Discussion of Final Draft Recommendations
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DR. TUCKSON: We are going to resume. We are going to now get to the discussion of the recommendations of the report. So if you all will take your seats, we will now begin with going through the report itself. Take it away, Kevin.

DR. FITZGERALD: All right. Thank you again, Reed.

Let me begin by just trying to focus our responses to the recommendations as we go through the report. So for each section of the report, we are going to review the key issues that we thought important to make clear. Then we are going to look at the current language of draft recommendations. So the emphasis here is on "current." Nothing is written in stone.

However, if you wish to change the language, you have to write the changes in blood. I just want you to know it is going to cost you. No. We certainly are open and encourage all improvements to the language of the recommendations.

Now, Suzanne is going to do this real time. So as we are making the recommendations, you will see them up on the screen, and you will also have what is in your books so we can do compare and contrast as we move along. The idea is that we will get these recommendations to where we want them to be.

Then, at the end, when we have done all the recommendations and all the subparts, that is when we will vote on them as a group. Why don't we vote on them as we go along? Because we may do something later on in a subsequent recommendation that makes us rethink the wording we used previously. So I want you to know that that all remains flexible. As we go along, if you want to go back and revisit something, you have something pertinent from a change we made subsequently, we can do that.

Then, at the end, the idea is we will take them all as a package and say this is what we want to put forward as our recommendation. If we have time subsequent to that, we can look at some other aspects, but that is only if we have time subsequent to that. The key today is to get those recommendations well structured and clarified.

As we are looking at the recommendations, things we want to keep in mind. Obviously, as we heard before, we are here as an advisory body to the Secretary. So, are these the recommendations we want to make to the Secretary. Are these recommendations the best way to address the opportunities and challenges that we raise in the report. And of course, if you are not satisfied with the wording of the recommendations, what changes do you suggest.

All right. The first section, Research and Development. As I mentioned before, it had the subparts Basic Research, Clinical, Translational, Infrastructure. Again, we are in Washington, D.C. so everything is acronyms, but sometimes it is good to know what the acronyms stand for. ELSI, of course, is the short way of saying ESLI, which is the acronym for Ethical, Social, and Legal Issues. So it is not the name of my cow, or "Eslie." Right. Exactly. Since it is backwards here.

"Eslie," "Elsie," right. "Isle." Oh, I never thought of that one. There we go. Issues in Legal, Social, and Ethics, or something like that. But in any case, however you want to put the acronym together, those are the issues that are to be addressed.

Let's begin with basic research. In the report, what we identified is that more basic research is required. That basic research needs to identify biochemical pathways and related biomarkers involved in drug metabolism and drug response, to refine and improve sensitivity of high throughput methods for detecting gene expression and drug response, and to look at gene loci specific variability in drug response. So as you can see here in the basic research, the focus is a great deal on what the response is going to be to particular drug therapy or drug intervention.

One example of a group looking at this kind of thing is the Genetic Association for Information Network. If you are wondering what that is, on page 24 of your report there is a small explanation of that. I don't want to go into that now, but you can follow along in the report as we go through it.

Moving from basic to translational, T1 translational research is performed to validate basic research findings and to apply that knowledge to development of pharmacogenomics products. So we are all familiar with translational research and what the intent of that is. Obviously, this has to be a very important part of the entire pharmacogenomics project. Another example there is the Pharmacogenomics Research Network. You can find that on page 25 of the report.

Then, of course, moving from translational to clinical, one aspect that is discussed in the report and that we discussed and also saw a great deal in the literature is the hope, at any rate, that pharmacogenomics can enable smaller, more efficient clinical trials. How would this be done? By using the test results to screen out subjects more likely to experience adverse drug reactions and of course, conversely, identifying subjects more likely to respond well to a drug.

So the whole idea, again, is to use that basic science information and data that is gathered to bring it to clinical trials and a greater focus on avoiding harm and gaining the benefit.

Obviously, in order to do that, you have to have the pharmacogenomic tests. How do you test people to see how they are going to respond to these drugs. What incentives are there to develop these tests. One would be projected market utilization and expected return on investment. As we mentioned, obviously, if you can avoid adverse events and improve benefits from any kind of drug therapy, that presumably would have a better return on your investment.

This would lead to positive clinical impact for test results because you would have the contribution of genetics relative to other non-genetic factors. In other words, now bringing in DNA sequence as a way of improving on our overall health care, which of course obviously involves non-genetic aspects. And of course, as we have mentioned already, hopefully reducing the prevalence and the severity of adverse drug reactions.

Now, obviously, since we mentioned early on we want to take into consideration some of the economic and financial aspects involved, gene patents and licensing practices are something that need also to be addressed because this is very much a driver in the arena.

So if there is going to be a development of these pharmacogenomic tests, how then does one look to see this development working alongside current drug development. Will there be a co-development of pharmacogenomic drugs and diagnostics.

We discovered that there is some resistance by industry to this process, although, hopefully, this resistance is being addressed. Not that the resistance is a bad thing. It is a good thing because it helps us to focus on the issues and formulate, hopefully, good responses.

Some of the areas that underlie this resistance: concern about market segmentation. Obviously, if you can focus on the subgroup that is going to benefit from your particular therapeutic intervention, then that is going to give you a smaller target population. Then, of course, there is uncertainty about FDA regulation of co-developed products. How is that going to be done.

In order to address these things, we presume that that is going to require new collaborations between drug and diagnostic companies and coordination of the parallel development processes.

In all, this could result in an expedited FDA approval, also in fewer label changes, and perhaps, in the greater likelihood, for provider uptake. If you know better what the outcome is going to be of a particular drug intervention, then you would be more likely to want to use that since you would have a greater likelihood of benefit and a smaller likelihood of any adverse event.

Another aspect which is interesting which has come up in several venues is this idea that there is the possibility pharmacogenomics could actually rescue some drugs and therapies that have been discarded because of the results that were found with them in clinical trials.

It could be the fact that in a broad population one only sees a very, very small change, whether that is small in reducing adverse events or small in creating a benefit. But that small change may actually be the fact that within the broad population there is a tiny subgroup that really does benefit, whereas most other people don't at all. So pharmacogenomics could help rescue drugs that have been found to be ineffective under our current trial process.

Then, of course, the post hoc analysis, the analysis done after these clinical drug trials, could distinguish this subset of good responders. This is at least something that is being considered as a potential benefit from pharmacogenomics.

Mara, please. Just push the white button.

MS. ASPINALL: Let me add, although I'm not sure it changes the recommendation, but just a comment on your comment that it may not necessarily be a very small piece of the population for which this is the case. It could be one for which there is a dramatic negative effect on a small piece of the population that it is critical that those come out.

I think in the report itself you talk about this, but I think it is important to link this to the comments on market segmentation because the idea that it could lead to a smaller market segmentation is one piece, but it could also lead to a creation of a market that otherwise did not exist. The two are close, but I think they are directly comparable.

DR. FITZGERALD: Right. Thank you. Actually, the focus at least we were looking at in our comments here today was on the resistances to the pharmacogenomics. Obviously, that would be an incentive. But you are absolutely right. Thank you.

So as we address these issues, one of the questions that came up was, well, let's see how we can perhaps delineate these incentives or these resistances, and this is one way in which we looked to do it. So as you mentioned, Mara, the testing does have the potential to improve the safety and efficacy of drugs already on the market even in a broad way. That would be a possibility.

So, what are the incentives for pursuing identification of these new indications. Obviously, if one still has a drug under patent, that would create a greater financial incentive. Obviously, that would be less if it is off patent. Again, if the adverse reactions are severe, then one has greater

incentive to address rather than mild. Of course, if there are alternative treatments available, there is less incentive because one can just use a presumably equally effective alternate treatment. So we just wanted to clarify the spectrum on that issue.

Looking at these small target populations and where pharmacogenomics might identify some, it raises the issue of what if it is a very small target population. We already have special provisions for orphan drugs and for humanitarian use devices, and these could encourage the development of pharmacogenomic products targeted to small populations.

The difference in this distinction is in the threshold for how these devices or drugs might be categorized. For something to be an orphan drug, the target population needs to be under 200,000 people. However, something to be categorized as an orphan diagnostic currently, our understanding is it has to be under 4,000.

One question is, if we are talking about the co-development of diagnostics and drugs, is that difference going to make a difference. Is that going to be a problem. In other words, the orphan drug could be favored in its development over the companion diagnostic. Is that going to be a problem. This too was raised in the report.

Moving from basic to translational, these were some of the issues that were raised in our investigation of pharmacogenomics. Obviously, the adoption of pharmacogenomic technologies will hinge upon evidence demonstrating the value of using these products both in clinical and public health practice. That is, as we mentioned at the beginning, the goal. Is this going to get us better clinical utility.

Also involved in this clinical utility will be the idea of cost effectiveness. At what point does the cost of a particular treatment begin to affect how it might actually be disseminated into the public, in spite of the fact that it might have significant clinical utility.

One of the major issues that we discovered, and this again, too, will run throughout the report; there just isn't sufficient evidence regarding the clinical utility of most pharmacogenomic products. In part, that is because we are early on in the pharmacogenomics process. In part, it is also that there hasn't necessarily been a lot of incentive to gather that evidence. That doesn't mean some groups aren't looking at it, but really, one of the things that we found was we didn't find sufficient incentive to produce this evidence, which of course is absolutely necessary if we are going to understand what the clinical utility of pharmacogenomics is to be.

Looking at the research and development infrastructure, pharmacogenomics research and development could benefit from sharing and linking of research and clinical databases, repositories and records. When looking at the report that was put out by the Secretary on personalized medicine, you find on the front of the report "The right treatment for the right person at the right time." Great. No one can argue with that. The question is, how does one get there.

One of the things that has become clear is in order to do that you have to have an inordinate amount of information and the ability to compare and contrast different data sets across different areas of infrastructure. How can these be better linked so that that sharing of information can occur.

There are significant challenges to this. There are IP concerns. There are variations in data formats. Electronic health records are still in very early stages of development. There are

different funding streams for all these things as well as different stakeholders, different administrative protocols, and different organizational cultures.

All of these issues will need to be addressed for us to get the sort of information sharing that we think is going to be absolutely necessary for moving ahead with the benefits of pharmacogenomics. As I mentioned, even though these challenges are very real, there are areas and groups that are beginning to look at these challenges. We have this list down at the bottom here -- there is a longer list, certainly, in the report -- of projects that are already attempting to address these challenges.

To the ESLI, ILSE, or ELSI issues, all ethical, legal, and social in the research and development of pharmacogenomics, here are some of the issues. Obviously, many of these will be familiar to you, but again, it is important to bring these to the fore. Certainly, privacy and confidentiality concerns are associated with sharing genetic information.

If the only way this goes forward is that researchers and clinicians have a great deal of access to very individualized, personalized information, how will those persons be protected from any misuse of that information. There will be tradeoffs. More access, more risk. So, how will we balance protection versus access and utility. This is one of the big issues that needs to be addressed.

Another that we discovered is that, currently, there are discrepancies between human subjects research regulations, especially for coded specimens. One example is the Common Rule versus the FDA regulations. If you want more specifics on that, you can look in the report on pages 51 and 52. That was another issue that we flagged as something that the Secretary could certainly help to have addressed.

