans Administration and the National Research Council, and it was established back in 1946, the Medical Followup Agency, and still exists today.

The studies that we do and have done at the Medical Followup Agency generally support the needs and requirements of the Department of Veterans Affairs and the Department of Defense. Many of the studies that we have conducted have been done with collaborative help from many, many academic centers and universities throughout the United States. In

fact, since 1946, there have been more than 500 studies conducted by the Medical Followup Agency using the cohorts that we have, and these have been published in the peer-reviewed literature. We're part of the National Academies' building on Fifth Street now and have been there for about two years.

The studies that we do, particularly in recent years, compare exposed cohorts of military personnel to non-exposed cohorts. It's pretty simple in terms of concept. The studies tend to focus on outcomes, whether they be morbidity outcomes or mortality outcomes — both the nature of those outcomes in terms of size and the types of morbidity and mortality. One of the things that is unique about the capability we have is that we have these historically based cohorts going back many, many years in time, and we get to examine them as if they were existing 50 years ago. We can follow what happened to them, since we know their current outcomes now, over this long period of time. These are known as retrospective cohort studies — very large and very powerful. They have many advantages.

These retrospective cohorts can be done very rapidly. Why? Because the time has already elapsed. If we start with a cohort of people from World War II or from Korea and look at what's happened to them today, we've had 50 years of experience, to look at survival curves and look at their morbidity and mortality outcomes. So, these studies can be done within months or years. These studies are also less expensive. Could you try to imagine how much it costs to conduct a Framingham Study of today over 20 years with the inflation, salaries, the costs of that research over time? But there is no inflation factor when you do a study that started 50 years ago.

Well, this all sounds great, but there are some disadvantages with retrospective cohort studies. For example, the study variables are limited to those that were collected historically. For example, if we wanted to do a study of oil well fires and we had a cohort of individuals who were exposed, and we had a cohort of military personnel who were not in the Gulf and not exposed, and the end-point what were going to look at was pulmonary disease, and we wanted to compare those two populations, if we didn't ask the smoking history in those cohorts, we would have a problem interpreting that data.

There is another problem with retrospective cohort studies, in that biases can be introduced if the comparison group is not similar to the study group except for the exposure in question. So for example, if you wanted to see whether or not malaria chemoprophylaxis would lead 20 or 30 years later to a greater incidence of lymphoma or to leukemia, and you compared a group that was deployed and required to take malaria chemoprophylaxis versus a group that didn't, and you didn't know the information about or didn't factor in the information about their employment — what kind of work they did while they were in the military; were they JP-8 handlers using jet fuel, or were they doing something else that also might relate to that same outcome — you could end up with a result that either exaggerated or masked the effect.

Let me give a quick snapshot of some of the studies that we have done in the past. This does not really do justice to the tremendous amount of wonderful work of hundreds of

people over 50 years, but it gives a quick idea about the types of things that can be done with these kinds of retrospective cohorts. Amputees with heart disease: The question was, if you had an amputation, would that increase your incidence of cardiovascular disease? A large cohort from World War II, where more than 12,000 Army individuals who were in the war was compared with individuals who did not have an amputation: Results indicated that mortality due to cardiovascular disease was seen in these veterans that had proximal traumatic amputation. That result led to changes in the VA compensation rules, so there were impacts to these kinds of studies.

Atomic veterans studies were done. The question was, did participation by soldiers who were witnesses to these atmospheric tests that were done back in the 1950s affect their health — their mortality specifically? Five different studies were done looking at 70,000 participants and 65,000 nonparticipants. That study showed that there was no difference in mortality, either total mortality or mortality due to cancer outcomes, in those two populations. So, it gave assurance that this was not a problem.

Another example — the tremendous number of prisoner of war individuals who were in the cohort that resides with the Medical Followup Agency. A study was done to look at whether death due to heart disease and cirrhosis in former POWs was different than for non-POWs. Large numbers: 9,000 study subjects, POWs, and 7,000 controls from three different theaters showed that indeed there was higher incidence of mortality due to cirrhosis and heart disease. That also affected compensation legislation for those individuals.

