Full Committee Discussion Large Population Studies Session
Huntington F. Willard, Ph.D.

DR. TUCKSON: First of all, a terrific report.

Could you, again, just level-set for us all again in your mind, or if anybody can, what the actual process time line is for everything? At the end of the day, if this is going to happen, how much time do we have in our recommendations in your committee to be able to give input before it's not relevant anymore to what's actually happening? Is this process going to go on for another couple of years?

DR. WILLARD: I can answer it from the standpoint of our committee and the task force work. I think we'd have to ask Francis or others to weigh in on exactly the timeliness of this. If we're going to go to all of this trouble and we're going to make recommendations, we certainly want the recommendations to be useful to the Secretary and not to come in post facto where they would be of limited or no use.

I think, depending on how far we get today with framing the issues and the approaches and mechanisms, we could come back to this full committee with probably a penultimate draft report at the next meeting. I'm looking at Sarah for her nodding or not nodding. But ultimately for this committee to then approve a set of potential recommendations to transmit to the Secretary, that's realistically at least two meetings down the line I would think.

MS. CARR: The other thing that we had talked about was taking our draft report and opening it up for public comment. It's what we did with the coverage report. So Kathi and I had a back-and-forth. A lot depends on the deliberations of the committee this morning and how much input you give and how far we can take the report, I think, after this meeting.

If we feel like we can put it to bed in draft form after this meeting -- and Kathi has indicated that she might be able to work with that and get a draft done in a couple weeks -- we can then take it out for public comment and actually have a report back in June that might, if there's time, reflect input from the public as well, or at least allow you to consider the public comment in relation to the draft that went out for public comment. So I think that might actually be doable, to see a final draft report in June.

DR. WILLARD: But that would mean the final report and recommendations would be an action we would take in October? Is that correct?

MS. CARR: Well, I mean, conceivably. I guess a lot depends on how things go this morning. But conceivably you could be looking at the final draft in June. It would be very heroic, I must say. And it would only, I think, be possible to allow for a 30-day public comment period then too. If you wanted to give more time and actually get it out there in a wider way, it might require more time than that.

DR. TUCKSON: Let me ask Francis to comment, and also in your comment, Francis, could you, if it's relevant, connect it to the budget struggles that are going on? Hopefully, by the way, I think you all finally got some money back or are about to get some money back to have a real NIH again.

DR. COLLINS: Do you want to see me cry this morning?

(Laughter.)

DR. COLLINS: So thanks for the opportunity to comment. Again, thanks to this task force that has put together a very thoughtful report, which I think outlines, in a very effective way, a whole series of issues that need to be addressed if such a national program, which really would be quite a landmark, quite a historic undertaking, were to get underway and something one would only want to do with a great deal of confidence that the important issues had been addressed.

Let me just say a couple of words about timing issues, but maybe first something about this RFA that has already been issued to try to collect public input about the feasibility and advisability of conducting a large-scale cohort study in the United States.

You have in your briefing books under tab 5 an excerpt from that RFA. It's not the whole thing, but the majority of the critical points are represented there.

Again, I know we're being careful here to say the Secretary's advisory committee did not ask NIH to do this. I did go back and review the minutes of exactly who said what at the end of the last meeting of SACGHS, and if I can quote from our chairman of this task force, Dr. Willard said, "I would think you have the sense of the committee that this is a high-priority item that no one knows how to tackle, and any efforts to learn more about how to tackle it would be welcomed." Okay. So we take that as not urging us to do this, but the notion that this would be useful information.

With that in mind, a lot of work went into then designing this RFA, particularly on the part of Jean McEwen and Terry Manolio. As you saw, it has now been issued. The letter of intent is due April 10. The applications are due May 10. They will get reviewed this summer. It will go to counsel in September, and we hope to have this funded during the current fiscal year, that is, by the end of September.

This is an RFA for a specialized center to conduct a variety of different kinds of approaches to seek public input about such a study, and that would be expected to include surveys, focus groups, and public meetings. We are hoping there will be lots of applications to this from the centers out there that are capable of doing such things. I would think this would be pretty interesting work for the appropriate applicants to plunge in on. And we have set aside $1.55 million over the course of two years to fund this effort. So it's a two-year effort.

As far as the timing question, we would expect the results of this to be reported out in September of 2008. So, again, that's a two-year time table from the start point, and I think probably to do this well, you can't compress it much more than that when you consider the planning that has to go into it and then the conduct of what we expect will be public consultation all over the country in various settings with different populations, different backgrounds, different socioeconomic status, access to health care, and so on.

DR. TUCKSON: Francis?

DR. COLLINS: Yes.

DR. TUCKSON: You put a lot there and it was terrific. Let me just make sure I've completely got it.

The first thing you said, which is important to hear, is that money is already put aside.

DR. COLLINS: Yes.

DR. TUCKSON: So there is something that will happen and it does not depend upon any further funding cycles to get it started.

DR. COLLINS: No.

DR. TUCKSON: So that's key. So that's real.

DR. COLLINS: That's real. That's from NHGRI's budget.

DR. TUCKSON: So, number two is that the RFA concludes on which date again?

DR. COLLINS: The applications are due May 10, review this summer, funding by the end of September of 2006.

DR. TUCKSON: September of this year, funding.

DR. COLLINS: Yes.

DR. TUCKSON: So, in other words, the train will leave the station. At the very beginning, the first leaving the station at any level in this project happens in September of '06. Something starts happening. Something will happen that the American people will want to be involved with this starting '06. Not theoretical anymore. It's moving.

DR. COLLINS: But, again, this is an opportunity to collect public input. It is in no way a commitment to actually undertake such a study, both because the public may decide they don't think is a good idea or we may never be able to identify the funding to conduct such a study.

DR. TUCKSON: Then the other thing would be is in terms of -- and I see some other committee members -- but, Francis, as you look at the questions the committee is answering, from your analysis of them, how do you view the overlap between what this September 6th initiative will do and its collection of information -- what is the overlap between the issues we have laid out and what this will do?

DR. COLLINS: I think it's pretty significant. I'll read you in a moment the bullets that we are specifically asking grantee applicants to cover in their proposals.

But let me say, though, right up front, this is not intended to be the full extent of a public consultation for a project of this sort. This is very much a first step. If the project, two years from now, appears to be gathering momentum, public consultation, as was just pointed out by Hunt, will have to be integrated into every step along the way, and this would only be sort of an initial snapshot of public opinions and public concerns.

Now, let me say the things that are being asked to be surveyed, as funded by this RFA, include the acceptability of the goals of the initiative for the U.S. as a whole; concerns regarding uses of data for individuals, communities, and the public at large; expectations about privacy protection; acceptability of open-ended consent, which will probably be necessary for a study of this sort; acceptability of a central IRB; optimal approaches to recruitment, particularly regarding identifying and contacting family members; the need for tailoring to individuals or communities

with special needs; expectations about return of information to individuals, communities, and the public at large; the need for an ongoing dialogue with participants regarding study goals and processes; the advisability of including or excluding children; and intellectual property concerns. That's not intended to be an exhaustive list but that is an exemplary list of the kinds of things we hope this public consultation will include.

DR. TUCKSON: Hunt, you're now back in because I actually wound up asking a question and you'll lead us through.

I just want to make sure that we're completely clear so everybody is on the same page here and we all understand. We have a set of things that we think that our committee thinks ought to be looked at. This is an RFA to look at certain things. So we have to see how the RFA, which is funded, which is going to happen, goes forward. It is not theoretical. We can't influence the RFA. It is already on the street. It is already there. So they are going to move forward. So our questions really have to deal with now the reality of that and then what things we see doing in the context of that.

So with that, Hunt, take it away.

DR. WILLARD: Thank you.

What I would say, though, is -- and then Francis said this as well -- this is simply a pilot project to do first-round public engagement issues. So that doesn't mean that our advice wouldn't be useful for a subsequent round of a much more extensive series of public engagement efforts.

DR. COLLINS: And can I say your advice would be useful in this round as well because this is a U01. This is the kind of a grant that involves extensive staff interaction with the granting agency in terms of the details of how the consultation is conducted. So if there are areas that this group is particularly concerned about that need to be emphasized, we're listening to that, and that's a great opportunity then to try to sculpt and craft this particular approach so that we are not missing the boat.

DR. TUCKSON: One other thing I should have asked before I turn it back to Hunt. This is actually asking you not to read the tea leaves of the future but more of your strategic intent.

There is a pretty strong commitment on the part of NIH, and HHS at some levels, to try to do this study. Obviously, you guys are pretty revved up about this. Is this public comment part meant to be part of a future go/no go decision from this RFA, or is it meant to help advise on how to do the study well?

DR. COLLINS: I think the decision about whether, in the United States, this study is ever going to happen is very much up for grabs. I think the scientific arguments for the value of the information are quite compelling, which is why many of us are, as you say, revved up about this. Certainly the group that we convened that worked on the details of a scientific plan and the study design came away from that experience, after more than 12 months of very hard work, unanimously convinced that this is the kind of study that would provide critical information about genetic and environmental contributions to disease the we otherwise will not have a few years down the road and which we'll probably regret not having.

At the same time, everybody recognizes that this is the kind of study which has enormous consequences, both in terms of public acceptance and in terms of budgetary implications at a time where budgets are under severe constraint.

So there is no certainty at all about whether all the discussion we're having, even if it becomes totally convincing scientifically and in terms of public benefit, will lead to a yes decision to go forward. There are no funds in the FY '07 President's budget to support a large-scale United States prospective cohort study. We're delighted about this initiative called GEI, the Genes and Environment Initiative, but it is not about a prospective cohort study. It is about case-control studies, also a very exciting opportunity and one that we welcome, but it in no way implies a commitment to going forward with this kind of prospective effort.

You've also heard, no doubt, that there are no funds in the FY '07 President's budget to support the National Children's Study, another prospective cohort study, which has had five years or now six years of planning, and which, at the present time, still is very much in limbo as far as the possibility of long-term funding support, again a rather expensive undertaking for which, frankly, I think the stomach is just not quite there yet in terms of the ability to support these things.

So I think our best task -- again, I appreciate the committee going forward with this -- is to continue to explore public receptivity and scientific value of this while waiting to see whether the funding climate can change in some way, recognizing that it may not.