Another area that has come up -- and this is not, again, just in the pharmacogenomics arena but certainly one that needs to be addressed within that arena -- is the concern that concepts like race and ethnicity might be involved in the development of pharmacogenomics in a way that is not beneficial and in fact instead leads to problems with greater healthcare disparities or even a confusion of exactly what biological categories are being addressed, versus more socioeconomic categories that are often used in our society. These issues also need to be flagged.

Finally, again, as we try to [look at this] from a variety of different perspectives, looking also from the perspective of industry, there are liability risks associated with questionable marketing claims, labeling omissions, or incorrect or misinterpreted test results. How will these areas of potential confusion and potential conflict be addressed in a way that everybody can move forward with the benefits of pharmacogenomics.

With that overview, we get at the draft recommendations. This is Draft Recommendation No. 1. It is on page 25 of your report.

At this point, I need to let you know that the wording you will see on these slides does not always match the wording that is in the report before you. Some changes have already been undertaken. However, as I said, we are here now to finalize. So what is on the slide, what you see on the screen, may vary from what is in your report.

This recommendation is on page 25. If you will notice, under No. 1 on the slide, you will not find two prepositions that are in your report. "Basic research on the biochemical pathways associated with drug metabolism and drug action." In the report it says "on the genes and gene variations."

Up here we don't have that. "Involved in these pathways and on," in the report but not here, "the functions of those genes related to the safety and effectiveness of drug treatments.

That is Subpart 1 to Draft Recommendation No. 1. Please take a look at it. Any comments, questions, or suggestions? Are people happy with this? This is our first recommendation. "NIH should put more resources into 1) basic research on the biochemical pathways associated with drug metabolism and drug action, genes and gene variations involved in these pathways, and the functions of those genes related to the safety and effectiveness of drug treatments."

DR. TUCKSON: By the way, can we assume, Kevin, that what is on the board is the newest [version]?

DR. FITZGERALD: Yes. What is on the board is the newest version.

DR. TUCKSON: So that is the one we are working from.

DR. FITZGERALD: Right. We are going to work from what is on the screen, and any wordsmithing we do is going to be put up on the screen immediately so everybody can see it. At the end, hopefully we will have what we have there on the screen.

Yes.

DR. GUTTMACHER: A point of clarification, I guess, for the NIH. When we say "more resources," do we mean a higher level than currently or do we simply mean continue to put resources into? If it is a higher level, can you tell me what the level is currently?

DR. FITZGERALD: Right. Compared to what. Compared to.

DR. GUTTMACHER: But I don't know whether it is compared to or simply "more" means continue to put resources in.

DR. FITZGERALD: Right. To be particularly precise, I'm just going to pull up what is in the report. First of all, the "more" that is there -- I believe this is accurate. I just want to make sure -- does indicate "more" in the sense of increased. I cannot give you the exact level of what is there right now.

DR. GUTTMACHER: Probably because the NIH couldn't tell you.

[Laughter.]

DR. FITZGERALD: Suzanne knows, though, but she is not telling. No.

So the idea here was to say this needed to be an additional effort. That answers your question.

Yes, Paul.

MR. MILLER: The recommendation is asking for NIH to dedicate more resources. Is there a problem with asking Congress to appropriate more resources as opposed to NIH basically taking from its limited pot, moving the deck chairs around, as a zero sum gain?

DR. FITZGERALD: We can't recommend to Congress. If you want Sarah to tell you officially, but --

MR. MILLER: No, I understand. I just want to flag that. Basically, the report is saying preference this immediate need and pressure on NIH over other immediate needs on NIH, when really the issue, I think, goes back to Congress in terms of appropriating money. I guess, given where we are and given the limitations on the Advisory Committee, that is the way it has to be. Is that correct?

MS. CARR: I think what you are getting is maybe you want the recommendation to either call for the request for additional funding or do you want us to specify whether we are asking additional funding or you want NIH to adjust its current priorities and the NIH director and the institute directors to --

MR. MILLER: My preference would be that it would be coming out of additional funding and that it is hard for me, personally, or for the Committee to say pharmacogenomics deserves a higher priority than cancer research or whatever. I think that is an implicit issue within the recommendation.

DR. TUCKSON: So, are you saying basically that the NIH should have available more resources, or we advocate that NIH have more resources to put into?

MR. MILLER: That would be my preference. I don't know if NIH has a problem with more resources or not.

[Laughter.]

DR. GUTTMACHER: It is a problem we could learn to live with.

[Laughter.]

DR. FITZGERALD: So we have a change here. "NIH should be given more resources to put into."

MS. CARR: Alan, what about saying "NIH should seek additional resources"?

DR. GUTTMACHER: The Committee could recommend that the Secretary seek more resources, since we are recommending to the Secretary. The way to fudge it would be to say "More resources be made available" without exactly saying how. Everyone knows what that means. You have to go out and get them somehow.

MR. MILLER: Maybe the way to fudge it or to identify the issue would be "NIH is in need of additional resources to put into."

DR. GUTTMACHER: "To increase its efforts in the areas of." Something like that.

DR. AMOS: Would it be appropriate to say something on the order of "The NIH should develop funding initiatives"? That is the process. You would actually develop an initiative with defined goals and objectives that would be submitted as part of your budget.

DR. WINN-DEEN: I guess it is my understanding that NIH prepares a budget request each year to give to Congress. So that is their opportunity to ask for what they need. That is, I think, where we were trying to get. They should define how much more resources they need and ask for those.

DR. FITZGERALD: Muin and then Julio.

DR. KHOURY: I guess this hasn't come up before, or has it, when there are recommendations from SACGHS going to the agencies. We would all like to have extra resources, whether it is NIH, CDC, FDA, et cetera. I'm not sure that we need to massage this one to death. But obviously, what needs to happen is the integration of genomics into all of these activities, from basic to translational. There could be a global statement at the beginning of the report rather than parsing out each one of these recommendations because they all require additional resources.

DR. FITZGERALD: And Julio.

DR. LICINO: Just one comment. Now it is pretty obvious that there is this time of very constrained resources, but even during the middle of the doubling when NIH did an initiative on pharmacogenomics, some institutes participated and others did not and chose not to. So I think that [we should] emphasize that it should be an area of importance with whatever budget you have. Of course we need new funds, but even when new funds have been made available in pretty large amounts, not everybody saw the need.

DR. FITZGERALD: Would people be comfortable with "NIH should receive and put more resources into"? That covers both. Alan?

DR. GUTTMACHER: Yes, I guess that would work.

DR. FITZGERALD: Thank you. Muin, no?

DR. KHOURY: Why do we have to say that? Because every single recommendation will have to say the same thing.

DR. TUCKSON: Why don't we just go through the rest of them, then. We have the spirit of this.

DR. FITZGERALD: We will put this down temporarily.

So, No. 2. First of all, is everybody happy with No. 1? We are just getting the sentence started here. Yes, Barry.

DR. STRAUBE: Barry Straube from CMS. As to the segment you have lifted out, "safety and effectiveness," which is the FDA statutory language, it is a victory, of course, as the report mentioned, if we get something declared safe and effect by FDA but payers can't pay for it.

At CMS, "reasonable and necessary" is the term. "Medical necessity" gets mentioned in the report quite a bit. I think one of the weaknesses we have had over the years is that basic research looks at safety and effectiveness but it doesn't look at medical necessity and gather evidence as much as it might to make the payment structure be able to respond.

So I would suggest that this ought to include some mention of either "medical necessity" or "reasonable and necessary." We will be talking later on when you get to the FDA place about how we are trying to work with them.

DR. FITZGERALD: Right. We will be. Emily.

DR. WINN-DEEN: I think we were trying to differentiate the basic research, understanding the underlying science, from the kind of things you are talking about, which come later in our recommendations as we get more into the translational aspects of it. At that point, absolutely, we want to be looking at those things. But if you don't even understand the basic biology of how a drug is working, then it is hard to move to the next step.

I think that is what we tried to do. We tried to break this down into several subsets. The first thing you have to do is the basic, and then you do the translational and clinical. At the end you obviously want to have all of those measures -- good, sound science plus the health economics -- understood.

DR. STRAUBE: I understand the logic. I'm just suggesting that I can't tell you how many times we have many, many folks, including around this table, coming in and we are asking for information that if it had been thought about way back in the basic science phase, it could smooth the road. That's all.

DR. FITZGERALD: Let me just get the sense of this. If we, at some point in one of these basic research recommendations, put that in, would that address it? Or would you want it in every one?

DR. STRAUBE: No, no. I'm just trying to sensitize the Committee.

DR. FITZGERALD: Actually, the next one, No. 2, might actually have a spot where it would fit very nicely, if I can hold that off just a second.

DR. STRAUBE: Absolutely.

DR. FITZGERALD: Yes, Mara.

MS. ASPINALL: Just one question on No. 1. When it talks about drug treatments, later on you talk about diagnosis as well. Does this one need to, or can it, broaden itself to say "safety and effectiveness of drug treatments and diagnoses" or was this really meant to be just the work on the therapeutics and not to include basic research on the diagnostics?

DR. FITZGERALD: So we would put in "effectiveness of drug treatments and diagnostics"?

MS. ASPINALL: Or "diagnoses," yes.

DR. FITZGERALD: Anybody have any problem with that? It is just more inclusive.

[No response.]

DR. FITZGERALD: All right. So, "diagnostics," good. Any others on this?

[No response.]

DR. FITZGERALD: Great. Let's move on to the second one. If I miss anybody, if your hand is up and I miss you, just throw something blunt and heavy. I will duck, but Reed will take it well.

[Laughter.]

DR. FITZGERALD: No. 2, put more resources into "Non-hypothesis-based approaches to the understanding of the relationship between genetic variation and individual's response to drugs." Yes. Please, Paul.

DR. BILLINGS: Could you give me a little background? I'm exercising Reed's admonishment for us new ad hoc types. Could you give me a little background on why this was included at all? It sort of sticks out, and I just wondered.

DR. FITZGERALD: Yes. Why don't you take it, because Emily can do this better than I.

DR. WINN-DEEN: The idea was that Recommendation No. 1 had a hypothesis-based approach that you are going to look at specific pathways, and we also wanted to include the fact that we don't always know. So we wanted to also open the possibility for non-hypothesis. Not assuming that you say a drug is working through this particular pathway and so we are only going to study that pathway but to look at more whole-genome kind of approaches to things.

DR. FITZGERALD: Anybody else on this?

[No response.]

DR. FITZGERALD: Great. All right. So we are going to keep that the way it is and move on the next recommendation, Draft Recommendation No. 2, which is on page 26 of your report. In this recommendation, what you have in your text differs from what is on the screen, and I will point out where.

"As knowledge of the underlying biology accrues, further research will be needed to translate this knowledge into the development of clinically useful PGx tests and," is not in your book but it is on the screen, "tests and technologies and to assess their clinical validity and clinical utility."

Mary, this is where I thought maybe we could add something along the lines of what you were thinking.

Below that, "HHS agencies should facilitate the development of clinically useful pharmacogenomics technologies by investing more resources into all components of translational research, including the translation of basic research findings into clinical trials." That, I believe, is not in the text. The "S" is missing in the report.

"As well as the translation of clinical research findings into clinical and public health practice and policy. One of the emphases of this translational research should be to foster," and I believe that is not also in the text of the report, "to foster the development of more rapid, cost-effective genotyping technologies."

Rather than just say "should be the development," we have put in also "to foster the development."

Barry, does this get at more what you were [saying]?

DR. STRAUBE: It does somewhat.

DR. FITZGERALD: Could we make it stronger with your language?

