Helen Meissner: Regulatory Science. I'm the Director of the Tobacco Regulatory Science Program at NIH. Before we get started, I just want to mention a couple of things about the webinar. First, very important, everyone who is participating in this webinar, other than the presenters, is muted. So, if you want to ask questions in the Q&A period, you will have to type those questions into the Q&A section on the webinar landing page. Also, we are recording the webinar, so, we will be able to hear it again if you wish and have access to the slides, which you will be able to find on the website, and I'll give you—I think the website is—we'll give you the website in just a moment. Also, if you have any difficulties hearing or anything like that, you can also email the TRSP mailbox if you're unable to type your question into the website. So I think that is all the housekeeping. We can move on.

Okay. One thing I wanted to point out right away is the fact that you'll note on this first slide that the RFA number is OD-17-006. We actually had to re-issue the RFA on Friday. The previous number was 003. Unfortunately, when the RFA was published, the text for the significance criterion was omitted and it came out in the publication and so, we had to re-issue the FOA in order to include that missing information. But other than that, there is nothing changing in it except for the number. So just don't be confused by that. So I expect that most of the people on the phone are probably familiar with TRSP, but for those who may be new, I'm just going to briefly tell you a little bit about who we are and how the program operates. So this program emerged as a result of the partnership between FDA's Center for Tobacco Products and the NIH. And it was assigned to the Office of Disease Prevention, so that is where TRSP is located, and that is kind of central to NIH. It's in the Office of the NIH Director. And as such, we serve as the primary liaison with the Center for Tobacco Products but also work across the NIH with all the participating Institutes and Centers to coordinate the FOAs and grantee meetings and other activities. So, I also always like to mention that TRSP represents an addition to the NIH Tobacco Research Program. I'm sure that many of you are familiar with the decades of research that NIH Institutes and Centers have supported over the years in tobacco control. And TRSP does not replace or diminish any existing research activities. Here is our web page, prevention.nih.gov/tobacco. And I recommend that you check this website from time to time. We do announce all funding opportunities here. We also have the entire CTP portfolio that is supported through the NIH, all the grantees you will find on the research portfolio section of the website, so that gives you an indication of the types of projects that are being funded. And so for today's agenda, we will first be hearing from Dr. Cathy Backinger, background on the FDA and Tobacco Control Act, and that be followed by Kay Wanke for discussing the components of the application, and then we'll be hearing from our science review officer Dr. Boris Sokolov, and then the grants management team at NCI, Carol Perry and Tawana McKeither will be talking about some fiscal issues to keep in mind. And then we will, after the presentations, open it up for questions and answers.
We have some questions that have come in already, but please feel free to add questions. So without further ado, Cathy, we turn it over to you.

Cathy Backinger: Thank you. Let me get my slides up. Thank you. Good afternoon, everybody. I'm going briefly kind of talk through a little bit about how we use our research at FDA to inform our regulatory actions. And as Helen said, many of you have heard this already so I'll be brief, but I think most people know that we have had authority to regulate tobacco products since 2009 and at that time, that included cigarette, cigarette tobacco, roll your own, and smokeless. And then just recently, a few months ago, August 8 to be exact, the deeming rule went into effect where basically we were able to assert our jurisdiction over all the other tobacco products that meet the statutory definition of tobacco. And I won't read all these but I think everyone, now we can look at the whole breath of all the tobacco products out there, either now or in the future, that would then fall within our jurisdiction.

So, what does tobacco regulatory science actually mean? I think for many of you on the phone, and I don't know who all is on the phone, you're used to applying to NIH for grants. And the NIH’s mission is a little bit different than FDA’s because it's more of a subset of tobacco research. But we need to understand science that will be able to inform specific regulatory questions. And what that means is rather than generating general scientific knowledge, we want to take the knowledge to have and translate it into specific scientific findings that can inform our decisions and actions. And so, it's a little distinct because we need to look at what can we do as an agency that would improve the public health and FDA's mission or CTP's mission, excuse me, is to decrease the morbidity and mortality caused by tobacco use. So, what I want to do probably for the bulk of my presentation today, is just kind of talk through, and hopefully this will help you think about how tobacco regulatory science is different than perhaps some of the science that you're used to doing.