Certainly in terms of your specific question, Reed, about the budget cycle, just a quick tutorial on how that works. The budget for FY '08 will already begin to get constructed by this summer. By June or July, those discussions will begin. That's the kind of lead time there is. So if one wanted to have an influence on that in some way, having a report out of this committee by June would be useful. Otherwise, it gets a little late to influence FY '08 and then you might slip back to FY '09. Those are just the realities of how this very complicated process plays out.

DR. TUCKSON: Well, that's what I was looking for, is that sort of sense.

So, Hunt, as you take it over, I think that what is in front of us -- again, I appreciate your continuing to keep this clear for us -- is if this committee feels that this is an important activity, really important in terms of the study itself, and we feel that it be conducted with certain public input considerations, then we're going to need, I think to be relevant to this, to be prepared to have something to say in June to the Secretary about this matter. And I think that come heck or high water, regardless of how sophisticated that is, we need to be communicating some sort of statement in June if we want to be relevant to the course of events. So I just suggest that there, and I turn it over to you.

DR. WILLARD: Joseph first, Cindy, Julio.

DR. TELFAIR: Thank you.

I actually have two questions, but I'll ask one and then I'll come back after the rotation for another one. Is that okay, Hunt? Okay.

The first question I have is that given everything that you said -- this is to you, Dr. Collins -- everything that has been put out in terms of this initiative, I was wondering, because it's a logistical issue and it's pretty important to making some decision about this, is the review committee for the proposal an internal or an external committee review on this? I'm not as

familiar with this type of granting process. So I just was curious on that because where the committee comes from, as you well know, is going to dictate what happens next.

DR. COLLINS: So that will be an external review committee. It will be a special review committee put together to review this particular RFA. It will be a review conducted by the Genome Institute's review staff, who I think are pretty well connected with the expertise in the field for this kind of a proposal.

DR. TELFAIR: Thank you.

DR. WILLARD: To follow up on that, Francis, can you say a word about the thought process that went behind making this a U01 instead of an R mechanism?

DR. COLLINS: We had various debates about this, and some people are even advocating it should just be a contract as opposed to a grant. We've actually had very good success in circumstances like this with the U mechanism which allows for a lot more involvement of staff in the ongoing conduct of a program of this sort, as opposed to where you give the money away and then you cross your fingers and hope that, two years later, the work product you were hoping for comes back to you. So while it's not quite as cut and dried as if you have a contract with timetables and deliverables, you still have a lot more ability to be sure that what you get for your $1.5 million is pretty close to the work product you were hoping for and you don't end up with something that's sort of way off the mark.

I think the consequence of our running this as a U01 is that people like Jean McEwen and Terry Manolio will be tracking very closely how the process is set up and how it's conducted and making sure, all the way along, that we're getting the kind of diverse perspectives that we need and the kind of specific issues addressed and something that will come back that will be useful for all of the decision-making that will follow.

DR. WILLARD: Cindy?

MS. BERRY: I was wondering if in the RFA and/or the task force's deliberations there was any thought to comprehensive, extensive media campaigns to educate the public first, or if not, was that by design? In other words, is it better to have people start with a blank slate? Because I think the general public is probably there. They have no clue about this at all. So is the objective to educate them first and then have the focus groups and surveys to gauge their thoughts after hearing from the media and others? Because most people get their information on health matters really from what they read about or perhaps their doctor. So I just wondered if that was a component or an intended component of this phase or whether, purposely, it's to be excluded until this RFA proceeds.

DR. COLLINS: Well, we're always going to be interested to see what creative ideas the applicants come up with.

I think a large media campaign might actually be quite misleading at the present time since we don't really know if we're ever going to do this study. So to try to educate people about it without that decision having been made, we may end up having a response to that that's something we don't quite know how to deal with.

I think the goal here is to do the education with the groups whose opinions are then being sought rather than trying to do education broadly across the general population because we're not going

to hear from everybody in the population. We might confuse the people who weren't part of the study.

DR. WILLARD: Julio.

DR. LICINIO: I have a question for you, Francis, because this Genes and Environment Initiative that's already out there sounds very compelling. You have the genes, we have the environment, so we can figure everything out. But I'm actually just reading here straight from the announcement. It says that there will be two components, the genetic and a technology development program to devise new ways of monitoring personal environmental exposures that interact with genetic variations and result in human disease.

So the way it sounded is the environment is just like toxins or things you can measure. All the psychosocial components of the environment, which are crucial like poverty, death, separation, trauma, abuse, whatever, none of these can measure the device. So when you talk about your large-scale study, do you think about the environment like toxins that you can measure with a machine or the environment at large?

DR. COLLINS: That's a great question. In fact, this GEI, Genes and Environment Initiative, having just been announced in early February, is something which NIH is now trying to figure out how will we actually conduct this research, assuming that Congress goes along with the proposal, which they may or may not. This is, at the moment, a proposal in the President's budget and we won't know for many months whether it's actually going to happen.

I'm actually very pleased with the way in which this has been put forward as a genes and environment interaction focus. And I think it does have some relevance to what we're talking about this morning, so I appreciate your bringing this up. Certainly the environment is much more than toxin exposure, and I think there's a good deal of sensitivity to that as we try to design how this $40 million a year effort would go forward, how do you try to push that agenda from sort of superficial analyses of measures of environmental exposure to things like stress and other kinds of socioeconomic factors.

But there also is a great need here, I think, to push the agenda as far as developing better technologies for specific environmental exposures, which would be very relevant to a large-scale population study. If we were starting such a study today, we'd want to be able to integrate into that every kind of sophisticated measure of environmental exposures, body burden, body reaction to such exposures. How can you assess the biological consequence of this kind of an exposure to the individual? And also, diet and physical activity, things that we currently measure rather poorly frankly, could be much more accurately measured with some of the new technologies that are coming along and just need, I think, a big push to get them to the point where they could be applicable in a very large study. And that is a specific goal of part of GEI.

So while GEI is not in any way intended to imply a commitment to go forward with a large-scale prospective cohort study in the U.S., some of the tools that come out of it clearly could be quite valuable for that purpose.

But I take your point, that when we talk about environment, we really need to talk about environment with a capital E and not think small.

DR. WILLARD: Emily?

DR. WINN-DEEN: I wanted to ask a question that comes with my background in GMP validation. Have you outlined any kind of an endpoint acceptance that if you achieve public acceptance at 80 percent or better, then you would proceed, you know, just some metrics that you would use to measure whether you should proceed to the next step on the basis of this public consultation? Or is this strictly just information-gathering without any real hard pre-ordained ways to analyze the data at the end?

DR. COLLINS: At the moment, I would not say that we have defined some kind of threshold above which positive responses have to rise in order to make this an acceptable project. Again, it's not as if you're asking one question of the people you're consulting with. You're asking them many different types of questions and the receptivity may be quite variable depending on the question and the group you're asking. Would it be acceptable to go forward if 98 percent of white people said fine and 15 percent of minority populations said fine? That would make you pretty uneasy, wouldn't it?

So I'm not sure exactly how we could predetermine those outputs. Again, we're depending on the applicants, really, to use their creativity to come up with the specifics of how to do this, so I'm not sure exactly how we would know now what the answer would have to be in order for us to be comforted.

DR. WINN-DEEN: Do you anticipate that there will be some way to measure whether you should go ahead based on whatever you get back? I understand what you're saying, that there are lots of questions. I guess my concern is that if you do a two-year consultation and you don't know how you're going to respond to the information you get back, it's an interesting exercise. It adds to some body of knowledge on people's sort of social reaction to various things put in front of them, but it doesn't really lead us to a positive way to say we should take the next step forward.

DR. COLLINS: I guess, Emily, I'm thinking of this more as an opportunity to find out where are the areas of greatest concern, which you could then adjust your study design to take account of and try to diminish those concerns as much as possible. I think the evidence we have from a much more informal, less structured efforts would suggest that there's a lot of the public that's going to be fairly positive about this as long as certain provisos are included, certain protections are included. I don't think we're going to find that there's very strong objections across the board to the concept, but I think there will be issues about the details that will come out of this kind of study that will inform whatever happens next.

DR. WILLARD: Joseph and then Debra.

DR. TELFAIR: No. Actually Ms. Masny was before me and then I'll go after her.

MS. MASNY: Just a question regarding, again, the public engagement. It said in our readings that the National Children's Study took about six years just in the development of their design and plan. I don't know. Was there any type of public engagement in their whole development of their program and if there's anything that we could learn from that?

And also several of the other initiatives from NIH, the Genes and Environment Initiative, has there been sort of a similar approach to try to get this public engagement? And would it be a worthwhile approach to review the approaches that they took, and are there any gaps there that we could then fill?

DR. COLLINS: So, with regard to the Children's Study, they've done a great deal of public engagement efforts during the course of these six years in various settings. I can't, off the top of my head, go through the specifics of exactly all of the various constituencies that they've consulted with. A lot of this has been driven by advocacy groups who are very enthusiastic about the idea of getting better answers to why it is that certain childhood diseases occur, and I think that has been probably the strongest voice. But they actually had already initiated, using funds from the Child Health Institute, a series of vanguard centers in specific parts of the country, each of which had a public interaction consultation component. So there's a fair amount of data there that could be certainly pulled out and made available to this committee.

For the GEI and the GAIN projects, these are projects which are focused on specific diseases where there have already been cases and controls studied as part of a clinical research project where lots of clinical information has already been collected and DNA samples have already been collected. The idea now is to apply whole-genome association analysis to those samples. So it's much less of a large population kind of question, but obviously, each of the studies that may end up getting the genome analysis done have already gone through some investigator-initiated effort to recruit those subjects and that's all been IRB-approved and certainly involves both informed consent and some, in many cases, ongoing contact with the participants. But it's really a very different kind of setting than I think what we're contemplating for a large-scale cross-sectional population cohort.

DR. WILLARD: Joseph and then Debra and then Jim.