DR. STRAUBE: I'm just wondering whether, since you used the language here of "into clinical and public health practice and policy," "policy" might entail coverage, but you might want to put "coverage" in there also.

DR. FITZGERALD: We can put "into clinical and public health practice, policy, and coverage." Everybody comfortable with that? Great. Good.

Who am I missing? Sorry. Paul, go ahead. Thank you, Mara.

DR. BILLINGS: I'm going to exercise this role one more time. The recommendation recommends genotyping technologies when in fact phenotyping is probably, in many cases, closer to the clinical reality of changing practice. So, what was the background for the final sentence, really?

DR. FITZGERALD: Well, again, it is not a situation where this is being emphasized to the exclusion of the other. Up here on the slide it says "to foster the development of more rapid, cost-effective genotyping technologies focusing on the pharmacogenomics." Phenotyping technologies would be incredibly broad, in one sense. That could involve all sorts of biochemical areas. Jim.

DR. EVANS: This must have gone by me in one of the conference calls, too, because as you bring up here, I think that does kind of stick out. I'm not sure why we necessarily need to or should emphasize very specifically "more rapid genotyping technologies." I think the first sentence really sums up what we want to go get to, and I'm not sure we should be that specific there.

DR. WILLIAMS: Kevin?

DR. FITZGERALD: Yes.

DR. WILLIAMS: One way to address this might just be to, in that last sentence, strike "genotyping" and substitute "diagnostic."

DR. FITZGERALD: That is one way to go. This was a recommendation that was made specifically by one of our members, who is not here at the moment.

We can either get rid of the sentence or we can put in "diagnostics." Is "diagnostics" better? Yes, Gurvaneet.

DR. RANDHAWA: If we could just go back to the beginning of the paragraph where we say "PGx technologies," and just restate it "PGx technologies" down [at the bottom.] Instead of making it more specific, we could just say "PGx technologies."

DR. FITZGERALD: Rather than diagnostic. Jim, you don't have a mic. Hold on. It's coming.

DR. EVANS: Again, I think when one thinks about translational research, it is extraordinarily important at that level to think about a very broad range of things that includes, as is stated, clinical validity and clinical utility. This gets far beyond diagnostics. I think that "diagnostics or even "technologies" is too narrow. I think we should just knock out that last sentence. There is much more clinical utility than technology.

DR. FITZGERALD: What Jim is recommending is we just cut out that last sentence completely. Emily?

DR. WINN-DEEN: I guess I will just do the counterpoint to that: if you only develop the correlation but you don't have a good way to deliver that for patient care. I think that is what we were trying to achieve by adding that sentence.

DR. EVANS: Yes, but I think by singling out one aspect, be it technology, diagnostics, one loses the important general recommendation, which is to encourage a neglected facet, which is translational research. I think that a specific recommendation there that focuses on technologies or that focuses on diagnostics runs the considerable risk of really punting it back to [the idea that] we need better genotyping platforms, which isn't translational research.

I would vote, and maybe it will come to a vote, for getting rid of that last sentence.

DR. FITZGERALD: Let's do it this way, I guess, first of all. We have two choices, it seems to me. One is getting rid of that last sentence and the other is somehow changing that last sentence.

Looking at that, is there anyone here who is against getting rid of the last sentence?

[No response.]

DR. FITZGERALD: So we could all live with that. Yet we have one person who doesn't really want to live with changing it even if it is changed. Why don't we, for right now, just get rid of that last sentence. Then, if we come back and say we need to be more specific later on, we can do that.

All right. Why don't you just delete it for now. Great. That solves that issue. Great.

Next is 3A, page 30. By the way, our crack mic technician is going to be crawling around. He should do whatever he needs to do because he is going to fix this and then we will be fine. So pay no attention to this person running around.

This particular recommendation is the same in both the report and on the screen. Again, on clinical research, Recommendation 3A, "Where study results will be used to demonstrate safety and efficacy to support a pre-market review application, sponsors and researchers should be encouraged to consult with FDA early in the study design phases. This would help to ensure that these studies have adequate clinical study design, e.g. sufficient statistical power, and quality controls in place should the research later be submitted for regulatory review."

Again, I think the idea was to get back at some of what Barry was talking about before, trying to look down the road and see if we can't pull these things more closely together.

Is your mic on yet? Yes, it is.

DR. STRAUBE: Again, I might suggest you put in FDA and CMS because, again, we are talking about parallel review at concept. I think that gets people in earlier.

DR. FITZGERALD: Sure. FDA and CMS. All right. Good. Any other suggestions or any other recommendations?

[No response.]

DR. FITZGERALD: Great. All right. We are going to move on, then, to 3B.

Now, again, this is different than what is in your text. We have "As appropriate" at the beginning of this recommendation. So, "As appropriate, NIH should consider making FDA's existing quality of evidence standards a component of their assessments of the scientific merits of grant and contract submissions."

Everybody is comfortable with that. Fantastic. All right. Great. On to the next, 3C.

"NIH should encourage grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program to ensure consistency in data standards that may affect drug prescribing."

Yes, Marc.

DR. WILLIAMS: I just had a question on this one. I'm sure there was debate about the word "encourage" versus "require." Given that NIH does have the ability to supply funds, it would be, as I understand it, within their purview to be able to require submission as part of the RFA. So tell me a little bit about why the word "encourage" was chosen as opposed to "require."

DR. FITZGERALD: You are absolutely right. That was discussed. My sense, and Suzanne's sense, of the discussion was that we leave it a voluntary program and not make it mandatory. [That] was something that was thought to be preferable.

DR. WILLIAMS: I would just note that it doesn't change the FDA's program from being voluntary, but for people that want to do research using NIH funding, there is nothing that would say that the NIH couldn't require it.

DR. FITZGERALD: Exactly. That is true. Alan.

DR. GUTTMACHER: I would just ask, if we did change it to "require," of whom should it be required? Every NIH grantee? I don't think so. You would have to add "As appropriate," I suspect, if you went from "encourage" to "require."

DR. FITZGERALD: Right. Is what you are saying, Marc; it should be of every NIH [grantee]? No.

DR. GUTTMACHER: I guess I would need clarification. There are certainly lots of NIH grants that have absolutely nothing to do with this area, so one would not require it of those grantees.

DR. WILLIAMS: Are you saying, Alan, that you would be comfortable if we say "NIH should require grantees and contractors as appropriate to participate"?

DR. GUTTMACHER: Yes, I think you could put the "as appropriate" any place in the sentence that you would like.

DR. WILLIAMS: That is the direction that I would favor, unless there are compelling reasons from the taskforce's discussion.

DR. FITZGERALD: Sylvia.

MS. AU: I think I would keep it as "encourage" because there might be some research done in special groups that would not be able to do the research if it was required of them to participate in the FDA Voluntary Genomic Data collection.

DR. FITZGERALD: Julio, did you want to [speak]? Your mic is on.

DR. LICINO: Yes. I think it is a very important thing because, if you make it optional, few people would deposit. I agree with Sylvia. But on the other hand, if you make it mandatory, it may affect some types of research. So it is a difficult one.

DR. FITZGERALD: This is basically where our discussion was.

DR. GUTTMACHER: That is where the "as appropriate" might work. It might be inappropriate to do it in situations where it would kill off the avenue of research.

DR. FITZGERALD: Let's get Paul and some other people. Joe.

DR. TELFAIR: I would use both "encourage" and then "as appropriate." Then you would encourage but it should be as appropriate. Here is the reason why: you still have to designate who would be responsible for monitoring whether or not that occurred. So, "as appropriate," it would go to the appropriate agency program, subprogram, et cetera, within the NIH and, I'm assuming, working with that. You would have to be able to do that. You wouldn't just leave it wide open.

The same arguments that are being made for "mandatory" should also be considered as to who then would be responsible for even monitoring whether or not those that are encouraged to carry it out actually carried it out and then what to do with that.

DR. FITZGERALD: Great. Paul.

MR. MILLER: Just as a matter of wordsmithing, or maybe it is just a style issue, I'm uncomfortable with throwing in the fray the phrase "as appropriate" because I'm not quite sure what that means. I think it is a really wishy-washy term. To the extent that you want to limit this thing, either this or even the previous slide -- and I bit my tongue on the previous slide -- then we should state exactly what we mean. I think "as appropriate" is so ambiguous it tends to confuse rather than clarify. That is my opinion.

DR. FITZGERALD: I have Marc, Gurvaneet, and then Steve Gutman. Marc.

DR. WILLIAMS: Just to respond to Sylvia and to Paul, from Sylvia's perspective, I think that there could be an exemption process for research where this would be a barrier to actually doing the research. I think, to Paul's point, what we are really talking about here is perhaps some language that would encourage -- and I don't know who this would be within NIH -- to basically develop policy around who would be exempt, essentially, from submission and under what circumstances that exemption would be reviewed.

MR. MILLER: I think that is fair. If I could just respond, it may be that you place some language in the text of the report explaining that rather than putting it in the recommendation. That might be as appropriate as anything for that phrase.

[Laughter.]

DR. FITZGERALD: Gurvaneet.

DR. RANDHAWA: My comment was, as we go further in this field, AHRQ certainly is funding one randomized control trial on genetics in Warfarin use. I'm assuming CDC will also be funding grantees and contractors collecting genomic data. So, is it viable to consider other agencies beyond NIH who also fund, or hopefully will fund more, pharmacogenomics research to be in this recommendation?

DR. FITZGERALD: So now we are adding. Mike, go ahead.

DR. AMOS: Just to clarify, to Paul's point, it might be wise to just include the statement "When genomic data is generated in a study funded by NIH, then." You say can "required" or "encouraged"; it is up to you guys.

DR. FITZGERALD: That would give us our specificity. Yes, Muin. Go ahead.

DR. KHOURY: Isn't this clinical research arena relevant to the clinical research that is leading to a pharmacogenomic application to be put as a test or as a tool? There is all kinds of research. I think we have reached the point where we are at this interface of translation between after gene discovery for pathways or whatever and trying to develop an application that then could be submitted to the FDA.

So "when appropriate" can be massaged to [apply to] the funded research that is designed to evaluate or develop applications to be used for pharmacogenomic practice. The encouragement or the requirement would be for that kind of research to interface more with the FDA processes, whether it is funded by NIH, CDC, AHRQ, or whatever. I know we will be funding some, but I know most of the funding will come from NIH, that's for sure.

So, "when appropriate" is not really about all genetic research. It is only the pharmacogenomic research that is leading to that application. It is probably a small fraction of the genetic research in drugs and development. We have reached a point in that translation pathway that is more distal and therefore more selective, so there could be some wordsmithing that goes along [with that.]

DR. FITZGERALD: That is what we are supposed to do. Right. So, smith away.

DR. KHOURY: So it is not really when genomic data are generated in a federally funded study. That is ridiculous because that involves hundreds and thousands of potential studies that will never make the light of day in terms of application.

So, when pharmacogenomic data are generated for the purpose of developing a pharmacogenomic application or test for use in practice, that is when the trigger happens. I'm sorry; I'm stumbling on my own words. Maybe others can help me here with the massaging.

DR. FITZGERALD: Steve, go ahead.

DR. GUTMAN: That is not entirely right because Voluntary Genomic Data Submissions are actually posited to look at the use of genomic data earlier in the life than at the point that a diagnostic device is poised to enter the market as a companion product. In fact, when a diagnostic device is poised to enter the market as a companion product, the Voluntary Genomic Data Submission process is the wrong process. You actually need to start thinking about the pre-IDE or the CDRH protocol review process.