So in general, we do four things at CTP. We do product standards, we do product review, we do compliance, and public education. So, I'm going to walk through each four of these to talk about the science that can be generated that can inform each of these specific areas. So, first I'm going to start with product standards. So I think everybody who has, and I'm sure you all read the act back-to-back, hundreds of pages. But section 907 gives us the authority to adopt product standards that is appropriate for the protection of public health. And in the interest of time, I'm not going to read these but you can see that we have wide authority to set a product standard whether it is for a component or constituent within a tobacco product, how we measure and test those, restricting on sales and distribution, and changing the form and content of labeling, just as an example. So, when we think about product standards, we think about, okay, so what do we have to understand? What are the questions? So, in thinking about protection of the public health, we have to understand the risks and benefits to the population as a whole. And as I go through these again, these are for you to think about what questions or research projects that you may think about proposing as part of your TCORS projects. We also have to think about the increased and decreased likelihood that existing users of tobacco products will stop using products, and then what is the increased or decreased likelihood that those that don't use tobacco products will start using them. So to think about decision points and raise questions that could inform a product standard, and I should back up just to say that we can't discuss publicly the product standards that we as an agency are thinking about or that we are working on or considering, because that could change the financial markets and that is a prohibited act. And I don't want to lose my job. And I don't think anybody else does either. So we can't talk about it. So some of this is kind of guessing. What is going to be most appropriate for the public health? But when you think about a research question, what
standard or what product standard could you possibly come up with that you could justify in relation to public health? What is appropriate? It has to be unambiguous and specific and measurable. We can't just say, let's just lower X constituent of tobacco products. The question is, why that constituent? Why that level? What happens if it is at different levels? So, to answer that, it has to be relevant to the situation and we have to understand if there is going to be a specific level. Again just using constituents as an example, not to read anything into that but just as an example, why that level and what would happen if it were above that level or below that level? So we need the standards to surround all that that would be most informative.

So, moving on to product review. I think most people who have been around FDA and CTP and TRSP now understand that all tobacco products have to have a marketing authorization from FDA in order to be on the market and there is different pathways. Again in the interest of time, I won't get into all the pathways, but each tobacco company that wants to have their product on the market has to submit an application to us and then we use the scientific evidence and the research that is both provided by the applicant and other research and science that is out there, to inform our review of that application and then help us determine whether that it will receive a marketing order. So, for a pre-market tobacco application, the question—and this is outlined in the Tobacco Control Act but I think I'm going to read each one of these because I think there is a difference and I just want people to understand. For pre-market tobacco application, the question we have to answer is, whether marketing that new product is appropriate for the protection of public health. And SE, which is substantial equivalence, which means that a company may have a new product and they are comparing it to a grandfathered or predicate product that has already been on the market since March of 2000... I'm going to get the date wrong off the top of my head. I think it's 2009. No, it couldn't be 2009. Never mind, I can't remember off the top of my head. But the differences between a new product and the predicate product raise a different question of public health. So it's a little different from PMTA. And then for modified risk tobacco products, the question we have to answer is, will the product, as it is actually used by consumers significantly reduce the harm and risk of tobacco-related disease to individual tobacco users and benefit the health of the population as a whole? Those questions are outlined in the Act, and those are the questions we have to answer when we are reviewing a tobacco product application using one of those pathways. And I'll come up with the date of the predicate if I can get my allergy-fogged brain back into gear. I'll get to that in a minute.