DR. TELFAIR: This is a two-part question, so it's sort of a connect-the-dots thing. The first part that I had, because it keeps coming up in different ways, is can you speak a little bit about the whole -- these are interrelated methods, time, and expected outcomes -- why the focus on these particular types of methodologies? I know it's a pilot study, but in terms of data, in terms of obtaining information, in terms of data collection, and particularly analysis, it's just going to be a little bit difficult given the time frame. But then sort of the expected outcomes of this based on the message that's going to go out.

My question earlier was already asked. Ms. Berry asked about the campaign because it's always effective if the public knows what's coming before something goes out to them. If that's not going to, it sounds like, happen, then the question I have, related to the methods and the timing and then what you expect, is what is going to be the message prior to this going out? That's the first part of the question.

The second part of the question is you said, at least in the initial part you gave to us, that it's a pilot study, which I understand fully. But there's a next step you hint at, which is that there's going to be more input, some other means. Can you connect those dots there a little bit?

DR. COLLINS: I'm sorry. I didn't completely understand your first question in terms of message. Message to whom at what point? I didn't quite get it.

DR. TELFAIR: Well, you're doing a public data-gathering type of process, even though it's targeted, because they eventually will pick groups and select groups. I understand that's up to the purview of whoever applies and dealing with the best way to come about that.

But the methodological research data on this is pretty clear that if you're going to do this kind of work, if there's some information that is given already that the public is expecting, this type of information that comes their way, people are going to ask them about questions. They're sort of

ready for it essentially and they're able to make more informed decisions, provide more informed information.

But then there's the part of analyzing that information, and you have a very short window of time for this. You only have two years to really do this. Those two are related.

But then the whole idea of the outcomes that then will lead to the next steps, you know, the outcomes of the work. And then next steps, which I know this is a pilot, but next steps for some other way of gathering this information, as you allude to here in the information you gave us.

DR. COLLINS: So, in terms of the people who do participate in this consultation process, again, I don't want to prejudge how our grantees will propose doing this, but the usual way involves some sort of initial educational material so that the public who you're asking the question of knows why you're asking the question and what the concept is, so that there are some facts on the table. And then you engage in a discussion, a conversation, either in a focus group format or in something more survey-oriented about what opinions people hold about that. Again, though, there's not in this model any sort of broad, general public education. It's focused on the people who are part of the study.

In terms of where this goes next, this is a pilot in the sense that I would never want to argue that this would be sufficient public consultation at all to actually conduct such a study. But since we don't know if the study is actually going to be conducted or not, I don't know what will come after the pilot until we have a better sense of that. If there is no budgetary enthusiasm for going forward with this, we may never do anything further than this, or at least not for a long time. This may be sort of it.

If, on the other hand, there's some momentum that can be built behind the scientific value of this, then I think every step along the way, in terms of the kinds of things that were on Hunt's slide, about you'd probably want to start actual collection of clinical information and DNA samples on some pilot scale, and you'd certainly not want to do that until you had additional consultation about how to do it and you'd want to be collecting information all the way along during those pilots that you might run in 10 or 15 centers. And only then would you contemplate scaling this up to the half a million or a million people which would be necessary for the full power of the study.

DR. TELFAIR: All right. Thank you.

DR. WILLARD: I've got Debra and then Jim and then Chira.

DR. LEONARD: Francis, on your list of bullets, under optimal approaches to recruitment, you emphasize how to engage family members, but one of the concerns that I see of doing this large population cohort project is engagement, how you engage the uninsured, the under-represented, the underserved. And I think unless those discussions happen, even in this pilot study, I'm very concerned that that's going to be a big hole that has to be filled because I think that those people are going to be the hardest to engage in this type of study. That's more a comment.

The other question that I have relates to terminology, and once terminology is determined, it's hard to alter. But this is being called a U.S. large population cohort study. So that implies that you have questions that you're asking. In reading this draft and participating in the task force, it's not clear whether you're going to be targeting specific diseases or whether you're really creating a

biobank, biorepository, medical data, environmental data repository that then can be used for any kinds of studies.

How you start selling this with this public engagement process, I think it's important to distinguish whether you are talking about building this repository that can be used then for any kinds of gene/environment disease studies or whether you're targeting it to specific diseases because the thought process for those who participate will be different.

Also, through the whole flavor of this report and how we word it, it's very different -- you know, which of these are you doing, and I don't think the committee, SACGHS, wants to be out of line with the thought process of the NIH.

So could you clarify that?

DR. COLLINS: Thanks, Debra. I appreciate both comments.

In terms of the reflection on the need to be sure we're sampling the underserved and the uninsured, a point well taken. It's sort of in here in terms of communities with special needs and later on in another paragraph, it talks about socioeconomic status and so on, but it could have been more clear that we absolutely need to find out the opinions that come from those sectors of the community.

With regard to the nature of the study, I think your point is very well taken. Maybe we shouldn't be using the "study" word. In fact, many times, those of us talking about this have come to that same conclusion. What we're really talking about is a resource. A repository somehow sounds like something that's a little sleepy and dusty and maybe sort of locked away somewhere and people occasionally go in and look around, but it's not really very active. This ought to be a resource for discoveries about every disease that's common enough to have enough incident cases during the lifetime of the project. And it is not going to be hypothesis-driven. It is not going to be driven by an interest in particular diseases. It's going to be a way, and a very efficient way, to collect the kind of data that you would need to study any disorder that occurs with a high enough incidence to have that kind of power represented.

So, believe me, more hours have been expended trying to come up with a really savvy, eye-catching, acronymic kind of title for this kind of effort, and I don't think we're there yet. But I think you're right. Maybe "study" is not the right term for what we're discussing here. It's a resource and it ought to be a community resource in the sense that it will need to have accessibility to hundreds, thousands of scientists who have good ideas about how to use it. It shouldn't be a closed shop at all.

DR. LEONARD: But then, in talking about this, I think you need to talk about the building of the resource and then subsequent to that, it will be fruitful for all kinds of studies. It might be more saleable if you separate resource or project or initiative -- whatever you want to call it, but a repository is rather dusty -- from all the kinds of things because it also gets to the enormity of the value of what you're really talking about. You can't not talk about the subsequent studies because I think you have to be prepared with access to the data issues and those kinds of things. But I think that this is a huge thing and maybe the committee can discuss this also further.

DR. COLLINS: That's a great point.

DR. WILLARD: I have Jim, Chira.

DR. EVANS: This is obviously a really promising study, and I keep thinking about ways of getting around what, to me, are the biggest obstacles to carrying it out. And that really, in my mind, is the fragmentation of our health care system.

One of the reasons this is so powerful potentially is its prospective nature. When I see a patient in Chapel Hill, if they've been seen 8 miles away at Duke or they've been seen 20 miles away in Raleigh, I have no idea what's going on. It's awful. And we face a huge challenge that Britain doesn't face, that Japan doesn't face because of that. This is especially important too with minority populations because their health care is even more fragmented.

I'm wondering if, given the emphasis and the interest in the electronic medical record and that movement that is clearly really important and is afoot, whether there's been any thought to trying to combine in some kind of pilot way this project with that. It seems a natural if you could couple those two things because if you can solve that problem, then I think you can realize the promise of the study, but it's a big problem.

DR. COLLINS: So that is a terrific point, and yes, there has been quite a lot of discussion about whether this could serve as a pilot for an electronic medical record system for the half million or so people who are involved in this study. If you could learn through the process of setting up such a record system on such a research basis where the problems are and where the solutions are, we might be a little bit further towards what otherwise is a rather slow-going, frustrating process.

DR. EVANS: And maybe a deal-killer. Right?

DR. COLLINS: Yes.

DR. EVANS: Just real quickly to follow that up, in the U01, it might be interesting to explore the public's views on that. One of the reasons we have fragmented medical care is people are so scared about privacy. The idea of a universal health card, a single ID card, is something that strikes terror in much of the U.S. populace, rationally or irrationally. I'm just wondering if in this pilot study, whether those kinds of feelings and ways to reassure the population and the safeguards that might need to be put into place would be useful.

DR. COLLINS: That's a good point.

DR. WILLARD: Chira?

MS. CHEN: From what I've known, there is a study similar to this, but on a much smaller scale, for adolescents in Marin County. It's a prospective study. Basically that study is actually spearheaded by the advocates. There is a high incidence rate of breast cancer in Marin County, and so they had this campaign to find out why there is such a high incidence rate. So they are actually doing a prospective study of adolescent kids, girls. They go to different schools to cover all the bases of the socioeconomic sectors, and then they pick them out and then they just do the watching, taking samples along the way. I think that's probably a patient advocate-driven process, and I think if we wanted to do something similar to that, we probably would need to find out if the patient advocates could engage on it, and if they could, it probably would get this thing working and started.

DR. COLLINS: No. I agree. A study of this sort, if it's going to go forward, you would hope to be able to engage advocacy groups, particularly for the disorders that are most likely to have discoveries made, which would be the common disorders, heart disease, cancer, diabetes, obesity,

asthma, hypertension, and so on. I think there is growing interest amongst advocacy groups about this model, although I don't think there's broad understanding yet about what is actually being proposed. At the present time, the way NIH has conducted research of this sort has generally been to set up a prospective study on a particular disease. We have the Framingham Study or the Jackson Heart Study that look at cardiovascular disease. The Cancer Institute runs a long list of specific prospective studies on particular cancers.

Here we're talking about trying to come up with something that is both more global and perhaps more cost effective because you don't have the duplications of following a lot of people who get a disease that didn't happen to be the one you're interested in. You're interested in everything, which maybe is a bit of a silver lining, by the way, in the budget requirement that if we did this study, we might not have to do a bunch of other studies that haven't been started yet because they would basically be brought in under that umbrella.

We did do a survey and put out an RFI that we got a lot of responses for to see what prospective cohort studies are out there. You've mentioned one and there are lots of them out there that are being already initiated. People are already being followed, sometimes for many years. And it does look as if you might be able to incorporate some of those into this new resource in a way that would take advantage of work that's already been done and money that's already been spent, but it wouldn't really suffice if your goal is to get a true snapshot of the population because there are vagaries of age distribution and geographic distribution and gender distribution and race and ethnicity distribution. You would not be able to populate more than about 25 to 30 percent of your resource with existing studies. The rest would really have to be recruited de novo if your goal is to get a real snapshot of the population.

DR. WILLARD: Julio? Or Chira, did you have something more to say?