If you are actually going to play around with the language, it is going to need to be parsed a little bit more cleverly than this. In the true exploration or feasibility stage, when you are playing around with genomic data in the context of the drug, the Voluntary Genomic Data Submission really hits the spot. When you have a companion diagnostic that looks like it is on the way, then you need to start thinking about a pre-IDE or a protocol review by the Center for Devices.

But I also agree with what Muin says that we better be careful what we wish for because we on FDA's end don't actually have the resources, depending on how generous NIH funding in this area is, to start looking at a lot.

I do think you need to step back, as ambiguous as it is, and put some kind of disclaimer in there, some kind of buffer. For one thing, the Voluntary Genomic Data Submission is an exploratory process, but as it gains experience it will start to create guidances and documents. It doesn't need to keep reinventing the wheel so that someone who comes along with a third model of a particular kind doesn't necessarily need to submit back to the Voluntary Genomic Data Submission because that route has been established.

I personally prefer allowing some kind of flexibility here, although I must say, I always thought that it would be really nice when you did have a new diagnostic product that NIH was funding that they require that they at least read FDA regulatory documents so they understand that research that is going to generate a product has certain obligations about quality control and following the protocol and doing things that may have a heightened exigency.

DR. FITZGERALD: So, for the VGDS, this Voluntary Genomic Data Submission Program, do you have wording that would fit that program for this recommendation? The mic is not on, Steve.

DR. GUTMAN: Let me see. So it would be, "Should participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development." No, after "Voluntary Genomic Data Submission" would be "the exploratory phase of drug development and the pre-IDE process when a diagnostic is thought to be essential in the clinical use of the drug."

That is a demarcation between the Voluntary Genomic Data Submission and the pre-IDE. In the Voluntary Genomic Data Submission, you may be in true genomic discovery and you are not sure about the need for a drug, or you may suddenly get that you need a diagnostic. When you know that you are going to need both of them to enter the marketplace as bride and groom, we are the wedding hall.

DR. FITZGERALD: We are still smithing here.

[Pause]

DR. FITZGERALD: Do we want to go back to "HHS should encourage" or "require"? "HHS should require grantees, as appropriate, to participate in FDA's Voluntary Genomic Data Submission during the exploratory phase of drug development as well as the pre-IDE review process." So, Steve, what comes after the "pre-IDE review process"?

DR. GUTMAN: "In situations where a diagnostic is thought to be essential to drug use" or "clinical drug use."

DR. FITZGERALD: "Essential to clinical drug use." I'm sorry. Scott. Sorry.

LT. COL. McLEAN: The language of "requiring" participation in a voluntary activity is kind of a wordsmithing issue.

[Laughter.]

DR. WILLIAMS: It is really not because, as I pointed out before, anybody can submit to that voluntary program that wants to. But what I'm saying is you are getting money from an HHS program, then you have to. That is completely consistent syntactically and semantically and any other way that you want to look at it. If you are getting money from somebody, they can require you to do something that might otherwise be voluntary.

DR. FITZGERALD: Yes, Paul.

DR. BILLINGS: I have a point and then a question. First of all, there are two Pauls now here. I would like to be referred to as "Paul the Lesser" and "Paul the Greater" next to me here, and "Paul the Wiser."

[Laughter.]

DR. BILLINGS: So, "Paul the Lesser," please, from now on.

Second of all, I'm a little confused. Segmentation can occur very early on either in the pre-clinical phase or in contemplation of the clinical phase of drug development. That segmentation in the contemplation of the collection of data may have nothing to do at the end with any labeling recommendation or so forth.

So I'm a little confused at this language as to how that is dealt with. I don't have a recommendation how to improve it. Steve just said in my ear a minute ago maybe you put "or" in the pre-IDE review process, because that would then cover people contemplating clinical trials but then not actually deciding that they want to submit with the segmentation data.

DR. FITZGERALD: This is what we have currently. "HHS should require grantees and contractors, as appropriate, to participate in FDA's Voluntary Genomic Data Submission Program," which may shortly be renamed to the Semi-Voluntary. No. "During the exploratory phase of drug development or the pre-IDE review process in situations where diagnostics are thought to be essential to clinical drug use."

One way to maybe wordsmith it just a little more is remove "as appropriate" since we are already saying what the conditions are at the end.

Jim.

DR. EVANS: Not withstanding Marc's comments, which are technically correct, I think leaving "requirement" and "voluntary" in there is going to create incredible confusion. I don't think there would be any problem with just getting rid of "voluntary." It is still a program and we could say, if everyone feels it should be a requirement, that they are required to participate in the Genomic Data Submission Program.

While you are right technically, I think there will be a lot of confusion.

DR. FITZGERALD: Wait a minute. Use the mic so we can get this all down. I have Andrea, and then Steve, did you want to get back in the game?

DR. FERREIRA-GONZALEZ: The name of the program is "Voluntary." I don't think we can change it.

DR. FITZGERALD: We could always use the acronym. Then people wouldn't have a clue what it is.

[Laughter.]

PARTICIPANT: I think it would be very odd to take "voluntary" out.

DR. FITZGERALD: Marc, go ahead.

DR. WILLIAMS: I want to come back to, I think, the point Paul Miller, or whatever "Paul" we are referring to him as now, [made.] Reference within the recommendation that the Secretary will convene the relevant HHS agencies to produce -- and I don't know whether these would be rules or regs or policies or whatever -- to address the specific circumstances under which this requirement would be active.

DR. FITZGERALD: Do you want that in the recommendation or do you want that in the text?

DR. WILLIAMS: I think it needs to be expanded in the text, but we are making recommendations to the Secretary so it has to be in the recommendation as well as in the text.

DR. FITZGERALD: "Convene the appropriate agencies to address implementation of this recommendation."

Marc, just to remind you and everyone again, that is why we are voting on these at the end. There is Recommendation 15A, which is a recommendation to say that an interdepartmental workgroup should be established to review all the recs to implement them. So 15A is sort of a grab-bag, trying to get at what you just said, but for all the recommendations. Is that okay?

DR. WILLIAMS: What you could do, then, is you could just basically say that "Implementation of this recommendation will be addressed per Recommendation 15A," something like that.

DR. FITZGERALD: Let's give Suzanne a moment here to get this together. Any other comments? Steve, please.

DR. GUTMAN: I would change the "or" to "and/or" because there might be circumstances where both processes are appropriate.

DR. FITZGERALD: Let her get the other one in there and then we will do that. Then, "and/or" rather than "or" in front of "IDE." There we go.

No, we didn't take out "voluntary." We are just going to use the acronym so no one knows what it is.

[Laughter.]

DR. FITZGERALD: "HHS should require grantees and contractors to participate in FDA's VGDS Program during the exploratory phase of drug development and/or the pre-IDE review process in situations where pharmacogenomic diagnostics are thought to be essential to clinical drug use. Implementation of this recommendation will be addressed in Recommendation 15A."

I'm sorry. Muin.

DR. KHOURY: Again, since you said that implementation of all the recommendations are going to be addressed in 15A, it seems a bit redundant to have that. Marc, with apologies to you, everything will have to be implemented in an orderly process with HHS agencies coming together. So just to single this one out seems a little bit odd to me.

DR. FITZGERALD: Would it be adequate to have asterisks? Looking ahead, we may have other recommendations we want to make sure relate to 15A. We could just put an asterisk. We just want to emphasize that it relates to 15A. We don't need it? No? All right.

All those who think we don't need this, pick up your glasses and throw them at Marc. No, no, no.

[Laughter.]

DR. FITZGERALD: Are you okay, Marc, with that? Hopefully it will fall under 15A. Presumably it will.

All right. How are we with the language, though, right now? "HHS should require grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program." If we just can't bring the public to greater clarity in the use of the English language, what good are we, right? All right. "During the exploratory phase of drug development and/or the pre-IDE review process in situations where pharmacogenomic diagnostics are thought to be" -- wait a minute. It is changing again. "Are thought to be essential to clinical drug use."

What did we change? What did you just change? "Its grantees," okay. Wait a minute. Get your mic, Sarah.

MS. CARR: It is just a small point. The "in situations" applies to both of the two. What if you began the recommendation with that phrase? Would that make it easier to follow?

DR. FITZGERALD: I see. The suggestion is to move that phrase to the front because it applies both to the VGDS and the pre-IDE. Okay? Okay. Move that to the front. Thank you, Sarah.

I'm sorry, Paul. Paul the Lesser. First is "Paul the More."

DR. BILLINGS: Paul the Greater and Paul the Lesser.

DR. FITZGERALD: Whether it is "additional" or whatever, but it is "more."

DR. BILLINGS: Exactly.

[Laughter.]

DR. BILLINGS: During the discussion of this recommendation, was there some consideration of what is going on in the drug industry and the non-grantee population and how there might be some harmonization of what is going on in the non-grantee world and in the grantee world?

DR. FITZGERALD: Yes, that was part of our discussion around this. It was part of why it was "encourage," I think, rather than "require," also. Are you suggesting --

DR. BILLINGS: I don't think it serves the purpose of this Committee to set up two parallels since they have two systems that don't really talk to each other. It doesn't serve the public interest either, by the way.

Now, I recognize that there are barriers, some important ones, but that doesn't mean that we can't recommend better harmonization or sharing of data or ways that that would happen.

DR. FITZGERALD: We do have that in the recommendations. Let me just make sure. I think it is further on when we talk about the information.

Marc, you wanted to say something.

DR. WILLIAMS: Again, I think it is just a matter of making sure that as we look at each of these recommendations that we understand what our Committee can actually do. We can only recommend to the Secretary, and the Secretary has no ability outside of monies that HHS controls that they may distribute to private entities to really compel them to do anything.

In the text of the report there is a lot of verbiage as to why it is important that there be communication, that there be consistency, and that we have, as needed, parallel pathways. But beyond encouraging the voluntary participation, there is not much else that can be done in the context of the actual recommendation.

DR. FITZGERALD: One second, Paul. Emily, then we will get back to you. Go ahead.

DR. WINN-DEEN: By taking the data format that has already been vetted with the PhRMA side and now asking the federally funded researchers to use that same format, the idea was that those things then would be more translatable across both the privately funded research as well as the public, rather than having the public set up a whole separate database structure and everything.

So there was method to the madness of choosing the FDA Voluntary Data Submission round.

DR. BILLINGS: Certainly, the text of that should be clear so that when the PhRMA folks read this they can get the idea of what we were getting at.

DR. FITZGERALD: Do me a favor. Take a look at the text. If you could see a place to put that, that would be great. Get that to Suzanne. Just to point out to you, when we get to 6A we are going to address this also with the industry.

So we have, "In situations where pharmacogenomic diagnostics are thought to be essential to clinical drug use, HHS should require its grantees and contractors to participate in FDA's Voluntary Genomic Data Submission Program during the exploratory phase of drug development and/or the pre-IDE review process."

Going once, going twice, sold. All right.

MS. ASPINALL: Paul the Greater has something to say.

DR. FITZGERALD: Paul the Invisible. No.

[Laughter.]

MR. MILLER: What do you mean by "are thought to be"? "Are thought to be" by whom? Why not just "diagnostics are essential"?

DR. FITZGERALD: So you want "diagnostics are essential"?

MR. MILLER: Yes.

DR. WINN-DEEN: I think you are still in the hypothesis stage.

DR. FITZGERALD: They are not always, so there is our problem. But, "may be essential."