One of the most impressive cohorts that the Medical Followup Agency has at its disposal is twins, 16,000 pairs of twins. It's one of the largest in the United States. In fact, the United States does not have a national [twins] registry; that's a problem in itself, but we have this asset. Between 1917 and 1927 there were 54,000 twin pairs born in the United States — white, male twin pairs. Of those, 16,000 joined the service during World War II — both joined the Service. Those pairs, which include both fraternal twins and identical twins, have been unbelievably useful in looking at genetic factors, hereditary conditions. In this particular study, the question was, are aggregation of risk factors to cardiovascular disease genetically based?

In this particular study, 250 identical twins and 248 fraternal twins were studied, and the studies showed that the genetic influence on blood pressure, glucose tolerance, and relative weight was very heavily genetically influenced, but the levels of cholesterol were not. So, you can see the implication. Now that we know the human genome, the opportunity for these twin registries to have tremendous study potential exists.

One of the more recent studies was on hepatitis C. We had a cohort, and still have a cohort, of Air Force recruits who were in the Air Force at the Great Lakes Naval Air Center in the 1950s. That's at a time when we were studying streptococcal disease, and in that process, serum was collected from all of those recruits, 8,000 of them. We also have the morbidity and mortality outcome of this cohort. So all kinds of wonderful natural history studies can be done using this kind of material. This particular study,

using that material I just described, showed that those individuals who are antibody-positive to the virus versus those who were not had a much lower rate of liver disease than was originally thought when the disease was first identified about 20 years ago.

Here are two examples of some recent studies that are ongoing. I can't even tell you what the results are because they are still taking place or in review right now. Khamisiya relates to the detonation of chemical weapons that were done in Iraq after the First Persian Gulf War. The question was, were the military personnel who were near that detonation exposed to sarin and other chemical agents that could put them at risk? Look at the size of this cohort, and the potential for coming up with some results based on the size of these populations: 100,000 people who were potentially exposed, based on meteorological modeling and knowing where the units were at any given point in time, versus 224,000 that were not under that plume. Those studies will be published, hopefully, within the next year.

My last example is the one that was briefly mentioned by Mark Brown earlier today, the SHAD Study, in which our Naval ships back in the '60s were exposed to simulant and real chemical and biological agents. Those 5,000 people who were exposed were wondering, is that going to hurt me? This study should answer the question, yes or no, and to what degree.

The Medical Followup Agency is continuing to conduct these types of epidemiologic investigations, taking advantage of these historical cohorts, that can do these things quicker and less expensively than prospective studies. Our list of cohort databases is extensive. We are seeking collaboration for future studies.

Because of the size and the nature of the type of work that the Medical Followup Agency does, there's tremendous power and promise to this work. I think there are tremendous opportunities for answering questions with the current cohorts that we have that might be of some value to the national good, both in terms of influence and policy.

James Peake:

The topic is the value of longitudinal studies, specifically from a policymaker's perspective. Part of the value is that you get products — a relational database — that have information that is recorded, stored, and has the potential for correlations. As those correlations are made, the data are turned potentially into information, potentially into knowledge, and then potentially into action. What we don't know will hurt us, but not everything we don't know will hurt us.

One of the byproducts, besides a relational database that's stored in the computer, is the fact that over time — and I think that's the significant piece — you start to have a variety of people who become knowledgeable about whatever subject you are talking about. They wind up being able to communicate by e-mail or by telephone. Sometimes,

it's just a matter of who you meet and being able to talk to one or another. Then again, the notion of a significant period of time builds up another kind of relational database.

Long-term studies start out to answer a specific question that has been asked by somebody who has a stake in what the answer is. That person may go off to another job or be distracted by another political situation, or that person or that agency may have different priorities come up over time, which is part of the issue with a long-term study. But ultimately, the value is to answer the specific question. What we've heard is that sometimes it will answer an implied question that may be more related, and therefore be really attributed to whoever paid for that study in the first place, or it will start to demonstrate unrecognized questions that can be answered by that set of relational databases.