MS. CHEN: I think to understand how the process occurred, it will help to do a more global understanding of engaging the public because these smaller studies, even though they are targeted to a particular population, but if we could use the information that was generated in those little pilots, how they went into the public and engaged them, maybe we could get some information out of that.

DR. WILLARD: Julio.

DR. LICINIO: I think the issue of the name of the initiative is -- you spent a lot of time talking about this -- a problem because in this very tight budget climate, if you go to Congress and ask for money for a resource or a repository, I don't know that they're going to be any more inclined. I think the current name, which is "Possible Large-Scale Studies of Genes and Environment, and Common Diseases," is okay because it implies that it's studies in the plural, not like one thing. It could serve many purposes.

But I think it's a bit of a dilemma because if you are strictly accurate, those who don't have a hypothesis, who don't have a specific goal for one question they're trying to address, it is not technically a study. But I think if you try to sell it by any other name to Congress, I don't know you're going to get any money. I don't know if you're going to get any money if you call it a study, but --

(Laughter.)

DR. COLLINS: Well, we had various names but they never really caught people's imaginations. One was AGES, the American Genes and Environment Study. Another was USA HEALTH, the United States Assessment of Heredity, Environment, and Lifestyle for Total Health. But USA HEALTH made some people think of a health insurance company. Sorry, Reed.

(Laughter.)

DR. COLLINS: So it didn't quite get above the threshold. But if you all want to put your thinking caps on and come up with something that captures the significance of what's being proposed, without having any negative buzz words like "study," that would be great.

DR. WILLARD: Sylvia.

MS. AU: Francis, obviously this study will need to be a multi-institutional study, multi-agency study. How much of that input would be put into this pilot study for multi-agencies, multi-institutes?

DR. COLLINS: We certainly, in the process of going through that 18-month study design effort, had input from a large number of NIH institutes and multiple Department of Health and Human Services agencies and even some from outside the Department like EPA. For this particular RFA, we also got input from several other NIH institutes, and we certainly used the discussions that had already happened in that previous 18-month study, plus the discussions that have happened around this table with the Secretary's advisory committee.

So I think we have a general sense of what other groups are interested in learning from this, and certainly, as we go forward with this, we are welcoming the opportunity to interact with all of the other agencies and institutes that have an interest, which is a lot of them. I think that will be a pretty open environment.

DR. WILLARD: I have Ellen and then Debra.

DR. FOX: I thought it would be useful to update the committee on what's going on with the Department of Veterans Affairs. It's been mentioned a couple of times. You have in your packets a recent press release that I'll elaborate a little bit on what's going on.

As I've previously reported, the Department of Veterans Affairs is developing a genomic medicine program that builds on ongoing genetic and genomic research efforts by the Department. The plan is really to make use of VA's unique assets, which really are in contrast to some of the problems that have been mentioned here in terms of, for example, we have a very comprehensive and sophisticated electronic health record system in the Department of Veterans Affairs. We have a very large, stable, and loyal patient population of close to 8 million enrolled veterans. We have a centralized and integrated national health care system which is not fragmented and we do have the ability to standardized throughout the system. And we have an already robust intramural research program that really allows us to apply uniform standards across the country.

So to take advantage of this, we are planning to develop what will be the largest adult genomic medicine research and clinical resource -- we are calling it a resource not a study -- in the United States. The program is expected to involve the collection and storage of over a million patients specimens, together with relevant demographic data and links to individual clinical records. So

the aims of the program are to improve not only the care of veterans in terms of their clinical care in research mode but also to benefit the health of the nation as a whole.

The VA genomic medicine program is proposed to have national management in Washington, D.C., with coordination among the Department of Defense, Department of Health and Human Services, and other agencies and resources in VA's central office. The genomic medicine activities will be conducted at multiple sites throughout the VA health care system.

The FACA committee has been established. The notice appeared in the Federal Register on March 16, and you have a list of the members of that committee in your packets. The committee will provide advice to the Secretary of Veterans Affairs on the scientific and ethical issues related to establishment, development, and operation of a genomic medicine program. Specifically, the committee will assess the potential impact of a VA genomic medicine program on existing VA patient care services, make recommendations regarding policies and procedures for tissue collection, storage, and analysis, and make recommendations on the development of a research agenda, and recommend approaches by which research results can be incorporated into routine medical care.

The time lines in the budget for the program have not yet been established, and I'll continue to keep the committee posted as events unfold. We're early in the development. And I will try to answer any questions if you have any.

DR. TUCKSON: First of all, thank you, Ellen, for that.

Mr. Chairman, I want to just make sure that the committee is cognizant of the clock. You've had an opportunity now to ask a lot of questions to Francis and so forth. There was a lot of stuff that our committee chairman has put out there for you as well. So as the next comments are made, based upon all that we've heard -- and I was glad to hear from the VA and that was an important observation as well. As the next comments are made, I think you need to really start tailoring in on what do you want to do by June, what is the advice to the subcommittee. You've got to lock in now because it's getting late. I'm always the bad cop. That's the problem.

DR. WILLARD: You were just one person too soon. Debra has a final comment.

DR. LEONARD: No, no. I was going to say shouldn't we get on with our development of recommendations because the time is running out.

DR. WILLARD: Thank you, Ellen, for that information.

I think I would lead this off with a general question for the committee members who weren't on the task force, as well as those who are on the task force. The question is, especially given our now push to try to get this finalized by the June meeting, whether the draft report and its list of issues is essentially too all-inclusive and that the risk of being at the 1,000-foot level is that we may make it more difficult for ourselves to finish it by June, or are people, in general, comfortable with the level of depth and the comprehensiveness and the breadth of the report?

DR. TUCKSON: By the way, speaking of comfort, if you've not noticed, there ain't no break. So this is not like kindergarten where you've got to raise your hand. You've just sort of got to roll.

DR. WILLARD: I assume that means you'll be leaving us, Reed.

(Laughter.)

DR. TUCKSON: There were a few people who were wondering where the break was.

DR. WILLARD: So let me throw that question out because I think we do need some feedback and it will help guide us for the remainder of our time here today in terms of how deeply we want to drill and how broadly we want to be sticking flags in the ground. So let me open that up. Joe.

DR. TELFAIR: Yes. One of the things it seems to get at that, because it will kind of put some structure around it, is two things. One is besides prioritization of the issues, it's also what will be the time. If we had to walk through each one of these in terms of setting priorities, would you also set a time frame related to that particular priority? I was wondering if that is reasonable to also have some discussion because it is a lot of information. It is a lot to try to cover, and it's hard to make that judgment whether it's way too much information because then you have to decide what you're going to cut and what to keep, what not to keep, what to modify, and that sort of thing. It seems a lot of time and effort has gone into pulling all this information together. Prioritization seems the first thing to do and then some kind of time frame around. In other words, if you do a study, can you build on the study over time and add parts to that as you go about doing the work itself, sort of a study, discovery, study, discovery, that sort of thing?

DR. WILLARD: Well, I'm not sure what you're asking in the sense that we're not trying to design the study. We're making recommendations.

DR. TELFAIR: No, no, I know, but in terms of structuring the recommendations, structuring what would go into the report and how we get it done, all I'm suggesting is prioritization is the first step in terms of making recommendations of what is a priority over another. But I'm also wondering whether or not there needs to be some temporal aspect to that as well.

DR. WILLARD: Well, certainly one approach could be -- and we don't need to do this part today as long as people are receptive to the idea and responsive to the idea of doing it from your desks at home -- is that we could prioritize the issues, essentially get a sense of the committee by a vote. That's how we dealt with our original prioritization process two years ago. And within the issues under each one of the policy sections, simply let the committee decide which seem to be priority 1, priority 2, or priority 3, and that, at the very least, would help us flip and flop different sections of the report in order to focus more intensively on the ones that everyone agrees are the critical issues.

But I think Kathi and the rest of us on the task force can take a look at whether any of them are temporally dependent on other issues, because there's no point in having something listed fifth if you have to do that one first before you get to the others.

DR. TELFAIR: Right, and that is my point. You can't just prioritize. You also have to look at the issues related to logistics and how would those would fit together logically. It may be that you would set a prioritization for things that are there. So, yes, thanks.

DR. WILLARD: Yes, Kathi?

DR. HANNA: When I was trying to put the information together that was coming from many different sources, the way the report is structured right now, I did try to organize it temporally. So the first question is research policy, go/no go, and then sequentially designing the study, what should you think about. As results begin to emerge, what kinds of things should you think about

because I thought that there might be some logical checkpoints along the way where you might have different kinds of public engagement mechanisms, but you certainly want to consider the full time line even from the get-go. But I tried to organize it that way because I thought there might be different approaches you would come up with depending on where the study is, either from its initiation to its final conclusion.

DR. WILLARD: Sarah?

MS. CARR: I think also, as part of the recommendations section of the report, you could provide additional advice to the Secretary about all the issues that are discussed and identified and say that in order to begin to think about whether to do such a study, the very first question that policymakers will need to address is the following. I think if you do that, you will probably find that the order parallels the order as Kathi has organized it. So that would also mean that you wouldn't have to do a rearrangement of the actual report too if you focused on the recommendations section.

MS. AU: I was wondering if there is a chance to break up the report to make it more palatable. We know what things need to be done first, like the public consultation. You need a general overview, of course, of what the project is, but if we're looking at things like getting something to influence maybe the Secretary for the budget year, getting something in a smaller chunk as a report and then doing chunks of the report as we work through this really large, large issue, and making it more palatable for people so it doesn't have to be this huge report on everything under the sun.

MS. CARR: Well, certainly there will be an executive summary of the report. That's definitely something we know we would need to do. Rather than that being a total sum of the report, that could be the things you want to highlight as well.

MS. AU: This is such an extensive study and such a huge issue and there are so many things that we do want to add into it and putting in detail. If you did it as parts, that there's a priority of what you need to do at the beginning, and then we can get more and more in-depth as we obtain more information from the pilot study and from other studies that are done and do the report not as a single report, but as parts of a report so that we can address the issues fully.

MS. CARR: So that would mean you would sort of indicate to the Secretary that the committee is going to be continuing to work on this for a long time, and that for right now, as the 2008 budget cycle begins, we want to tell you the following about all of this, so focus only on that. Hunt, I don't think the task force really considered that approach. That's kind of a new thing.