DR. WILLIAMS: But I know where Paul is coming from because, if somebody says "Well, I don't think they are," that can be used. We need to be adequately explicit about what we mean and avoid the weasel words where people can kind of get around.

MS. ASPINALL: How about have the --

DR. FITZGERALD: Wait a minute. We have already here "In situations where," right? So, in a situation where pharmacogenomic diagnostics are essential. It is the situations that count. That has to be designated by somebody. That's fine. It doesn't have to be in situations that are thought to be. It is just in situations where, and then someone has to designate what those situations are. Is that okay? Okay.

MS. ASPINALL: You may have resolved it with doing that, but I agree with getting rid of "are thought to be." I think the question is, at what point do you know they are essential. That is the key issue.

DR. FITZGERALD: That will have to be determined. That is Recommendation 15A.

MS. ASPINALL: I'm there.

DR. FITZGERALD: So now we have, "In situations where pharmacogenomic diagnostics are essential to clinical drug use," and then from there. You didn't change anything else, right? Okay.

All right. I look around. Going once, twice, three times, sold. Next.

Remember we can come back and revisit these if new thing come along, but let's keep moving. Until we vote on it, nothing is ultimately, truly, concretely final. Unless we don't get to a vote.

This is for your information. This will not be in the recommendation, but we just wanted to flag some of the recommendations that came from the public comments. This was one of them.

"HHS should enable the investigation of biomarkers associated with drug response by encouraging sponsors of federally funded clinical drug trials to request appropriate biological samples from research participants." Marc? No. Mara, please.

MS. ASPINALL: Maybe it is implied, but it seems to stop a little short of doing something with those samples. When it says to request samples and get the appropriate permissions for relevant testing?

DR. FITZGERALD: In other words, they would have to be done with informed consent and all that sort of thing, right? I'm presuming.

MS. ASPINALL: And something has to be done with them, as opposed to just getting the samples. So maybe the thought is it is implied and it is in the text, but it seems to me that it was missing the second half, which is we are not just getting samples for samples, we are getting samples to be used --

DR. FITZGERALD: Biomarker-associated drug response research.

MS. ASPINALL: Yes.

PARTICIPANT: You could say something like "to facilitate pharmacogenomic or biomarker research."

DR. FITZGERALD: I think the first part says "HHS should enable the investigation of biomarkers associated with drug response." I thought that was the target?

MS. ASPINALL: Is that enough?

DR. FITZGERALD: But, is that not clear? We could rotate things around. We could put that in the end if you want to do it that way.

MS. ASPINALL: That, to me, makes more sense because you could just say "enabling" in the broadest way and they are requesting samples from the research participants and they are done. From a public comment [standpoint], as people get more concerned about requesting samples from participants, I think it is important to connect it with what is going to be done with those samples.

DR. FITZGERALD: So, "HHS should encourage sponsors of federally funded clinical drug trials to request appropriate," "in order to enable the investigation of biomarkers"?

MS. ASPINALL: Maybe the other way. "In order to encourage the investigation around biomarkers, HHS should encourage sponsors of trials to request the appropriate samples and" -- I lost myself here. I would add "and get the appropriate permissions for" --

DR. FITZGERALD: I think informed consent and all that would obviously be implied. They are not going to do anything that is. They better not, anyway.

MS. ASPINALL: Because, again, that would be relevant to all the recommendations.

DR. FITZGERALD: Right. Exactly. Gurvaneet and then Michael.

DR. RANDHAWA: I'm just concerned we are getting bogged down with the granularity here. Comparing this recommendation with Draft Recommendation No. 2, which is so broad that you are facilitating all kinds of technologies by translating basic research and clinical trial into policy, in this recommendation we are just talking about access to some biological specimens in one situation only.

But this is a larger issue. There has to be a national biobank. That is needed. There are other kinds of infrastructure issues here. This is just one part of this process that we are focusing on. So I'm not sure why we chose to focus only on this part.

DR. FITZGERALD: In part, in response to the public comments. I think also in part we thought this was reasonable in that response because when you talk about, obviously, the need for the biobanks and the repositories and large population studies and all that, some of that was already addressed in the Large Population Studies Report.

So the question, I guess, is, is this too granular? Which it may be as a recommendation and we don't need to put it in. But this was in response to the public comments, which we thought was a way of further specifying some of the things that had already begun to be addressed in the large population studies.

Go ahead, Suzanne.

MS. GOODWIN: Can you look at Recommendation 5B? Does this get closer to what you are talking about? 5B, 5D, 5A.

DR. RANDHAWA: It could come in there, also, because in 5B, as you are ending it, you talk about analytic validity, which is really getting into specimens and using them.

MS. ASPINALL: That would make me more comfortable, too, because I think this one, just as a recommendation that we are getting samples for the public but not enough connection to other things. So I think this raises anxiety from the public as opposed to reducing anxiety.

DR. FITZGERALD: The reason this is in here is because, in the public comments, somebody said specifically this needs to be recommended. Now the question is whether or not we think it does. So if we don't think it needs to be recommended, we can just get rid of it because we have too many anyway.

I had Mike and then Jim and then Mara again.

DR. AMOS: If you are going to include this recommendation, I think it is critical that, really following on to Gurvaneet's statement, right now there are no standards for either obtaining, storage, or utilization of any biological specimens. There are no national standards for that.

So if you are going to include this recommendation, I would highly recommend that additional language be placed in the document to support the development of standardization for handling such specimens.

Now, if you are going to pull this out and put it in 5B, I will just jump ahead a little bit. If you are going to put it in 5B, maybe you should add NIST to the laundry list of people that everyone should work with.

But somewhere in this document, and it is a little anemic in this regard, you really need to emphasize the need for technology and sampling standards.

DR. FITZGERALD: Let me make sure I have it right. Jim and then Mara.

DR. EVANS: I was just going to really reiterate, I think, Kevin, when you were trying to point out why this was suggested. I think there is some valid rationale in having it, maybe with the modifications that Michael suggested.

The point being that clinical drug trials don't necessarily collect pertinent data and, really, the entire promise of pharmacogenomics rests on collecting certain samples, namely DNA, so that they are available for study when we begin to get response data, et cetera.

So I think it is a reasonable recommendation. I think something to the effect of what was just suggested about incorporating that into a usable, more comprehensive structure [should be included.]

DR. FITZGERALD: Mara.

MS. ASPINALL: I definitely agree that we have to provide some additional context. I think the question on No. 3 or No. 5, or maybe both, is this is the Clinical Research section and No. 5 is in the Establishing the Evidence Base section. My assumption, and again I'm looking at the public here, is that the idea is we wanted to mention it in the Clinical Research section because if it is not there it feels like it is missing.

I will try to spend a little time because I can't do this in real time, but I think we need to add some additional specificity on, as Michael suggested, what this means, how the samples would be used, or at least consistent with appropriate new national guidelines on this kind of work.

DR. FITZGERALD: "To enable the investigation of biomarkers associated with drug response within the development of national guidelines," or something along those lines? Just think about that. We have a few more comments to go to. Sarah.

MS. CARR: I just want to ask, I guess especially Mike, in terms of the standards and guidelines you are recommending, you are talking about technical issues rather than the ethical and legal issues? Because I'm sure you are aware of the NCI's guidelines. Those are focused, obviously, on oncology samples.

But, are you suggesting, and others suggesting, that that is what is needed for this field? The way in which the samples are collected and stored, there needs to be standardization along technical lines?

DR. AMOS: Right.

MS. CARR: So it would be, in a sense, taking what NCI has done in oncology and focusing in on what is needed in this field?

DR. AMOS: Even NCI is in the process of putting more money into developing the standards for, for example, tissue because there are no real standards yet for how to collect and fix and store tissue samples for molecular pathology evaluation. So, yes.

DR. FITZGERALD: If we take a look at what is on the screen that Suzanne just put up, "To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical trials to request appropriate biological samples from research participants. HHS should develop guidance on how samples should be collected, stored, and shared."

Wait, wait, wait. I have Andrea. With the mic on, please. Thank you.

DR. FERREIRA-GONZALEZ: For our previous report in large population studies, did we ever recommend the development of these standards? Did we already do that?

DR. FITZGERALD: I have that on my computer, but I would have to dig that up. I'm trying to remember. Hunt is not here.

MS. CARR: Yvette, do you know? There is certainly a call for consideration of all the ethical issues. I think it was focused there, more on the ethical and legal and societal implications but not so much the technical, if I recall. But Yvette knows that report backwards and forwards.

DR. FITZGERALD: We will check with Yvette on that. Marc, go ahead.

DR. WILLIAMS: Just looking at the list of verbs at the end there, the one that seems to be missing is "used."

DR. AMOS: Yes, "utilization."

DR. FITZGERALD: Great. It was. It was one of the recommendations in the report. In the text, the body of this, we can obviously footnote that. That is a good point. We will make a mark, or someone will. That is a great idea. We have wanted to do that. We have wanted to integrate these reports. Exactly.

I have Gurvaneet and Michael. Still on this, right? We have to move on this, but go ahead.

DR. RANDHAWA: I think this is still incomplete because it is not just how well the samples are collected and stored, actually the issue is how well the clinical data are associated with the samples. Do we know if it is the same biological condition, the same disease, the same subtype. So that richness of clinical data is, I think, a major impediment, not just the technical issue of how well you collect and store it.

DR. FITZGERALD: But we have here how these "samples and their associated clinical data," if that is okay, "should be collected, stored, shared, and used." Good. All right.

DR. AMOS: Just one quick one. I was hoping that maybe you could change "request" to "obtain." Requesting is requesting. There is no --

DR. FITZGERALD: Well, you can encourage sponsors to obtain. You can do that, right? Because that doesn't require their sponsors to obtain. You could require the sponsors to request. But you can't do both. So we can encourage the sponsors to obtain, or we can require sponsors to request. Take your pick.

Marc.

DR. WILLIAMS: No, I'm not going to use the "require" word, but I would like to suggest that the recommendation actually explicitly reflect the recommendation from the Population Study Report because a lot of times people don't read the whole report. So if we bury it in the text it won't be seen. That is consistent with what we have done in other reports where recommendations reference recommendations from other reports.

So whenever that is in there, I just say that should be inserted there in the recommendation, not just in the text.

DR. FITZGERALD: So you want the words from the other report put in here.

DR. WILLIAMS: Not the words but the specific reference.

DR. FITZGERALD: Oh, I see. A reference. Got it. So put like Footnote No. 1. Got it.

All right. We are still on this one. Julio.

DR. LICINO: I just have a comment. This is a little bit of a quagmire because --

DR. FITZGERALD: I think we have noticed that.

DR. LICINO: -- when you collect the samples it is very important to serve consent [so that] the patients know that the samples or the genetic data is going to go to the FDA or to regulatory agencies who are going to have access to that because the patient has the right to withdraw the consent and then to request that the data be changed. But once it is sent to the agency, I don't know that you can take the data away from an individual person. I don't think it is even possible to do that.

It really impacts a lot on the design of the studies, so I would maybe add a word here saying that future studies should be designed in a way that would permit deposition of data with the FDA if appropriate. If a study was not designed for that, you can have a sample but you cannot do it.

DR. FITZGERALD: Now, if we are developing guidance and standards on how these samples and their associated clinical data should be collected, wouldn't that be part of those guidelines and standards? Obviously it would involve informed consent, but it would also involve which ones are appropriate to that or not. Is that okay?

DR. LICINO: I guess so. I think it goes a little bit more than that. It is not the collection, it is the intent of the study.