Okay, when we look at a product, what are the things we have to consider? So, the applicant submits all kinds of information such as materials, ingredients, and again I won't read all of these. But basically everything that makes up that product as well as marketing. And then we also have to look at the impact that product has on appeal, for example, addictiveness, exposure, toxicity, initiation, and cessation, and then we have to take all of that as an agency and translate that into understanding what the impact would be on morbidity and mortality. So you can see that it can be quite complex when we have to combine all of the different information from the different scientific disciplines.

So moving on to compliance and enforcement. So, one thing this we have also authority in the Act is that we are responsible for implementing and enforcing the provisions in the Act. And what that means is that we go out and monitor the industry for compliance. So we can go into manufacturing facilities and do inspections. We can go into retailers, so local convenience stores to make sure that they are following no sales to minors. We can inspect and do surveillance on importers. So, we can do that
because we have—we are tasked with enforcing the actions. And then we can have due violations if we find issues.

Did that move forward? Sorry. So just—a lot of this isn't necessarily germane to I guess research, but I just wanted to make sure that people know that also part of our compliance is looking at adulterated products. And you'll see the very last one is that we can go into—a product is considered adult rated if it's in violation of modified risk claim restrictions. So, companies can't make a claim that their product is modified risk without first getting a marketing order from us, an authorization. So, research could be informative around if there are products making modified risk claims. And then we also have authority under misbranded products. And just looking at the top bullet as an example, we can do a violation if a product has false or misleading labeling and advertising. And I think one perhaps recent example is with Natural Spirit where we sent letters to them because they were using the terms, “100% additive-free” and “100% natural” and found that they were in violation of the act. So as far as research, having data that would support compliant actions are strongest if they're specific to a specific case or product. But also generalized research can be informative that can supplement the existing evidence from our—I just got confused because someone handed me the note. The date of the predicate is February 15, 2007. I was on the right track and then I stopped myself. [ Laughs ] I don't know why I did that. February 15, 2007. So this is great if anybody listens to this after the fact when I messed up. I blame it on my allergies.

So research can inform and supplement evidence that we could use when we are looking at compliance and enforcement.

And then the last section is around public education. I think many people are familiar with FDA's public education campaigns. It is in the Act that we can and should educate the public on the health effects of tobacco products, and we have got a number of campaigns that are out there both media campaigns, campaigns on the web looking at-risk youth, looking at multicultural youth, and looking at rural youth who would use smokeless tobacco, and then the LGBT young adult community. So thinking about how science and research can inform public education, it's helpful for us to understand to help identify misperceptions around among users and non-users. What are the appropriate and the best approaches of communication to reach certain segments of the population? What are the messages? What are the right way to frame messages to reach vulnerable populations? What are the right testing around promoting behavior change and then making sure that it is in a format the public can understand?

So, let me now move on to what is in the RFA and just talk about the domain. So I just went over the four areas that FDA or CTP could use science to inform our regulatory actions. So in the RFA, I think if everyone's read that, we have seven scientific domains. And I'm not going to read each one of these but I want people to understand that this TCORS pretty much runs the breath and gamut of the scientific areas that could inform tobacco product regulatory activities. So, toxicity, specifically looking at novel alternative toxicological approaches. Looking at addiction. What are the characteristics of different tobacco products and effects on addiction and abuse liability? Health effects. Understanding short- and long-term health effects, particularly cardiovascular and respiratory health effects including inflammation. Other areas include... behaviors. So understanding knowledge, attitudes, and behaviors related to the different tobacco products and how now with attitudes of behavior changes with different changes in tobacco products. And we just talked about this in public education, but how can we effectively communicate to the public and vulnerable populations regarding nicotine and the health effects of tobacco products? It's not just media campaigns; it's all different ways to educate the public. Marketing, understanding how people or why people become susceptible to using tobacco products. It's
within a class of tobacco products like for example, smokeless as a class, or e-cigs as a class, and also products within classes and then also the different transitions. Then research to help understand what is the impact of potential regulatory actions. One example in this area is modeling to understand if we were to take an action in an area, what could reasonably be assumed as the impact on the population? Now I wanted to also just in my last couple of minutes, talk about what do we mean by a characteristic? We outlined this in the RFA too. So a characteristic pretty much encompasses everything that is in a tobacco product. That’s the materials, that’s the ingredients, includes if there is additives, flavors, design of the product, composition, heating source, other features that could include harmful and potentially harmful characteristics. All of these can be embedded or incorporated into those seven previous domains I just mentioned.