MS. AU: I think only at this meeting we were told that, for budget considerations, we need something by June.

MS. CARR: For 2008 I guess, would that be a focus on public consultation then for the spending of additional resources?

MS. AU: I think it would depend on what the committee decided was the starting and the endpoint could be for the first priorities.

DR. WILLARD: Well, let's remember, we're not designing the study, nor are we necessarily making a recommendation of go/no go. We haven't been asked that question. We're simply supposed to lay out on the table for the Secretary, to do with as he wishes, a series of possible

approaches that would help him get to the question to the go/no go point. So even in terms of what might be valuable, what might go into the FY '08 budget, that could be absolutely anything. It might only be public consultation, but it might be early pilot projects, and presumably Francis and others would be deeply involved in that process, and our input isn't necessarily asked for nor expert in that regard.

Sarah?

MS. CARR: Hunt, I think you've made a really good point. Sylvia, this is a very complex thing in that we've identified many issues. In some ways, I sort of think personally that it's incumbent upon the committee to let the Secretary know. Look how many issues there are. It is rather daunting, but it might be important for the Secretary. I'm sure he already has some indication of this, but to see them all laid out in a big report and in a thoughtful way I think might be of value.

DR. LEONARD: I agree with you, Sarah, that having the whole picture presented is a better way. I'm afraid that if we focus on what we think should be done first that we're not giving him the perspective of the entire project, and a lot of the discussions that have already gone on on all the different areas of concern that need to be addressed.

DR. WILLARD: Robinsue and then Emily.

DR. FROHBOESE: Just a quick comment. I definitely second Debra on that and do feel that a comprehensive approach is very important.

But also, given the fact that there seemed to be very frequent, new developments and new projects that are starting, the VA project, a couple of other projects that have just started within the past couple of months, I know that there's an appendix that talks about other efforts, but other initiatives that have started both on the federal and private level I think will be really key to highlight here and how any efforts that we might be involved in would be coordinated with or integrated with those efforts.

DR. WILLARD: Emily?

DR. WINN-DEEN: So, first, I wanted to say I sort of like the outline here where you're starting to make arguments in favor of the different things. It reads a lot like the sample ballot that you get that describes arguments in favor of proposition 103. What seems to be missing is the other side of the story. I think to have a balanced report, we should help the Secretary understand both the arguments in favor, as well as the arguments against that he may have to overcome and deal with. So I think that's an important aspect that should be in this, at least brought to his attention.

I also think in view of our sort of ongoing role to urge coordination of effort and all of that kind of thing among agencies and within agencies, that it would be very useful for the Secretary to receive a comprehensive view of what's going on already, as Robinsue indicated, both within his own organizations as well as in some other places like the VA, so he can get a sense of the fact that this is sort of a continuation or an evolution from a series of smaller studies that have set the stage and led us to the point where we're just about ready to consider something on this scale and scope. It's not just coming out of nowhere.

So I think from that point of view, that perhaps someone from NIH could be really helpful in terms of writing a section that really describes how the different things that have gone before -- you probably already have this in your word processor there somewhere, Francis -- have led up to

this and the lessons learned and how various compositions of things that are out there already can be used to leverage moving forward on a study of this magnitude.

I think you get to the point where you're eventually going to have to sell this to a funding agency, the U.S. Congress. You're going to have to sit on the other side of the table and think about what arguments you would want to have in front of you for that funding. They have to be very persuasive arguments, and you can't just tell one side of the story. You have to tell the whole story.

DR. WILLARD: I believe we have about 45 minutes at this point.

There are a group of slides, the first of which I've got up there now, which were essentially straw man either mechanisms or approaches. They're written essentially in terms of being recommendations or could be couched in terms of specific recommendations. These are on the slides that are in your folders as well.

There are four related research policies, this being the first of those, and these came a little bit from the task force and its conversations. It also came from staff and its deliberations, and they're literally just ideas thrown out for people to either respond to or to guide us as we go on to the next stage.

So this first one really points up the need for consultation with the scientific community as well, not just the public at large, to address, in particular, the issues of leveraging the half dozen or more existing efforts that are already out there.

I'll start this off and then others should chime in. I'm not sure what the approach is here except to broadly consult where no man has consulted before.

(Laughter.)

DR. WILLARD: But to ensure that the broad scientific community is part of that. Obviously the scientific community has been engaged at one level already in the task force that Francis had.

Joseph?

DR. TELFAIR: I'm just wondering whether this is actually -- let's see. I'm trying to put this as euphemistically as I can -- a redundant recommendation because it sounds to me like everything that has been said, this has been done already at some degree. You spent the time with a number of different groups and committees and you've spent it in information-gathering and you constructed that, and this committee has come up with this report, as well as, Dr. Collins, you've come up with the RFA you put out already. So I'm wondering whether or not this has already been done.

DR. WILLARD: Certainly it has been done with a group of scientists, including some that, as I understand, were nay-sayers in the beginning and then came along with the process and became believers, if I remember the story correctly. But there is a large number of people in the broader scientific community who either know nothing about this right now or what they know, they don't like because they view this simply as a challenge to their funding for their own priorities, and this doesn't happen to be very high on their list of priorities.

So Francis couldn't possibly have taken on all of them, nor would he necessarily want to, but the Secretary may wish to have some mechanism that allows one to touch base with the broader community.

DR. TELFAIR: Well, then I'm wondering. I understand, okay. Well, then do you need to be a little more specific then?

DR. WILLARD: No. We don't need to wordsmith here. As long as Kathi and Sarah are taking notes, they'll get the sense of how to revise the language.

DR. TELFAIR: All right. Then I put this as a question related to this particular slide. Do you need to, even if it's broad, have a little bit of a good working definition of what broad means?

DR. WILLARD: Julio?

DR. LICINIO: If I remember well, when the Human Genome Project started, it was during like a dry funding period and there was a lot of practice like FASAB sending letters to you. From what I've seen now, the level of opposition to this is actually smaller than to that back then. Am I delusional or is that true?

DR. COLLINS: I think it's a little hard to draw the comparison because I think Hunt is right. A lot of scientists haven't heard about this possible project, and maybe as it gets more broadly discussed, the intensity of those who are unhappy because of this concern about the budget might go up. I don't know.

Certainly you have to be careful here. If you're intending to obtain unanimity from the scientific community about going forward with something, that will mean you're not doing anything very ambitious or interesting. So the goal of consultation of the scientific community ought to be clearly laid out ahead of time, that it is not necessarily to convince everybody that this is worth doing. You won't succeed at that. The Genome Project, when it started, was probably opposed by about two-thirds of the scientific community. Yet, looking back on it, it was the right thing to do.

DR. WILLARD: Other comments, Debra?

DR. LEONARD: In this, there isn't really a detailed presentation, if you will, of the scientific utility of large population resource. Has that process been done? That's different than opinion polling or selling. But is there hard scientific data and how can that be presented to the scientific community at one level, to the public at another level? Because I hear a lot of skepticism as to whether you really will attain the power to be able to identify genetic markers, et cetera.

DR. WILLARD: Go ahead, Francis.

DR. COLLINS: Terry Manolio, who is a well-regarded genetic epidemiologist, is actually writing a review on just that question for Nature Review's Genetics, which I hope will be out in a couple of months, which really does try to go through in pretty rigorous fashion the scientific arguments for the value of this data and how it's different from the kind of data that you would get from a case-control study or other study designs.

DR. LEONARD: Can we get that?

DR. COLLINS: Yes, as soon as it's in a form where you could call it finished. It's under construction at the moment, but it should be, yes, distributable pretty soon.

DR. WILLARD: Other comments here? Agnes?

MS. MASNY: This is just a question. I think in the report, when we read it, there was the question of whether the research policy overview would be that of a hypothesis-driven versus sort of this resource, and it seems like that was answered. But I think the other question that may go to this slide about the broader scientific community input is the issue of the pooling of current case-control or cohort studies or do we construct a new association study. I think those were sort of the those in favor of. That's where the two sides went and whether something like this could be addressed in this light.

Or the other approach is that since we're doing a pilot with the community engagement, would there be one way to actually look at using some of the current existing case-control studies to maybe answer some of the clinical questions that Debra just brought up, the clinical utility?

DR. WILLARD: I think the issue of clinical utility is obviously not an easy one to address, especially when you're dealing with, if it takes a million subjects to know whether it's going to work, then no one is going to have the data to do that. I think it's useful to see the review that Terry is putting together.

But, Agnes, you're absolutely correct. There are well-respected scientists out there who say this is nuts and we could do 10 case-control studies of a reasonable size before one should do this. And that's an open debate that we should acknowledge.

MS. MASNY: Would it be feasible to actually do a feasibility study maybe with a few of these people that already have registries maybe for a specific disease population to actually see if some of these gene connections with the SNPs and the variations that we're trying to zero in on is actually feasible to do even in a smaller population?

DR. WILLARD: Well, Francis, correct me if I'm wrong, but certainly those studies are being done and they're well underway.

DR. COLLINS: So, for instance, the Framingham Study is about to engage in whole-genome association analysis of a substantial fraction of the participants. The NCI is funding whole-genome association analysis of large prospective cohorts on breast cancer and prostate cancer. So you will start to see some of that data generated.

Again, one of the goals of a prospective study -- I don't think I have to remind this group because you've thought about this a lot already is to identify what the environmental contributions are and what biomarkers might exist in terms of prediction of disease before disease is actually diagnosed. Those two things come very poorly out of case-control studies, if at all. Hence, the logic behind arguing that you really need both these study designs if you're ultimately going to get the answers we need.

DR. WILLARD: Linda.

MS. JOHNSTON-LLOYD: I just wanted to point out that we're addressing the vulnerable populations of the uninsured as part of the U01, if they are to become part of the pilot study, and reaching out to the community for engagement. One positive outcome that could result from the

study is the fact that we would increase the understanding of health information around genetics among these populations who we know have limited literacy skills. To me, to get them to participate, they're going to have to first understand it, as we all know.