DR. FITZGERALD: Right. But it would also involve "which should be collected," right? We need words here.

Who else had comments before? Mara, did you have something, too?

MS. ASPINALL: I just had a small one, which is sometimes we call it "drug response," sometimes we call it "drug metabolism," sometimes "drug prescribing," which I think they are meant to be the same.

DR. FITZGERALD: Oh, up there? Okay.

MS. ASPINALL: Not in this recommendation but comparing recommendations. Like, the last one we called it "drug prescribing" as opposed to "drug response." If folks think that those are interchangeable, I'm fine with it.

MS. GOODWIN: Which term is preferred?

MS. ASPINALL: I like "drug prescribing," which was broader than "drug response." That is how we did it on the last one, so it would suggest that we tried to be consistent with that.

I may be working off of the old version.

MS. GOODWIN: Do you know which previous recommendation?

MS. ASPINALL: 3C.

DR. FITZGERALD: "Drug development"?

MS. ASPINALL: Maybe it got out of 3C. It was there at one point.

DR. FITZGERALD: If everybody agrees "drug prescribing" is the preferred term, we can stick with that. No? Okay. That was a mistake.

DR. WILLIAMS: But I don't think we necessarily need to parse it. I think that the concept that Mara presented is a reasonable one, that we need to be consistent with our use of language.

DR. FITZGERALD: Yes.

DR. WILLIAMS: Rather than try and fix that here, which may be well impossible since we keep going back and forth, just a charge to the taskforce to say you need to be looking at "drug" and use the same language consistently unless there are specific reasons in a recommendation to make it different.

DR. FITZGERALD: Let me remind you, this is a finalization process. We don't have a chance further on from here.

DR. WILLIAMS: It's called lunch, Kevin.

[Laughter.]

MS. ASPINALL: Why don't we leave it as it is and then maybe as we look at the recommendations over lunch we can choose a word.

DR. WINN-DEEN: I just want to say, I think I agree with Mara because "prescribing" takes into account both response as well as ADRs.

MS. ASPINALL: That is what I was trying to get to.

DR. WINN-DEEN: Whereas if you just say "response," then you have left the other side of the whole PGx thing out.

DR. FITZGERALD: Steve.

DR. TEUTSCH: "Prescribing" gets you into the whole utilization and downstream consequences, and this is about clinical research, primarily, and really finding out what relates to the response, good and bad. I would leave it the way it was.

DR. FITZGERALD: All right. We are at loggerheads about whether to "respond" or "prescribe." Let's put it this way. If we started with "response," let's use that as our default. Are you okay with response in this recommendation? Is that okay, Emily? Or do you need "prescribing"? Since this is clinical translation.

MS. ASPINALL: How about we leave it as "response" now. I would like to, as we go back to it, just look to see if it needs to be consistent.

DR. FITZGERALD: Sure. Emily?

DR. WINN-DEEN: Yes. I think either we can leave it at "response" or "response/ADRs" or something.

DR. TEUTSCH: ADRs are responses.

DR. FITZGERALD: Right, right. Adverse drug response.

MS. ASPINALL: If you think it covers that, that's fine. I was trying to get the concept that it wasn't just initial drug response, that it was broader.

DR. FITZGERALD: All right. Everybody is good? All right. Let's go one more time through this.

"To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS should develop guidance and standards on how these samples and their associated clinical data should be collected, stored, shared, and used."

We could put in parentheses here or we could put a footnote, "Also see Recommendation," whichever number, "from the Large Population Studies Report." Okay? Okay. Great. Next. What? Not okay.

[Laughter.]

DR. FITZGERALD: This is why the NFL has that problem with that new rule. You can freezer the kicker at the last second.

DR. KHOURY: We want clinical data. What does that mean, Gurvaneet? We say this is drug use. Do you want other types of data, like risk factor data? When you are trying to link records and you are looking at outcomes, there are other data that are related to gene-environment interaction here.

DR. FITZGERALD: Wait a minute. Gurvaneet, did you have --

DR. KHOURY: What did you have in mind with "clinical data"?

DR. RANDHAWA: I was just trying to add on to the step that the initial recommendation as it was phrased was to focus on the biological sample collection and use. Now, depending on the context of how it is going to be used, it could be purely clinical or it could have more of a gene-environment, public health usage. So that I would leave up to the Committee as to how broad you want to make it.

DR. FITZGERALD: How about if we have now "associated patient data"? Is that better, worse?

DR. KHOURY: Not all participants are patients, however. They could be healthy individuals.

DR. FITZGERALD: "Participant data"?

DR. KHOURY: Because that keeps it vague. There is some clinical data but there is also drug use data and environmental, risk factor data, nutritional data, whatever.

DR. FITZGERALD: Marc and Paul the Questionable.

[Laughter.]

DR. WILLIAMS: This is in the context of developing guidance and standards. I think the point that Muin is bringing up is basically something that will be addressed in developing guidance and standards in terms of that. I don't think we need to parse it out anymore.

DR. FITZGERALD: Paul.

DR. BILLINGS: My comment is, there are two "shoulds" in the second paragraph. Maybe you should turn the second one into a "will."

DR. FITZGERALD: All right. Muin, developing the guidance and standards, would that be part of what sort of data would be involved?

DR. KHOURY: Yes.

DR. FITZGERALD: "Other participant data will be collected, stored, and used." Where did you get the "should"? Oh, there. Got it.

All right. Now, try again. "To enable the investigation of biomarkers associated with drug response, HHS should encourage sponsors of federally funded clinical drug trials to obtain appropriate biological samples from research participants. HHS should develop guidance and standards on how these samples and other participant data will be collected, stored, shared, and used. Also see Recommendation whatever from the earlier Large Population Study."

"How samples and data" -- what is this? You have to push your button.

MS. CARR: How about --

DR. FITZGERALD: Wait a minute. We want to be happy with this.

MS. CARR: But I think it will help with that earlier discussion. "How these samples and the data associated with them will be collected." Then you have all the data associated with them. You don't define it one way or another.

DR. KHOURY: I like the word "participant" more than "data."

MS. CARR: The samples come from participants, don't they? We are not talking about anything but sample participants. Participant samples.

[Laughter.]

DR. FITZGERALD: Wait a minute. This is starting up again. Jim.

DR. EVANS: I agree with Muin. I think "participant data" is subtly but importantly different from just the accompanying data. That could be concentration of the sample.

DR. FITZGERALD: I hear people leaning toward "participant," where we have it now. Going once? No?

All right. So again, Sarah, what was your comment?

MS. CARR: How about "participant samples"?

PARTICIPANTS: No.

DR. EVANS: We are talking about the participants and other things --

MS. CARR: Their samples.

DR. EVANS: No, no, no. The sample is the chunk of tissue, the serum, the white cells, the DNA. What we are getting at here is --

MS. CARR: And all the associated --

DR. FITZGERALD: The crowd is turning uglier, Sarah. I would bail on this one if I were you.

[Laughter.]

DR. FITZGERALD: I don't know. I will throw Reed in front of you, but that is it. Beyond that, forget it.

I think we are good, right? Or, wait. No? Yes? No? Why? Who? Don't even ask, right. No, I think I have to ask.

All right. Next, 4A, page 35. Here we go. By the way, no one leaves until we are done, just so you know. If we are here at three in the morning. Isn't that how it works, Reed?

DR. TUCKSON: No question.

DR. FITZGERALD: "HHS should ensure that sufficient resources are available to FDA to build on and implement the agency's efforts to develop guidance on the codevelopment of pharmacogenomics drugs, and diagnostics. FDA's guidance should clarify the review process for codeveloped pharmacogenomics products where the drug is subject to FDA review but the laboratory-developed companion diagnostic test may not be. It also should promote collaboration between drug and diagnostics manufacturers."

Paul the Unimaginable.

DR. BILLINGS: Paul whatever I am. Again, can someone clarify why diagnostic manufacturers are specifically noted and why not, for instance, the laboratory industry, which is the major provider of these tests now?

DR. FITZGERALD: Emily.

DR. WINN-DEEN: The lab industry is right in the sentence before that.

DR. BILLINGS: Did I miss that somehow? Because of "laboratory-derived companion diagnostics," is that what you mean?

DR. WINN-DEEN: Right. I think what we were trying to ask FDA for was guidance on both aspects, those tests where they are just available through fee-for-service laboratories as well as tests that would be put in a box by an IBD manufacturer.

DR. BILLINGS: Right. But we want collaboration amongst all the entities in the provision of these things, don't we? In the last sentence it says, "Promote collaboration between drug and diagnostic manufacturers," but in fact we want collaboration across the whole spectrum of providers in this field.

DR. WINN-DEEN: Yes. So we get back into does FDA have purview over the labs. This recommendation was directed specifically at FDA to develop guidance.

DR. BILLINGS: I see.

DR. FITZGERALD: Mara and then Robinsue.

MS. ASPINALL: Can I make a suggestion that doesn't get to the issue whether FDA has purview, because I understand that is a bigger issue than even three in the morning. But I wonder if we just want to say "diagnostic companies" because that encompasses both manufacturers, lab service companies. It is broader, and the FDA has some draft guidance now and has ASRs that oversee things that the laboratory service companies do.

DR. FITZGERALD: Robinsue.

DR. FROHBOESE: I wanted to go back to the point that Muin raised earlier on when we were talking about the first recommendation, and that is use of the word "resources." This recommendation is calling for HHS to ensure sufficient resources are available. Recommendation No. 1 asked for NIH to put more resources into. Then we see Recommendation No. 5A, HHS should provide resources.

I think those are the only three that specifically talk about resources, and unless there is a particular reason why in this recommendation and other recommendations there is a need to emphasize resources, I would agree that we should just have an omnibus recommendation at the end, perhaps expanding when we get to it, Recommendation No. 15B, to talk globally about looking at needed resources to carry out the recommendations.

DR. FITZGERALD: In changing this one, how would you [phrase it]?

DR. FROHBOESE: I would just start with "FDA should" --

DR. FITZGERALD: "Build on and implement"?

DR. FROHBOESE: -- "build on and implement the agency's efforts."

DR. FITZGERALD: And then refer to 15B. Michael.

DR. AMOS: I'm just wondering if this recommendation covers when a drug company develops its own diagnostic. Is the language inclusive of that?

DR. FITZGERALD: That was trying to get back to your point, Mara.

MS. ASPINALL: No. My point was a different point. My point was the difference between diagnostic manufacturers and other kind of diagnostic companies. I actually think the way it is written now, "by diagnostic developers," does include that because it would say it doesn't matter what kind of company, it is a developer.

DR. FITZGERALD: All right. So we have "diagnostic developers." Good. What are we changing?

MS. GOODWIN: Sarah is asking that this be there.

DR. FITZGERALD: You have to talk into the mic.

MS. GOODWIN: Sorry. Should we say "PGx drugs and diagnostics" or "development of drugs and PGx diagnostics"?

DR. FITZGERALD: So, "drugs and PGx diagnostics."

DR. WILLIAMS: Codevelopment is the operative thing here. You are talking about a specific drug and a specific diagnostic that goes with that drug. It doesn't need any additional explanation.

DR. FITZGERALD: Marc, what are you saying? Should we go back to the way it was or do "PGx diagnostics" or just say "drugs and diagnostics"?

DR. WILLIAMS: No, I think the "PGx drugs and diagnostics" is just fine.

MS. ASPINALL: I would agree.