So, it builds a body of knowledge and a cadre of knowledgeable people who will potentially turn the power of information into decisive actions that are data-driven decisions. What are some of the problems with them? One is they do cost money. And, what is the purpose of policy? Some of it, of course, is fiscal policy. The issue when you are talking about health studies — and that's not the only kind of longitudinal study there is — starts to boil down to distributing resources, compensation. We all know that politically, some of those great studies haven't affected much at all, despite the science. So there is a political component to that, because they are used by the policymakers, not the scientists.

Another aspect of what longitudinal studies can do is mitigate risks, whether they are cost risks for the future or whether they are a personal risk. There is a fiscal imperative, and then there is a moral imperative in trying to get the right answers, to do the right thing by our people. For us in the military, those soldiers, sailors, airmen, and Marines are our people. My interest in it is what I can do to make a difference for my soldiers. What we sometimes tend to do with longitudinal studies is look for the next longitudinal study as opposed to saying, “Okay, what's our hypothesis here that then allows me to make a good coherent recommendation to a policymaker?” Part of our problem with longitudinal studies is that no policymaker is going to have the time to be really able to sit down and understand it.

So, part of it is communicating these longitudinal studies. They have to be communicated in terms of a hypothesis that allows a policymaker to make a rational judgment that is either going to mitigate the resourcing issues or mitigate the costs, or act on the moral imperative of doing the right thing by people, depending on what that policy stakeholder's responsibilities are in this arena.

Where do we go for the future? We've got to be able to make these studies a byproduct of how we normally do business, because they do get to be expensive over a long period of time. I'm an advocate for our digitized longitudinal query-able patient record that will ultimately allow us to glean these insights as a byproduct of how we do business, instead of paying a whole industry to go back and re-look at things and try to reconstruct history. What if you want to sell breast implants. Is there a hypothesis that those are safe? How

long is it going to take over time to prove that, despite just getting FDA approval? Maybe we need to build that kind of thing into the policy process of allowing those to be on the street. On heart valves, the industry knows by serial number what heart valve is in what person.

Maybe we need to apply that on a broader plane that allows us to glean information as a byproduct — that will allow policymakers to say, well, this is a good thing or a bad thing. Maybe our policy ought to say that because the FDA has approved it, you're going to be protected from harm fiscally from a bad result, as long as you are collecting the data and putting it into a central source. I think there are ways we need to think about those kinds of things, instead of just saying, well, here's my hat and I'm a really good researcher and interested in this question, so give me some money to study it.

Discussion:

Susan Mather: Time and automation increase the whole problem of proprietary rights to information — we all know that information is power, and researchers know this about as well as anybody. So, it's not just proprietary from the standpoint of a product that may be sold or may make a lot of money or may make a lot of trouble for a manufacturer, it's also the proprietary value of information. How do you make that information available to other researchers? There is a research industry now, too, that has a great interest in the data that they have collected.

I think that is one of the problems that we are going to have to struggle with, and then the whole issue of how to inform the participant of possible sidetracks that this research might take, so that they're aware that their data could and perhaps should be used for other studies; and how do you get prospectively their permission to do that, under our current understanding of ethics?

Joel Michalek: [Principal Investigator, Ranch Hand Study] I am an active federal employee, civil servant, of the United States Air Force, so it's hard for me to speak on my own. I must tell you that the official policy of the Air Force is that this study will end on October 1, 2006. Having said that, there are some details that would fill in some of the concepts mentioned earlier. As to who are the stakeholders for this Ranch Hand Study, well, you should be reminded that about 60 per cent of the participants are controls. The controls were C-130 air and ground crews stationed in Southeast Asia between 1961 and 1975. Their birth years range from 1908 to 1956, pointing out that many of those early veterans who were there in 1959 were in fact World War II senior officers, probably. These men were of another generation. The age range in this study is very wide.

We are now seeing things in the control group that we hadn't even imagined that we would see in 1978. There are papers in progress right now to describe those, and I am not

going to spell out details. This study is one of incredible depth and one of incredible expense to our government.

The records summarized by Mike Stoto have led to the digital scanning of over 6 million documents of, we think, every health record ever collected on every individual over their lifetime — from their family physician, including those collected by us at our periodic physical examinations, including records on their children up to the age of 18. That is on all live births produced by these men, and all non-live births and records of their wives during the period of pregnancy, including bad habits such as smoking and drinking during the period of conception.