So I would think that that might be something -- I don't see it specifically, but on the bullets, it said charge to the grantee, that that would be a key, important component in that. That really goes along with the Secretary and the Surgeon General's real caring about the health literacy of the people in our country. That's kind of a side comment, but it does tie in.

DR. WILLARD: Debra, and then I want to move on I think.

DR. LEONARD: I move that we agree to this and like move on others. I don't know whether anyone disagrees with this.

DR. TUCKSON: All in favor?

(A chorus of ayes.)

DR. TUCKSON: Nays?

(No response.)

DR. WILLARD: The others are even easier, notwithstanding the wordsmithing. This one here relates to the potential value of a collaborative model of project leadership and management. It speaks to the issue that many different agencies and units within HHS have an interest here and even already have a thumb in the pie. He will have to use his leadership to figure out how best that should go forward.

Any comments on this? Debra?

DR. LEONARD: Is this getting at the heart of academia and the single investigator promotion process? The interdisciplinary nature of this and the way academia currently works is by the single investigator doing hypothesis-driven. So part of what has to be done here is the engagement of academia, and I don't know how you do that. But this has huge implications in engaging the scientific community. If they still have to get promoted in academia based on their grantsmanship, then anyone who's not the principal investigator on a project is not going to participate. So I think this is coming in other ways to academia with the whole NIH Roadmap, but I think that's particularly significant here.

DR. WILLARD: The HHS Secretary is close to all-powerful, but to expect him to reach into the hornets' nest of U.S. academia --

DR. LEONARD: But it's the engagement and having them understand where this goes. That discussion is already ongoing in academia. Maybe this reflects back to the first one that we just voted to pass. I mean, that's part of the engagement of the scientific community also. That's one of the fears that scientists may have in going down this road and investing so much because it will be multi-disciplinary approaches and grants that will be given to access this resource.

DR. WILLARD: I think there are points there that we can certainly highlight in the report because that's a point well made.

Kathi?

DR. HANNA: Yes. I think this particular recommendation was -- maybe it's not clear enough -- meant to focus on, I think, the governmental level not at the academic level.

DR. WILLARD: This is NIH, VA, et cetera.

DR. HANNA: This is HHS-wide. Right.

DR. WILLARD: Joseph.

DR. TELFAIR: I'm adding to this because I was going to say that already there are several of these types of announcements that are made from multiple institutes and multiple agencies that collaborated to co-fund these projects. To just give some grounding to this, and maybe add that to the recommendation to look at some of these other successful models that exist, that would help a lot there.

DR. WILLARD: Okay, those are good points.

The next one -- Mr. Chairman, I don't see the need to vote on these as we go because we're not at that stage yet.

This one is even, I think, easier to consider.

DR. TUCKSON: By the way, just in the interest of time, though, if we sort of say okay, move on, just note that that means you're saying yes because we're not going to go back and play around with this.

DR. WILLARD: Well, we'll play around with the wording, but we're not going to --

DR. TUCKSON: Right.

DR. WILLARD: This is your opportunity to speak.

This one relates to broader consultation and looking for possible leveraging with the international community and the private sector. I think to some extent, both of those are already ongoing, at least from some perspectives, but it's well worth having the Secretary focus on that approach. Debra, you look --

DR. LEONARD: I agree completely. One of the things that I'd like to suggest is that if such a biobank would be created in the U.S., one of the benefits of having cooperative or collaborative arrangements with other biobanks is for cross-validation. So you do a study in the U.S. and you use similar cohorts from other biobanks then to validate whatever markers are done. If investigators in the U.S. don't have access to those other biobanks, then that cross-validation won't happen as readily. So that may be one of the things to explore in these collaborative types of agreements.

DR. TUCKSON: Hunt, what I would also say is I think on things like this, first of all, it's always important to state the obvious over and over again, given that we are in D.C. But I would say this. And we're not here to write the language, but I think if you just as a general template for these things, where they are ongoing, given Debra's point, where things are happening, I think if

we say because the committee is interested in facilitating this and that, we are aware that people are looking at such and so and so, therefore we hope the Secretary will take advantage of that and help to move those ongoing activities forward more rapidly. That's sort of the spirit, I think, of what a lot of these are getting at. So we're sort of saying there's a reason why we want you to do these things. We're aware that certain things are happening. We are here to say that those are important things which we hope that you will pay attention to and thereby not have to reproduce the wheel.

DR. WILLARD: Okay. Any other comments on this one?

(No response.)

DR. WILLARD: The fourth of the approaches laid out under research policy, the fourth and last one, relates to attempting to ensure that there's widespread and ongoing support for a stable investment in this. I'm not sure how much of that is under the HHS Secretary's purview because the budgetary process -- correct me if I'm wrong, Francis, or anyone else among the ex officios -- you can't fund a 10-year program up front without continuing to revisit that every FY. Is that correct?

DR. COLLINS: Every year is a new year.

DR. WILLARD: So it can be spelled out, but it will take an ongoing series of broad consultations and making sure there's broad engagement every year so that it continues to have support and doesn't get stopped before it could be of any use.

Debra?

DR. LEONARD: Are there lessons to be learned from the Framingham Study and the way that that got -- I mean, that's been continuous for years, and there are others.

DR. COLLINS: Since 1948. That's right.

DR. LEONARD: All right.

DR. COLLINS: You could also look at the Genome Project, a project that had to be conducted over 13 years to succeed. Basically once you get it started, you need to ramp up to whatever the stable level of funding is, and that has to find a home somewhere that becomes part of the base so that it's not one of those things where you really have to start from scratch every year. But there is an opportunity to debate whether the base is too high or too low. So Framingham is funded by the Heart, Lung, and Blood Institute, so it's in their yearly funding where that support comes from.

DR. WILLARD: Other points or comments here?

(No response.)

DR. WILLARD: Then we have two slides, three possible approaches relating to research logistics, one dealing with the issue of stratifying the sample population. This is not solely a research logistic question because this clearly reaches across into the public engagement domain at the same time.

Does anyone want to comment or address that first one? These two are obviously related.

DR. WINN-DEEN: I guess I'm a little confused because I thought we were trying not to have a stratified population, but have a population that would be representative of many things. So I'm not sure really what even this means.

DR. WILLARD: Well, I think the issue that has come up in many quarters -- the Human Genome Project is a good example and the HapMap is a good example. We have the genetics and genomics community that's making some arguments about the scientific rationale for or validity of various descriptors. Then we have another branch of the government that every year has you tick off boxes that say which one of those groups you think you belong to. I think even in the planning for this -- again, we're not presupposing how such a project may unfold, but there are identifiable population groups where everyone puts up a flag and says we've got to make sure we get enough from that group or we need to find ways of getting full engagement from that group. So there is a stratification in terms of recruitment and trying to make sure the data are readily applicable to "identifiable" subgroups, depending on how you identify them.

DR. LEONARD: Well, I guess I would rather say it for assuring diversity in the projected sample population. Stratifying to me is not what you're striving for here. What you're trying to do is, when you do this 500,000 people, you've got enough representation from all the subgroups that you can make statistically valid conclusions. You're not trying to go out and say, all right, we're going to, a priori, say we're going to collect X number of people who say they have a family history of heart disease.

DR. WILLARD: No. I think this is more stratification of population groups, not clinical groups.

DR. EVANS: And I think you have to have stratification or you get stratification bias if you don't delineate. So that's a statistical necessity to stratify your populations, or you end up with bias.

DR. WINN-DEEN: Yes. I guess I just object to the word "stratifying." Can't we use diversity or something?

DR. WILLARD: You're absolutely right. This is prospective. So you're not saying we want 20,000 cases of disease X because that's not the purpose of a prospective study, but you do need to identify we want 100,000 members of this population subgroup, or that's the goal.

DR. LEONARD: One of the concerns I have with at least the stratification scheme that was presented and developed through the NIH committee that got together and then one of the speakers that came and presented to us -- there's a lot of stratification based on census markers, if you will. So that takes into account potentially economics and race, ethnicity, but it doesn't necessarily reflect genetics.

But if this is a gene-environment-disease study, what about environmental stratification? I know different areas of the population, but one of the speakers said why not stratify based on lives near a toxic dump, doesn't live near a toxic dump. So I think that this scientific discussion is really important to makes sure that we're not stratifying in a knee-jerk way, which I don't mean to insult that committee that did a lot of hard work. But I'm not sure that the environment stratification is really well thought-out, and maybe that's something that GEI could also be considering as ways to stratify by environment, even though "stratification" is the wrong word.

DR. TELFAIR: Whenever you engage in the process of trying to include certain groups of persons, at least initially you always run into the problem of just making decisions about who to include and not to include. It seems to me that in terms of taking a step back and making the recommendation, it would be better to have a clear and consistent definition parameters for systematically identifying and assuring representation of the desired samples, and then let whoever comes on board after that make the decisions about how that will be done because if you do it that way, it leaves room for decisions to be made. I think the argument here has been made pretty clear. You don't want to have preselection when preselection itself may be flawed in some way. You want to be able to get to a point where you can make some really good decisions. So I recommend that.

I know we're not trying to tweak the language, but it just seems to me leave it open to the point where you can allow whoever this consulting and scientific community group comes together to make some of those decisions, but really give them some directions about what I hear everyone saying is about representation. So I would recommend that as sort of a way of tweaking the language here to cover both the first and the second bullet.

DR. WILLARD: Francis.

DR. COLLINS: Again, just in the name of not starting from scratch when there's already, I think, at least a straw proposal out there, the work group that looked at this tried to balance the number of different parameters that you could try to match the study population with the general population without it becoming logistically impossible and came up with, as I remember, seven or eight, which included age, gender, race, ethnicity, urban versus rural, geographic location in the U.S., which has some relevance to environmental exposure, as does urban versus rural, socioeconomic status, level of educational achievement. Those were all down there. If you try to go to a longer list, you pretty soon end up with very small numbers of individuals in each cell, and then you lose power. So you have to kind of think about the balance between those issues.

But it was something the group thought pretty long and hard about, and certainly I would suggest starting there, but I'm not assuming that that's the right final answer.

DR. WILLARD: Other comments here?

(No response.)

DR. WILLARD: That's useful.

The last bullet under research logistics is dealing with best practices for how one gathers and collects clinical information over the course of the study. Some of this, of course, is related to the electronic medical record prospect. Some of this deals with samples, as well as data information.