DR. FITZGERALD: Michael, go ahead.

DR. AMOS: By saying "codevelopment," doesn't that limit you because then, by definition, it has to be codeveloped with the drug. There will be other diagnostic tests that are pharmacogenomic.

DR. FITZGERALD: Those are addressed in other recommendations. This recommendation is specific to codevelopment.

All right. Let's read what we have now, I think. Wait a minute. Not yet. Emily.

DR. WINN-DEEN: I think the middle sentence, "FDA's guidance should," needs to take into account both processes where the diagnostic is developed by an IBD manufacturer and where the diagnostic is a laboratory-developed test. Somehow when we changed the last sentence, we lost the whole manufacturers part of the IBD industry.

DR. FITZGERALD: So, what would you recommend?

MS. ASPINALL: How about "and" instead of "but"?

DR. WINN-DEEN: Wait, wait, wait. I'm just trying to see where the right place to put this is.

DR. FITZGERALD: "Is subject to FDA review and the laboratory-developed companion diagnostic text may not be."

MS. ASPINALL: "And the laboratory-developed companion" --

DR. WINN-DEEN: The middle sentence is just one case where the drug is subject to FDA review but the diagnostic might not be. We need the companion sentence for when the drug and the diagnostic are subject to FDA review.

MS. ASPINALL: Could it be broader and just say, "The FDA's guidance should clarify the review process for codeveloped"? Do we need to clarify it all? Just say "codeveloped PGx products"?

DR. FITZGERALD: Andrea.

DR. FERREIRA-GONZALEZ: Take the "but the laboratory" out.

DR. FITZGERALD: Pardon?

DR. FERREIRA-GONZALEZ: Take "but the laboratory-developed companion."

DR. FITZGERALD: Wait a minute, wait a minute. Again. One more time. Take?

DR. FERREIRA-GONZALEZ: Take the part, "but the laboratory-developed companion," out.

DR. FITZGERALD: Stop the sentence after review."

DR. FERREIRA-GONZALEZ: Yes.

DR. FITZGERALD: Get rid of the rest of the sentence. There you go.

DR. FERREIRA-GONZALEZ: Some of these issues will be further dealt with in the next report.

DR. FITZGERALD: So, delete that part. We don't need the "including"? Get rid of "including." Start with "products." Okay. Try it again. We are into brevity, if we can do it.

All right. Let's see what we have. "FDA should develop and implement guidance on the codevelopment of pharmacogenomics drugs and diagnostics. FDA's guidance should clarify the review process for codeveloped pharmacogenomics products. It also should promote collaboration between drug and diagnostics developers." Muin, first to wade in.

DR. KHOURY: What do we mean by "should promote collaboration"? What does that mean?

DR. FITZGERALD: Beat them about the head and shoulders. That is how we do it here.

MS. ASPINALL: The text talks about some ideas where they could work together where they have pre-IDE meetings together. The Voluntary Genomics Submission data, in my mind, is one of those examples.

DR. FITZGERALD: We do have examples in the text. That is good enough? Okay. Anybody else? We need to move, and it looks like we are going to move. This looks good for the moment. Let's go to 4B. It is also on page 35.

"FDA's Office of Combination Products should coordinate the review of pharmacogenomics tests and drugs among the various FDA centers/offices to minimize delays in approvals of codeveloped pharmacogenomics products and to ensure timely access to such products."

[No response.]

DR. FITZGERALD: Great so far. Yes? All right. Excellent. Everybody is happy? No, Muin is not happy.

DR. KHOURY: Once you specify which part of FDA is needed to do the job, you can delete that third line, "among the various FDA centers and offices." It seems redundant to have that third line.

DR. FITZGERALD: Shorter is always better. "FDA's Office of Combination Products should coordinate the review of pharmacogenomics tests and drugs." Is this to go? "To minimize delays in approvals of codeveloped pharmacogenomics products and to ensure timely access to such products." Yes? Yes. Excellent. Thank you. Wait.

[Laughter.]

DR. FROHBOESE: I think by taking out "among the various FDA centers/offices" the sentence may be too broad. So I would suggest the qualifier "should coordinate the FDA review." We are addressing only FDA, is that correct, as opposed to NIH review or CDC review?

DR. FITZGERALD: Yes, yes. Good.

MS. ASPINALL: Does that bring into account the fact that some tests are not reviewed by the FDA that wouldn't, by this, just become reviewed by the FDA? I was going to have a slightly different comment, but that may broaden it enough to get to that. Some of the PGx tasks are not under the FDA.

DR. FITZGERALD: But we are talking just FDA's review of PGx tests, right?

MS. ASPINALL: Well, I think with the addition it helps clarify that.

DR. FITZGERALD: All right. Going once, going twice, sold. On to the next. Great. No. 4C is on page 39 in your book, and there is a distinction between the way we have it on the screen and the way it is in your book. We will have to discuss that because there could well be a significant difference.

"HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products, especially for smaller," on the screen it says "markets." In your book it says "patient populations." "Markets" was our later rendition. Why markets? I think people wanted it to be broader than "patient populations."

DR. WINN-DEEN: So, are you saying we need to go beyond orphan drug kind of legislation and create a new thing that is based on markets instead of number of patients?

DR. FITZGERALD: I'm trying to recall why. I can't remember. We certainly can go with "patient populations." We are just putting in what was recommended. So if people want "patient populations," we can certainly do that. Is that okay, "patient populations"? Fine.

DR. WISE: I have a question on that.

DR. FITZGERALD: Sure. Please, Paul.

DR. WISE: Paul the Least.

[Laughter.]

DR. WISE: There are very large patient populations that represent very small markets. That should be captured in some way. What do I mean by that example?

DR. FITZGERALD: Yes.

DR. WISE: Development of drugs that would be extremely useful for millions of people around the world but are considered small markets. Incentives should be developed in accord with those considerations as well.

DR. FITZGERALD: I think in fact that may have been one of the points behind the "market" thing. Yes, Mara.

MS. ASPINALL: Maybe a question, but I think it gets to what Paul is getting to. You did in the summary the 200,000 patients or below for drugs. Where does the 4,000 come from? Is it related to the humanitarian drug exemption?

DR. FITZGERALD: Device.

MS. ASPINALL: Device exemption, sorry. But the HDE brings in a number of other regulations around it. It has to go through IRB approval. It can't profit off of it. It seems to set up a very different standard, not only just the numbers. If the 4,000 is also subject to HDE, it seems to have a whole other hurdle of necessary regulations, approvals, and profit restrictions that the orphan drug piece does not. That was half a statement but really a question.

DR. FITZGERALD: Emily.

DR. WINN-DEEN: I think the point we were trying to make was to point that out. First of all, those two numbers are out of sync with one another. If you have a PGx system and it is orphan on the drug side, why is it not orphan on the diagnostic side. I think Steve Gutman provided the Committee with some insight that, really, the HDE is the only diagnostic mechanism that is available in an "orphan" kind of status. There isn't an equivalent to orphan drugs.

Correct me if I'm wrong, Steve.

DR. GUTMAN: No, that's right.

DR. FITZGERALD: Jim and then Mara.

DR. EVANS: I think that Paul the Wise's comment is a very important one and was, I think, the driving force behind changing it to "markets." Why not include both and say "for smaller patient populations and/or markets."

DR. FITZGERALD: That is, I think, what we are going to try and do, include both. Yes, Mara.

MS. ASPINALL: I think this gets to it in that way, the patient populations and markets, but do we get to a recommendation that goes to Emily's point about the differential here between the diagnostics and the drugs, or one that may not be effective?

DR. FITZGERALD: There is no recommendation that is specific for that, but we discussed that and whether or not there needed to be. The thought was, anyway, that what we were getting at was what we should recommend to the Secretary and not necessarily force something on that specific issue, though the understanding is that issue certainly would be addressed as part of the process of following up on these recommendations.

That left it open to how it might be resolved. We weren't going to recommend how to resolve it specifically.

MS. ASPINALL: I understand about how. I guess I'm recommending it should be more explicit, because I don't think you get it from this.

DR. FITZGERALD: Marc.

DR. WILLIAMS: The question that relates to the explicitness is whether it is under the Secretary's purview. In other words, is that able to be done under rulemaking or is this something that would require a legislative change to effect it. If it is the latter, we can't make an explicit recommendation about it. If it is the former, then we can.

DR. FITZGERALD: Sarah.

MS. CARR: I think you could recommend to the Secretary that he seek a legislative change, if it did require a statutory change. Does it, Steve? Is the 4,000 in statute?

DR. GUTMAN: I actually don't know.

DR. FITZGERALD: Mike. I'm sorry.

DR. AMOS: Just a logistical question. If I were looking at this recommendation if it were published in a list of recommendations, I think the way you are going to present this is you are going to have a separate sheet with a list of the recommendations along with part of an executive summary?

DR. FITZGERALD: No. This will be part of the executive summary. This is part of the executive summary. There is not a special list just for the recommendations.

DR. AMOS: But, is there enough information in here that someone would know what you are talking about with this recommendation if it stood alone?

DR. FITZGERALD: If it stood alone.

DR. AMOS: Yes. If it stood on its own in a list, a separate list.

MS. ASPINALL: I would agree with Michael. I think in and of itself this is a piece of it. But I don't think it gets to, as Emily described it, the differential and the need to relook at, maybe at a minimum, the small patient/market issue around diagnostics. I don't think most people, if they are not in this room, would notice that.

DR. FITZGERALD: Granted there is always this tension between how much should go in the recommendation as far as exploratory materials and how much goes in the text. Now, there is more, obviously, in the report on all this, as we already saw.

Since it is a recommendation to the Secretary, as you say, if the public is seeking more information about what is explicitly involved in this, they can certainly look at the larger report. Even in the executive summary there are additional materials.

I guess the question is, if we want to wordsmith this to give it a little more content, how would you do it? What extra sentence or whatever would you want to put in? Suzanne is doing it right now. We need help, so if you have something. Michael? No. Marc?

DR. WILLIAMS: I have a suggestion. I think the issue that I have heard is it would be sort of a "whereas, therefore." "Given the inconsistency between the numbers of patients for orphan drugs versus the numbers of patients that would qualify for orphan devices and the inconsistencies between those two sets of rules, it is recommended that." That would at least give it some context.

DR. FITZGERALD: Wait a minute. Jim?

DR. EVANS: I don't know. I think that having the boxed recommendations brief and to the point makes a lot of sense. Then immediately under it you can say those kinds of things and put it in context.

I think brevity should be something we seek as long as it is clear and there is explanatory information accompanying it, even in the executive summary. They don't have to dig through it.

DR. FITZGERALD: Joe likes that, too. Wait. Steve?

DR. TEUTSCH: I think we have to be careful when we get into the sizes of these different things. It is very much the cost of development of these different things, drugs versus devices versus diagnostics, that lead you to needing different kinds of economic incentives. I think that is in here.

I agree with Jim that shorter is better.

DR. FITZGERALD: All right. Is this short enough? Let's take a look. Wait a minute. So, "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products. Specific incentives should be identified for smaller

patient populations and/or markets to address inconsistencies between prevalence thresholds for orphan drugs and orphan devices."

No, too much. Kill the sentence. There we go. "And/or markets" we definitely want. "For smaller patient populations and/or markets," right.

So we are back to, "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics products, especially for smaller patient populations and/or markets," and making sure that that is explicated clearly in the materials.

Yes, Mara.