Everything has been checked and triple-checked up to three times. All databases are complete and correct. Every database, every report, every article has been reviewed up to three times by our own advisory committee and by the National Academy of Sciences and by journal referees. This study is probably one of the few that has ever undergone the level of scrutiny that I have just described. I can't imagine any other study that has this level, which is a tribute to our Congress, who built in these controls to ensure credibility.

Credibility was on the table in 1976 when we wrote the protocol, and it's still there today. If you want to contemplate a future of the study beyond 2006, I suggest you read the latest books on risk management and risk communication, which would recommend two advisory committees — one like the kind we have today of experts in toxicology, medicine, statistics, and another advisory committee of stakeholders, such that the principal investigator, such as myself, would have to defend results not just to the scientific community periodically, but to the stakeholders, to the critics, to the skeptics, and to those who have a mistrust of government. They should be there to grill the scientists and let us explain our methods and hear their ideas, too.

There's an incredible mountain of information here that has been collected with your tax dollars. It all sits at the Air Force Research Lab in San Antonio at Brooks Air Force Base. Any of us would be available to respond to any questions you may have by e-mail or indirectly through the National Academy of Sciences.

Michael Stoto: One of the strong themes that ran through both panels was the potential value of existing information that comes out of regular healthcare in a variety of military and other settings. Another theme that was a little bit more subtle is the theme of stakeholders. Since a lot of these studies have been initiated, there have been major changes in our understanding about the ethical obligations that researchers have to their study participants, particularly in HIPAA regulations that have come into place in recent years.

I am wondering whether people are thinking about this as a barrier or a facilitator to studies of this sort. I hope it's one of the things that the IoM study takes up with reference to the Ranch Hand. I don't know what the consent procedures are when people join the military — can something be said at that point so that their records can be used in the future? I don't know if people are looking at these issues.

Susan Mather: I think our growing, or at least changing, understanding of ethics in dealing with human subjects complicates this, but necessarily, when you think of some of things that have happened in the past, and also the value of information about yourself to you, there is that interest, and it can be both enlightening and dangerous to have information about yourself used in certain quarters.

The whole issue of how do you translate research into practice? How do you apologize when you make a mistake in that translation? I think there is a science, probably the evidence-based medicine movement, but evidence is not going to address all of the problems. The translation of viable good science into good practice is one of the problems facing the stakeholders and the researchers, I think, together.

Rick Erdtmann: Clearly, historically, when we're using individuals who were in the military back in the 1940s, the bioethics and the rules were a little different then. But that doesn't eliminate or relieve us of our current obligations. All of the studies that the Medical Followup Agency conducts are done after careful review by our investigational review board at the Medical Followup Agency, or at the Institute of Medicine. In fact, it's at the National Academy level.

If we're doing collaborative work it requires IRB approval from the other collaborating institutions, regardless of how long ago the study material or the subjects were involved in the study. All of the material that has been published is published anonymously. That is to say, you can't look at any of the material and say, oh, that was me or not me. But clearly, I think there does need to be a look at the current HIPAA rules. As someone else pointed out earlier this morning, this is the time to look at the policy of those HIPAA rules as it affects the opportunity to conduct long-term studies, as long as we're not jeopardizing the privacy of individuals who participated in the study.

Robert Graham: This is exactly the point that I was going to make, in regard to the civilian sector. Most of our discussion here has been about the military sector. I think the definitive answer at this point in time about the impact of HIPAA on research is that we don't know. People are still trying to figure out exactly what the regulations require.

Physicians in the private sector, the individuals running healthcare systems in the private sector who would like to have an organized structured way, whether it's short-term or long-term, to pursue some of these questions, are really having to ask at almost every interface, is this permitted? Is it permitted in the way that I want to do it? Unfortunately, a lot of the response, based upon those interpreting the regs, is nobody's asked that question before. We are going to have to think about it.

Five years down the road, we'll have a body of regulatory or case law; we'll have a much better idea about what is permitted. I think General Peake's comment is absolutely prescient. The ability to capture what goes on in the transaction in the healthcare system electronically so that you have a data storehouse that at a point in time can be queried in a

structured fashion consistent with whatever the provisions are then, of ethics and HIPAA, can be an enormous benefit for us.