Again, I don't think it's particularly controversial in the sense that any group who is contemplating this has already done much of this as they've moved ahead.

Emily?

DR. WINN-DEEN: So since this is envisioned to be a long study period, over which time, technologies, and markers and lots of things may evolve, can we put something in here to encourage the data tracking and all of that to also be open to changing technologies or new methods? I think some of the older studies suffered a little bit because the way it was done at the

beginning of the study has evolved over time and now you can't really do that same imaging test or whatever in the way it was done 10 years ago or 20 years go. So there has to be some way of dealing with the fact that technologies evolve over time or even if there's a new something that you want to measure.

DR. WILLARD: There must be similar language in whoever planned the Space Station out there that we're currently building, but it has to change and will continue to change if they find whichever pieces are missing.

Other comments on this logistical issue?

DR. LEONARD: Hunt?

DR. WILLARD: Yes. Sorry.

DR. LEONARD: Should that in some way have a statement tying it to the EMR initiative?

DR. WILLARD: I've already flagged that. You're absolutely right.

Regulatory and ethical considerations. This is a very long one, but it essentially invites the Secretary to convene a group of many representatives who are represented by the ex officios here and others in order to examine all of the sort of regulatory and ethical issues and come up with a list which would add a set of approaches that would be necessary.

Again, I suspect this is already being done in some quarters, but Ellen?

DR. FOX: The wording seems to imply that implementing the regulations would deal with the ethical issues, and I just want it to be clear that a lot of the ethical issues you have to deal with are not really answered by the regulatory requirements in this case.

DR. WILLARD: So one might want to separate those two.

Other comments?

(No response.)

DR. WILLARD: The other side of consulting with that group of experts is consulting with the study subjects themselves on an iterative basis around the issue of the protections that they either need or feel they need or both. Again, it anticipates that this is a multi-decade process here so that there will be substantial changes both in terms of what is of concern today may not be of a concern later and vice versa.

Comments?

DR. WINN-DEEN: So is this really aimed at having an ongoing ELSI component that is there? You know, it's not just at the beginning where you've asked the questions and then, much like the Human Genome Project, had an ongoing ELSI component. I mean, is that really what this recommendation is?

DR. WILLARD: That could certainly be one such mechanism.

DR. WINN-DEEN: Okay.

DR. WILLARD: Joseph.

DR. TELFAIR: This is just to enhance a little bit of what's there. It seemed to me that this recommendation also deals with the power relationship that's going to emerge out of this. If you are paying attention to at least the last part where their recommendation is for enhancing protections, it means that the subjects in the project are actually making recommendations to those who are studying them on how to improve aspects of the project. That sits very well with me, but I'm just concerned about where it would sit with those who are actually conducting this work and whether or not you need to make that real clear, that this is going to need to be considerations of the power relationship between those who are being studied and those who are actually conducting the study.

DR. WILLARD: I think it's fair to say that there probably are a number of models that one could consider and, in fact, are probably being considered or implemented by other countries that are further down this path in terms of what level of ongoing discussion and engagement with participants is in place. I don't think anyone contemplates sort of saying, well, great, you're on the hook, we don't need to talk to you. But there are obviously different levels and frequencies with which one might want to work with the participants. And frankly, some participants may not want to be involved on a regular basis; others may choose to be.

DR. TELFAIR: Yes. This kind of approach to engagement, which is participatory in itself -- the science around participatory work, though, really involves the question of letting those who are subjects make decisions to what level they want to be involved. There's no question about that. So there are models that exist. There's a whole area of work that actually models this very well. It seems to me that we can, as we go into this, just make recommendations for whoever is doing this to look at those models. I agree with you. I'm actually enhancing what you're saying, but there are models right here in our own country. That is done in participatory research models that involve this. So I would recommend that we put this as a part of this part here if we're ever going to do this. There's another part coming up that we also would add that too as well.

DR. WILLARD: Debra?

DR. LEONARD: So in a way, this goes back to the resource versus study language and objective of this project. If it is a resource, then the managers, the leadership of that resource basically act as honest brokers, if you will, to anonymize data to allow access to investigators. So that may be another advantage to having this set up as a resource rather than as a study because then some of the inducement or subject interactions are reduced because they're just creating a resource as opposed to wanting them enrolled for certain purposes. There's less conflict I think.

DR. WILLARD: Then in the public health realm -- the approaches are beginning to look very similar, but now in the public health realm in terms of evaluating, disseminating the findings with those who have expertise in public health. Here I think both this and the next one deal with this dichotomy of whether this is a study which is going to have results or whether this is a resource and the results actually come out in a nearly infinite number of other studies that will be funded in order to examine the data. This, if anything, calls that question into stark relief. I mean, at some point -- and I'm sure Francis wouldn't disagree -- this either is a study that has results that people will examine or it is simply collecting all of the data and those who have been made available to scientists to carry out further studies, future studies. It has to be one or the other. I guess it could be both, but it either has to be one, the other, or both. It can't be vague.

DR. LEONARD: In calling it a study, you basically skip over all the access to the resource issues because it's a study and so there will be results coming out of it as opposed to building the resource and then how do investigators -- the equitability issues of access to that as scientific resource, et cetera.

DR. COLLINS: So, again, we talked a lot about that in previous discussions about the study design. I think the basic idea was you would collect a certain amount of clinical information and medical record information and physical exam information and genetic information and environmental exposure information on everybody who's part of this. The database that gets generated by this resource would be accessible to anybody who agrees to a certain number of stipulations about not trying to identify who the participants were.

A lot of the early sort of associations of genes, environment, and disease would come out fairly directly of that database. But people who are really interested then in digging into a particular disease would be able to mount a much more sophisticated analysis in a sort of case-cohort model, identifying the incident cases that appeared, going back and determining more sophisticated information about those affected individuals perhaps with imaging, perhaps with additional laboratory studies that you couldn't possibly afford to do on the entire cohort.

So it's a little bit of both. The idea would be you would have a basic set of information that in itself was pretty powerful about diseases that occurred at a high enough frequency to have power for analysis, but that would be sort of a foundational floor and then you'd build on top of that a lot of disease-specific, more intense investigations that were mounted by specific investigator interests.

DR. WILLARD: Emily.

DR. WINN-DEEN: Can you just clarify? Because now I'm a little confused.

DR. WILLARD: Who are you looking at?

DR. WINN-DEEN: Francis. What you just said was you envision it as being a database rather than a bioresource.

DR. COLLINS: It's both.

DR. WINN-DEEN: Okay, thanks.

DR. WILLARD: Julio?

DR. LICINIO: I have a quick question about the issue of anonymity even if you call it a study and if there is like an initial study that will mostly be a resource that will lead to a lot of new research.

But one issue that I think is even more worrisome now than what I was aware of before is the issue of anonymity. I don't know if you saw, this past weekend or the one before, the New York Times Sunday Magazine had an issue about sperm donors. So just through the information that people put there like describing themselves like who you are and the family background, you just get some of the key features. I'm sure that in this study there are going to be much more identifying features than you have just in the description of a sperm donor. And you Google that and you find exactly who the person is. Many people have been identified. You need like five or

six identifiers and you Google that and you find the person. So that I think should be a key issue of the initial engagement process because for those who participate, I don't think you can guarantee anonymity with all of this information available about the person.

DR. COLLINS: I think that's absolutely right. I think any guarantee of anonymity, if you're talking about this degree of data collection, is not something that you could legitimately put forward. There's going to be a risk.

DR. EVANS: Not only that, but what you're collecting is the ultimate identifier.

DR. COLLINS: Right.

DR. WILLARD: I think the parallel with the Human Genome Project is pretty legitimate here. Yes, the Human Genome Project was about collecting a resource, namely sequence data, which are now available for everyone to enjoy and study. But it was a study at the same time. There were data being collected and analyzed in order to have that sort of first pass of what the genome was and what it would mean. All of that was part -- correct me if I'm wrong, Francis -- of "the Human Genome Project" before you blew the whistle and said that's now done and we move into another phase.

That makes me feel better. I was afraid I totally misunderstood the Genome Project.

(Laughter.)

DR. WILLARD: The second of the public health ones. Here again, this assumes because this is asking for or at least considering the possibility that project leadership would convene on a regular basis to review research results. This again, depending on how you read that, it's either to review the results of a study and potential answers to questions or it's to review the collection of the data and the availability of the resource, dealing with sort of logistical issues there. This is coming in the section under public health, so the intent is to be in the former category, but depending on whether examination of research results is or isn't part of the actual initiative or project or whatever it's called, this one may need to be reworded a bit.

Comments here?

(No response.)

DR. WILLARD: And the last one under social implications is, in fact, one of the most specific ones, which I think we probably should discuss appropriately, which is that the HHS Secretary would consider establishing essentially a standing advisory committee, perhaps independent of, perhaps not independent of the actual leadership of the project itself, that would periodically look over the shoulders and examine the social implications of the project working with the public at the same time in order to be sure that there is no new set of concerns that are coming along. This is a little bit of a watchdog effort.

And what isn't stated here is who that standing committee would report to. Would this report directly to HHS? Would it report to whichever agency is going to lead this project, et cetera? And one could imagine different ways of putting that forward. So I think for us, it's to get a sense of whether some kind of a standing committee on social implications is a good idea. We can, of course, leave it up to the Secretary to decide who ought to be advised by such a standing committee.

Jim?

DR. EVANS: Would this be separate from oversight within the effort itself about privacy, IRB issues, or would it be part and parcel of that?

DR. WILLARD: I think the intent of this is that this would be sort of on the outside looking in, which would be complementary to what you're describing, which is a very large effort on the inside that would be involved on a routine basis.

Joseph.

DR. TELFAIR: Along these same lines, the question would be would this also be influenced by the mechanism or the construction under which this project would be funded? For example, if it's a contract -- well, it depends on the city. If it's a resource or if it's a study and then who you're accountable to, in other words, who's providing the funding, that will influence decisions of how this committee is both constructed, what it's made of, and how it functions.

DR. WILLARD: You're absolutely right.

DR. TELFAIR: So that would be the thing that we need to consider when we're looking at this as well.