MS. ASPINALL: Maybe I have a simpler one. I guess the fundamental premise for me that I'm concerned about is, for orphan drugs, the system works as an incentive. For orphan devices or tests, the system currently works I think as a disincentive, with more restrictions than incentives.

Although I appreciate Jim's comment, I think we have context in a lot more of the other recommendations than this one. I don't think we are adding too much, but at a minimum to say the "development of PGx products and diagnostics," if you think about products as drugs or PGx drugs and diagnostics.

DR. FITZGERALD: Rather than "products."

MS. ASPINALL: Yes, so it is clear. Because some people will consider products being drugs. Not everyone. But I wanted to highlight "diagnostics" because I think the HDE process today works as a disincentive.

DR. FITZGERALD: Right. Paul.

DR. WISE: Thank you. There are really two concerns here. One is this technical conversation about different types of pharmacogenomic developments. But there is a great sensitivity that I think generated in part the conversation around this recommendation coming into this meeting and that is outside of the issue. There is great sensitivity about small patient populations and very large populations that are small markets. In other words, large populations of people who can't pay.

If it was going to require greater technical precision to address the points that you are making, it is also going to have to be balanced by a strong statement that also elevates this issue of small patient populations and markets. So if you are going to put in extra language to clarify that, it might require moving to a 4D that explicitly elevates or addresses the sensitivity around small patient populations and small markets.

DR. FITZGERALD: Look at what we have now. Is that sufficient emphasis?

DR. WISE: If more language was going to be placed to clarify the issues that you are raising, my concern was that --

DR. FITZGERALD: It would be lost. Right. Got it. George, look at what we have now. "HHS should engage all stakeholders in identifying and providing incentives to encourage the development of pharmacogenomics drugs and diagnostics," rather than "products," "especially for

smaller patient populations and/or markets." Does that get to where we want to go? Yes, yes, yes? Yes. Excellent. Very good. Next.

We are supposed to break at noon, so if we can get one or two more done, that would be dynamite.

Page 43 is where you will find Draft Recommendation 5A. "HHS should provide resources to identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics. Progress will require high quality data resources, improved methodologies in the design, conduct, and analysis of observational studies, and empirical research on the evidence and standards necessary for making decisions for various purposes (for example, coverage, clinical guidelines, performance metrics) in different clinical contexts."

This is getting at establishing an evidence base. Everybody seems happy. No? Paul.

DR. BILLINGS: This is, again, a background question. The report is surprisingly devoid of the evidence of current use of testing. In other words, there isn't a table that shows what the frequency of use of TMPT or P450 testing or whatever. So we are advocating for the establishment of the database, yet there doesn't seem to be any review of the data in the report. So I'm curious about why that occurs.

DR. FITZGERALD: Mostly because the data is not there.

DR. BILLINGS: What does that mean? The people who are providing the tests are not keeping data; is that what you are trying to tell me?

DR. FITZGERALD: Marc, go ahead.

DR. WILLIAMS: Yes, there are a number of different issues. First of all, any sort of an outside agency that wants to review that, because of the coding deficiencies, can't collect the information. You can't tell based on genetic CPT codes whether this was a TMPT test or an invader assay or a BRCA or whatever.

So the third-party payers that may want to look at utilization can't develop data or ask how many of these tests are being done. Manufacturers are variable in terms of their willingness to put their data out for public review in terms of numbers, results, et cetera. So there are no sources of data in the available public literature that can give any sort of an estimate about utilization on this.

DR. BILLINGS: Can I just follow that up? Does that mean that the Committee or somebody asked the providers of tests in this sector to voluntarily provide the data and they refused?

DR. FITZGERALD: No, we didn't do that. Steve, go ahead.

DR. TEUTSCH: This is actually an issue that is addressed in the Oversight Report. We talk about much more the translational process into clinical decision support. There is a section in there, and I think it is worthwhile making sure that we cross-reference appropriately in anticipation.

DR. BILLINGS: The Oversight Report is going to come out much later than this, presumably.

DR. TEUTSCH: No, I understand.

DR. FITZGERALD: Steve, actually, we can't. My understanding, from what has been implanted my brain by Sarah, is we cannot anticipate because nothing has been voted on yet for that report. But I think that report could then certainly reference back to this one. You can do that.

But no, we didn't attempt to do that because our idea was to look at what the terrain is currently. The terrain currently was that that information wasn't available.

DR. BILLINGS: I'm aware of the lack or the unevenness of the published data, but that doesn't mean that there aren't ways of voluntarily providing at least some of the parameters of this data. Some of these tests have been in the public domain for a long, long time.

DR. FITZGERALD: Was there something you wanted to then address in the recommendation?

DR. BILLINGS: I think it is a striking deficiency of this report that there is no compilation, or at least some comment about the compilation, of data in this area.

DR. TUCKSON: We will make sure we go back into the narrative of the report and reference the fact that there is stuff going on. The key word in this recommendation is the word "progress." Maybe we can deal with it that way. Let's beef up the narrative a little bit.

DR. FITZGERALD: Jim. No, okay. Barbara.

DR. McGRATH: I wonder if it would make it simpler just to remove some of the methodology part, the words from "progress will require." Just state something like "Using acceptable methodologies" or something in the top and then explain in the report what methods you are suggesting. Aren't those standard methods for clinical validity, utility, and cost effectiveness?

DR. FITZGERALD: We did have a discussion on that, and some people thought it was important to have that detail, but we can still have that discussion.

Who is going? Steve.

DR. TEUTSCH: I can go either way. The point is that the methods aren't developed and they are not accepted generally in the use of observational and some of these other things. Now, whether you want to include them here is another question, but there is a general problem in a lot of the evidence-based medicine approaches. It is not unique to this. How to incorporate them in an accepted manner is still a subject of considerable debate.

DR. TUCKSON: Let me just ask Barry and CMS, on this word in the recommendations: "In empirical research on the evidence and standards necessary for making decisions for various purposes, whether it is coverage, clinical guidelines, performance metrics," from your point of view, is [it] research on the evidence and standards, or research that supplies the evidence? I mean, we know what the evidence and standards are, don't we?

I'm wondering, are you trying to suggest we should try to do more research on what evidence and standards are necessary to make decisions, or research that answers the evidence basis of making these decisions?

I think the people that are making clinical coverage decisions and guidelines decisions pretty much know what those guidelines are. They don't need any more research on the guidelines; they need the answers.

DR. STRAUBE: I think it is primarily for coverage purposes, Reed; the latter. So I would agree with you.

I was going to suggest that in fact in the parentheses there we put "coverage, clinical guidance, performance metrics." Something that will sit well with the Secretary, believe me, since he usually talks about this would be value-driven health care, putting that in there, too. It goes beyond those three categories. It gets into improving quality, improving efficiency, et cetera.

DR. FITZGERALD: So, to add "value-driven health care" after "performance metrics."

DR. STRAUBE: Correct.

DR. FITZGERALD: "Value-driven health care." Did I miss someone over here? Marc, go ahead.

DR. WILLIAMS: Just to respond to Reed, I think the issue for me relating to your specific question is that the key issue in the first sentence is "identify evidence gaps." I think we don't necessarily know what those evidence gaps are. Some of them may be related to quality of evidence. Some of them may be related to actual clinical data. So I think it captures the points that you made.

DR. TUCKSON: The reason why I was asking, and you hit it exactly, was it sounded like there were two moving variables in the equation and I wanted to lock one in. It is the evidence gap that is necessary to answer the paradigm of decision-making as it exists in the real world today. I didn't want to figure out what the paradigm of decision-making research is and then figure out what the gaps are at the same time. You are trying to hit two moving targets.

Basically, let's move it along, folks. We know what it takes to answer these questions. We know how people think about it every day. Now let's provide the data and the information necessary to answer the questions.

DR. FITZGERALD: Did you want to recommend a change in the wording?

DR. TUCKSON: Yes. "Research that supplies the evidence" instead of "research on the evidence."

DR. BILLINGS: It has been my experience that the evidentiary requirements differ amongst different agencies, private, public, so forth and so on. Unless, Reed, you are going to allow for some harmonization, again, of what the evidence standards are and have them have some bite across the public and private sector, I don't know quite exactly how you are going to resolve that.

DR. FITZGERALD: Jim.

DR. EVANS: I would advocate leaving it the way it is, Reed, because I don't think it is a no-brainer as to what evidence really is important and what should drive change, acceptance, et cetera.

Muin works on this stuff. I think he might want to weigh in, or he might want to run out of the room.

[Laughter.]

DR. EVANS: I would advocate leaving it the way it is.

DR. TUCKSON: Can we say both? Can we say "research on the evidence and standards necessary" -- all right. That's fine. If you want to leave it there, that's good. I don't want to prolong it. I will withdraw the suggestion.

DR. FITZGERALD: That is a marvelous template by the Chair to lead us forward into the afternoon, to be very open. Yes, go ahead, Mike.

DR. AMOS: If you are talking about analytical validity and you are talking about standards, I want to bring up the point that there are only a handful of actual physical standards for diagnostic tests available. If part of your evidence gap is the reliability of the assays, then you really should put some additional language in here regarding the actual physical standards and standardizing the technology and the platforms.

DR. FITZGERALD: So what would you recommend?

DR. AMOS: I will have to think about it.

DR. FITZGERALD: No, you have to have answers. Hold on, hold on. Andrea, go ahead.

DR. FERREIRA-GONZALEZ: I think we will deal with that in the next report, even though we can't talk about the next report, the Oversight.

DR. FITZGERALD: Right, right. Sarah, can we say in this report that another report is underway that is going to attempt to address it, or something like that? So we can footnote? Okay. We will make sure that is in the text, that that question is being addressed more completely in a subsequent report. That we can say. I don't think we can say exactly what we are going to say.

Robinsue.

DR. FROHBOESE: A very quick edit for consistency. Should we take out "should provide resources" and it should read instead "HHS should identify and address evidence gaps"?

DR. FITZGERALD: Are people comfortable? Okay. Great. Thank you. "HHS should identify"; do you have that? Great. Ready? Here we go.

"HHS should identify and address evidence gaps in the analytic validity, clinical validity, clinical utility, and cost effectiveness of pharmacogenomics. Progress will require high quality data resources, improved methodologies in the design, conduct, and analysis of observational studies, and empirical research on the evidence and standards necessary for making decisions for various purposes (e.g. coverage, clinical guidelines, performance metrics, value-driven health care) in different clinical contexts."

We have been told we are done.

DR. TUCKSON: We are done. Now let's do a quick process check here. If we think about this, we have now from when come back at 12:45 until 4:30 to go through all the rest. So I think we are about okay. I'm a little nervous, but we will push through.

What did you say?

DR. TELFAIR: I haven't said anything yet. I was getting your attention.

DR. TUCKSON: You got it.

[Laughter.]

DR. TELFAIR: Just maybe a point of order. In other work that we have done in other groups, we have set a time limit on progress related to certain activities, given how you break it up. I realize that there may be a need for process on some of these things, but I think that if we set a time limit that will accelerate our thinking and really make us come to a decision much quicker.

So if the plan is to try to get through a large set of recommendations before the end of the day, I would recommend, and that is a group decision, that we set some kind of time limit on the amount of dialogue we have, either by recommendation or by block of recommendations or some parameter of time that allows us to really be focused.

DR. TUCKSON: Thank you for that. We are going to do the quantum calculus in just a second and, during lunch, figure out where we are, how many recommendations we have left. That is great, Joe. I think we will do that. But one way or another we will get through it.