But, again, from the civilian sector, we aren't even barely to the starting line there. I think that's where the Veterans Affairs Department and the military services, because they do have the advantage of dealing with a defined population and with a more highly structured system, are going to reap some of these advantages earlier, and hopefully in a way that the rest of us who are trying to figure out a way to get that into the civilian sector can profit from it.

Susan Mather: The pressure for VA as I feel it— and I'm sure DoD feels the same thing — is just-in-time research. I mean, they don't want the answer 12 years from now or 25 years from now. They want the answer yesterday.

Because we are often working under those kinds of pressures, both from our congressional oversight bodies and from our stakeholders themselves, we may need to raise these questions earlier and more urgently, and also have the ear of some of the people who actually are going to think about it and make these decisions. I think in some ways, federal research can benefit private-sector research in ways that aren't really thought of, by defining some of these questions and getting answers in a much more systematic way than what is possible in a fragmented academic kind of world.

Mark Brown: I think in this panel, and to a lesser extent in the previous panel, the theme came through of the economic advantage of mining existing databases — taking advantage of existing databases as a cost-saving means of getting the same information that you would otherwise have to perhaps develop a very expensive longitudinal study. This seems like a pretty good idea.

Regarding the various databases that MFUA has access to — the twin registry and some other databases going back to World War II of military personnel, is there a new generation of data coming down the pipeline now? Are you getting data on more-contemporary veterans that could answer more-recent questions? The question occurred to me as you were talking about cardiovascular impacts of traumatic amputations. Perhaps the way we treated traumatic amputations then is different now. It seems as if there would be value in looking at new databases as they come along, new generations, new cohorts.

Rick Erdtmann: I'm going to answer that with two comments: yes and no. The yes is, we are adding new cohorts. Richard Miller [previous Medical Followup Agency director] just finished a study before he retired looking at the use of medical care prior to going to fight in the Persian Gulf war, and whether or not an individual was registered in the registry, what the connection or linkage was with usage of healthcare prior to the war. That cohort consists of many thousands of individuals, and that will be added to our collection. The Khamisiya study will have information on those individuals who participated. So, we are adding new cohorts all of the time.

The reason I say “no” is that we are having trouble with the twin cohort. We did a pilot study, but we don't have a twin registry. A lot of countries, Sweden and the European Union, have this humongous collection of twins, and we don't have a mechanism in this country to do that. That's a sad thing, because we can learn so much, now that the human genome is known, about the nature of disease from these twin studies. We do not have a new collection of twins.

We are trying to get that established with the Recruit Assessment —RAP— survey. That survey instrument is about ready to be used. One of the questions that currently is in that survey is: “Are you a twin?” So we have an opportunity to now establish a new twin registry, but if that fails in RAP, we don't have any other model out there for that.

Richard Miller: Many of the things that MFUA has done in the past have been done because DoD was not doing them. To a great extent that is no longer true, and the operation of DMSS and the increasing automation, not only of inpatient data, but outpatient data as well, is going to make it a whole lot easier for the DoD to do internally a lot of the studies that in the past they have had to contract out.

This makes us happy for the nation, and for the Department of Defense, but a little sad to see that Rick will be increasingly doing historical studies, and the newer cheaper, faster automated studies quite appropriately can be done within the DoD.

Tim Wells: I'm with the DoD Center for Deployment Health Research. As a military researcher, I am involved with case control studies, retrospective studies, and also the Millennium Cohort Study. As researchers, we all know that there are advantages and limitations in study designs, so we choose our studies appropriately — also with the type of data that we are collecting.

Computerized data sources have disadvantages, as do self-reported data, but we try to use the most appropriate study designs and types of data in our studies. The advantage, I think, to the Millennium Cohort Study is that we should be able to answer questions that we can't with other study designs. Sure it's expensive. It's going to cost us millions of dollars, but it's been estimated that over a billion dollars have been spent already on Gulf war research, and we still have several questions that remain unanswered. So you just have to look at cost and benefit. I think clearly there is a need for longitudinal studies.