DR. WILLARD: Other comments here. This is the one that's closest to a specific recommendation for an action that the Secretary might take. I don't know if the ex officios, Ellen or Francis, have any reaction to this and whether there's a role because within the NIH or the VA, you would have your own advisory groups already, of course, and the question is, is there any value in having an independent, freestanding standing committee?

DR. COLLINS: I think any program of this sort would have to have this kind of input from a group that was clearly not influenced in some way that rendered their opinion suspect. So they'd have to be on the outside looking in.

But whether that is something that would happen naturally in the process of setting up a project of this scope -- it might very well -- whether this is something the Secretary would need to set up separately, whether this might actually be a function of SACGHS at some future time, because some of the things you're talking about here sort of sound a bit like SACGHS, just in the name of avoiding committee proliferation, it might be good to point out that there may be ways to do this that don't require setting up a brand new, separate committee, that there may be aspects of this function that could be conducted by existing groups.

DR. WILLARD: Ellen.

DR. FOX: I guess it also would depend on the relationship between the agencies and the nature of the collaboration. If there's really a true collaborative effort, then the committees that are dealing with each agency might not be sufficient to step outside and oversee the entire effort, in which case this would be important.

DR. WILLARD: Other comments from anyone?

(No response.)

DR. WILLARD: Well, those are the sort of straw man approaches and lead-ups to potential recommendations that the task force came up with and staff came up with. The question is, have we forgotten anything? Do any of you have your sort of favorite approach or recommendation that is now missing? Debra?

DR. LEONARD: Well, I kind of made an outline of the project and all the different parts of it, and many of these recommendations cover those different parts, but there are certain ones that seem to be not covered in any recommendations that we may want to think about adding. So the public engagement and feedback process is covered by 1, 3, and 9. If you think about setting up the biobank, there's enrollment, which is covered by 5 and 6, if I number these sequentially. There's medical data that would be gathered. That's addressed by 7.

Environmental data will be collected. That's not really addressed by any of our recommendations. I think there's tons of work to be done there, and so we probably need to encourage support of GEI or other kinds of environmental data collection initiatives, how that will be done, engaging the scientific community or whatever.

There's also then specimens and genotyping, and do we know everything that there is to know about specimen handling and storage and do we want renewable resources? Is that fairly well already known? And we may not need a recommendation there, but we may.

And then the ethical, social, regulatory issues are addressed by recommendations 8 and 9.

Then if you have the biobank set up and if it's done this way, how do you access the biobank? And there seemed to be fairly straightforward ways of doing that through grants, applications, et cetera. So I don't know if we need a recommendation for that.

Then once you have results, there's an emphasis on communication to the public in the recommendations, and that's 10 and 11.

But there seems to be a hole of how do these results get translated into clinical practice. That's a big hole in my mind because that's why we're doing this, is to influence medical practice, to have better patient outcomes, et cetera. So we may want to think about how these results will be translated into diagnostic uses or risk assessment uses, therapeutic strategies and preventive strategies, because I'm not sure prevention is really very well developed.

And then there's overall funding, which is addressed by 2 and 4, and then external oversight is addressed by 12. I guess we're assuming that there will be internal oversight set up, which we discussed, but there is no recommendation about that.

So those would be the areas that I think where we may want to think about additional recommendations.

DR. WILLARD: That's a very useful structure and a way to think about it. I'm sure Sarah will reach for your list that you just drew up.

Yes, Bernard.

DR. SCHWETZ: There are three points that I would like to make that cut across your recommendations. One of them has to do with achieving diversity among the population that you would like to eventually recruit. You're well aware of the resistance of some subpopulations,

particularly the minority populations, to participate in research. And I think if you don't have some effort ahead of time, you won't achieve it here either.

One of the things that we've learned from OHRP, as we've tried public outreach programs particularly with the American Indians and Native Hawaiians and Alaskan Natives and other populations, is there are structures that have been built up to protect these populations from researchers because of the abuses of the past. If you try to bypass those, you will not be successful in reaching those populations.

So one suggestion would be to figure out a mechanism by which you can work through their existing infrastructure to allow them to reach their populations and not the investigators in order to achieve success in those populations.

Another one has to do with seeking regulatory input. I would suggest that sooner or later some of these regulatory issues need to be faced. In the same way with the National Children's Studies, if they're not addressed early, they become significant stumbling blocks later on. And I would encourage that you would form some kind of a regulatory group that can be advisory, but if that group gets together and makes recommendations and puts it up on a website or some other way, it won't be very successful if you don't have the IRB community and the investigators involved because if all they see is something on a website, it doesn't tend to get their attention, as opposed to developing these best practices and some of the thoughts on how to make this study proceed to allow the study to proceed without hurdles, get those communities involved early on and don't just let NIH and OHRP and FDA write some guidelines for how to deal with these regulatory hurdles that doesn't involve development by the people who are actually going to have to make the decision about the protocol. And that's the IRB community.

The third one is the public will be skeptical, and you've talked about that. One of the reasons the public might be skeptical is because they don't know what's going to happen with their samples when they get it in the bank. And I would recommend that you consider developing guidance now to address the question of how can samples be used out of the database or the biobank so that the people who are considering participating would know at this point, for example, the requirements for IRB review for any studies that would be based on their samples. Do IRBs have to be involved or not and under what conditions can these data be deidentified so that perhaps they're not human subjects research from then on? I think you might find the public to be more understanding and interested if they know what's going to happen down the road and what protections they will have, as opposed to simply contributing genetic information, samples, and then wonder a few years later what's happening to it without the knowledge that they have some protections.

DR. WILLARD: Thank you for that.

Other comments?

(No response.)

DR. WILLARD: Well, Sarah, we're at the point at which, together with Reed, we were supposed to determine next steps for the task force and for staff to further draft this. Is Reed hanging in the hall, do we know?

MS. CARR: He had to step away for a few minutes.

DR. WILLARD: Okay. I think in terms of next steps, let me go through at least one possible way of proceeding, which is that Kathi, working by herself initially --

(Laughter.)

DR. WILLARD: -- take what we've heard this morning and work that into another draft which can then be cycled past the task force, which may want to have another one of its phone conference calls in order to deal with that, and then get that to a point where -- I mean, at some point, we have to be able to say now it's ready to go out to the public for public comment. Does that version have to be approved by the full committee or can that be a task force version if the committee so chose and gave us that latitude?

MS. CARR: I think it can be a task force decision if the committee feels it wants to put that --

DR. WILLARD: So then let me throw that question out for the full committee on whether the full committee is sufficiently happy with what you've seen and what you've heard this morning that you have some degree of confidence that the next draft will be sufficiently mature to go out to the public under the name of the full committee. Let me turn it the other way. Does anyone object to that?

(No response.)

DR. WILLARD: The chairman is happy.

DR. TUCKSON: The chairman is happy with it.

DR. WILLARD: Okay. And then having gone out for public comment, the public comments, Sarah, would come back in.

MS. CARR: Correct.

DR. WILLARD: And the task force would consider those?

MS. CARR: Well, staff will summarize them and the task force will review them and decide what to do about them in terms of the report.

DR. WILLARD: And that will take us then to a near-final report with near-final recommendations that would then go out to the full committee for final action ideally at the June meeting. Do I have that right?

MS. CARR: Right.

DR. WILLARD: Debra.

DR. LEONARD: Hunt, I think something that the whole committee needs to decide upon is, is this going to be presented as a two-stage process of building a resource and then accessing, or is it going to be studies, plus the resource? Because it's different in how you frame the report.

DR. WILLARD: Oh, I don't think that's up to us to make that call. I think if Francis were here, he would even say it's not up to him to make that call. This is just the early days and who knows how it's going to come out? I think we have to inform the Secretary of the sensitivity around

those issues and simply highlight those issues that are relevant to sort of plan A versus plan B versus plan C.

DR. LEONARD: I think that needs to be clarified then in the report, that there are these different scenarios of how this could be done.

DR. EVANS: But I think that regardless of what you call it, there will be results coming out. Right? Even if it's just research. There will be studies embedded in it. So I think we have to deal with that larger fact that these things are going to have to be dealt with because it will be a de facto study even if we call it a resource, don't you think?

DR. LEONARD: Right, but some of Dr. Schwetz' comments were if you define how you access the anonymization of data, those kinds of things, that's a real step that hasn't been defined. When you call it a study, it's kind of a resource and a study all in one as opposed to then accessing later for studies, either additional or --

DR. EVANS: Yes, I think those things will have to be addressed. Right.

DR. WILLARD: But our job is simply to point out to the Secretary that that's an open question.

DR. LEONARD: I didn't mean that we were deciding how it was --

DR. WILLARD: Then he will have to decide on it, or he through his office will have to decide on it. I'm less concerned about study versus resource because, as Jim said, at some point they merge. But the deidentification versus identification issue is absolutely fundamental. Either there's information potentially going back to these half million or million participants to guide their future health care or there isn't, and that seems pretty fundamental.

Does anyone not like the process I just outlined, which is coming up with another draft, the task force taking it to the point at which we can go to the public, the task force and staff working with the public comments to get to a final draft or a penultimate draft that will come to the committee prior to the June meeting? So the next time most of us will see it will be June.

DR. LEONARD: Can it go to the committee at the same time it goes to the public? I think that that's reasonable so that they have time to provide input as well.

DR. WILLARD: I realize that you have precious little time, except those of you flying from the west coast, to look at this version of the draft prior to this meeting. So I think that's a good point. We can certainly anticipate that.

Any other comments from anybody?

(No response.)

DR. WILLARD: I'm sure our chairman is listening. He's coming in just now. Let the record show that we finished our work 5 minutes before we were supposed to.

DR. TUCKSON: I've been monitoring you carefully in the other room and observing everyone personally. Congratulations. Good job.

We are going to have lunch, which is made and specifically wrapped for each of you individually in bite-sized portions, you'll be happy to know. Now, the deal is we've got to come right back. So what time do we start again? 1:30. The people who are not on the committee go downstairs. So we start again at 1:30.

You guys are terrific. That was difficult but a satisfactory conclusion. Thank you.

(Whereupon, at 12:27 p.m., the meeting was recessed for lunch, to reconvene at 1:30 p.m.)