Also, the outcomes that we are looking at are common chronic diseases as well as mental health, but that doesn't mean that we have to wait 20 years to be able to answer those questions. We've just finished enrolling our first approximately 77,000 individuals, and we will be able to cross-sectionally describe where the military is right now, which we previously could not. We have approximately 12 spinoff studies already in design phases, so we can look at issues in regard to, are there differences in response? We can look at the electronic data, look at their healthcare that individuals are using in the electronic data, look at those individuals who responded versus non-responders and ask, is there a difference in their healthcare usage prior to enrolling in the study? We can get

a lot of information from a prospective study, and it's not just necessarily limited to the outcomes from the design of the study.

Who are our customers? They are quite varied. They're healthcare policy individuals. Right now, there is an issue about anti-malarials in the military, and what health effects they have. Some of the research that might go on will involve individuals enrolled in the Millennium Cohort Study. So we already have a cohort established that we can tap into to answer some of these quick healthcare policy questions.

We have individuals in the military. Well, how does military affect my health? They're our customers. And the general civilian population —moms and dads, when they're thinking, do I want my son or daughter to join the military, they can look at this Millennium Cohort Study and say, well, all indications are this or that.

Susan Mather: In VA, we're all for the Millennium Cohort Study as well and are heartened to hear you talk about spinoff studies, because I think it's important to publish frequently with these studies to keep people up to date with what's happening to share what information that we have.

One of our criticisms — in the past, sometimes DoD research set out to answer a specific question, and once they had the answer to their satisfaction, there was less interest in publishing it. Of course, it is not as easy to get things through the chain in DoD as it perhaps is in some universities, although I'm sure there are researchers whose universities are giving them problems who would might question that assumption. But, I think it is important that things be published as they show up, so that other researchers can look at it and it can be discussed in the way that peer-reviewed literature is traditionally. Also, I think it's important not to publish it just as a monograph that sits on shelves and is almost impossible to find a copy of. If you are going to publish a monograph, make sure that monograph is available through some electronic media. That's something that's possible today that wasn't as possible ten years ago.

Dave Roberts: I'm from HIMSS. I've served two tours of duty on Capitol Hill, one for the Senate and one for the House. In my 23-year history, I've never heard of the Medical Followup Agency. How does this agency work with decisionmakers, who are really begging for information? How does this Institute of Medicine organization get the data to them? Does Congress tell you what studies you focus on, and how does this play in? What role does DoD play in this?

Rick Erdtmann: First, the Medical Followup Agency — and the Institute of Medicine — is a private non-profit organization, not part of the federal government. We don't lobby Congress. Certainly, any study that is being contemplated, whether we're proposing it to a potential sponsor like the Department of Defense or Department of Veterans Affairs, or whether it's mandated by Congress, very early on in the course of that study, we do get those who are interested, in either the House or the Senate, who sponsors the bill that relates to the particular issue in question — we get them involved in early

discussions. That is part of our policy, part of our practice, and we do it virtually 100 percent of the time.

Maybe we should advertise more. Maybe we ought to do that better and market ourselves, because I think there is a lot that we could offer for future studies. Our main focus and our main core business is to actually conduct the studies rather than try to get new business. But I think we could do that a little bit better.

James Peake: I think it's a good question — about any of these organizations that do research, even within our own house, DoD. We have the Defense Medical Surveillance System with 30 million serum samples and a tremendous database now of, basically, patient encounters. It offers the opportunity to go back and start doing some of those kinds of studies. But what you have to do is formulate the questions — there ought to be a hypothesis about what you're asking.

We are sometimes reacting to [Congress] — you know, give me an answer tomorrow about the last 100 years. But, it talks to the value of having these kinds of databases that have been started for sometimes different reasons. They give us the opportunity to answer those kinds of questions acutely.

I think there are longer-term questions, particularly in the area of prevention. The conventional wisdom is that we can prevent a lot of disease. Well, we need some really good prospective longitudinal studies that show the ROI on that, so then maybe we can start mandating some of those kinds of things within a public health context in the military — outside the military, to be honest with you. I guess the point is, it ain't just the researchers that have a responsibility here, it's people like me and other policymakers that need to think beyond just what is going to be the question du jour.

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