And then, also wanted to mention, this is also outlined in the RFA, some of the areas that we are deeming non-responsive. I should point out it doesn’t mean that they are not relevant or appropriate to our regulatory authorities. It just for this RFA, we wanted to have a little bit more of a narrow focus than we had with the original RFA that we released five years ago because we have learned a lot in the last five years so we wanted to kind of narrow the focus. So again it’s not to say that these—and I’m not going to read each one of them, you may have questions about it—but just to say it’s not that they are not relevant or appropriate but for this RFA, we wanted to limit some of the research ideas that were coming in from your applications. So, just to end now. I think Dana actually showed this or something like this, in the castle presentation earlier today. But we have a lot of different scientists that we need to bring to bear to all aspects of our tobacco regulatory science portfolio and how that science then builds the evidence base and helps to inform our regulatory action all the way from the product and all those parts. The user and then the population as a whole.

So, lastly, just in summary, when you’re thinking about projects that you may consider as part of your TCORS application, please be specific. Think about what are the characteristics of the product? What is the population you’re studying, and what are the impacts that you’re researching on the population health? And make sure that it’s measurable and that you’re also considering evaluating other potential variables within that research question. And with that, I’ll end. Thank you. And that is my newest grandchild but it's not, because now we have four. That's the third. I know, right? [Laughs] Thank you.

**Meissner:** Thank you, Cathy. So now I’m going to turn it over to Dr. Kaye, who will be talking to you about the components of the RFA and what is required.

**Kay Wanke:** Thanks Cathy. You did a good job of setting the stage for the research. So I’m going to be talking about the elements or components of the application itself. So keep in mind that what I’m going to cover is not comprehensive, so please read the RFA. I’m just going to be covering the highlights here. Note that the mechanism is a U54 so this is one of the ways that the current TCORS is different from our previous rounds. So now we’ll have cooperative agreements, as opposed to the P50s. And broadly, the purpose of the Tobacco Centers of Regulatory Science are to establish the scientific Foundation for Regulatory and Policy Issues, as Cathy said, so it will inform the work of the FDA Center for Tobacco Products. We are seeking to build the research capacity and scientific expertise in order to inform these areas, and we are looking to ensure both a stable ongoing research enterprise and a flexible, responsive, and collaborative resource. So, again, that helps to explain the cooperative agreement mechanism, and it will make the next components we discuss more illuminated. So I’m going to describe the TCORS components.
Another way that this round is different and we have electronic application. So for those who might have submitted an application in the first round, we had paper applications. These components correspond to the electronic pieces of our modules, you might say, of the application. There is an overall component, and that will include the description of the integrative theme, a minimum of three research projects, an administrative core that will have the rapid response component, and a career enhancement core. All those are required components. There is also the potential to add optional core if they are justified and appropriate for your application.

So I'm going to describe each component briefly and touch on the highlights. The first is the overall component. And in that component, you'll be describing, in addition to the overall goals of the center, describing each of the pieces of your projects and your different cores. You'll also be describing your integrative theme. So this is important. The expectation that we have is that the whole of your center is greater than the sum of the parts, and we would like you to characterize it by describing an integrative theme that characterizes your center. This could be a unifying goal, it could be a targeted area of research, or it could be your expertise, your specialization. What you would bring to bear on that building research capacity and scientific expertise goal that we have. So again you have a little bit of leeway in deciding what your integrative theme is, the way you will put forward your center and describe it. It could be broad; it could be focused. It could be organized around a variety different topics. You could pick one. Examples could be a research need or gap that you're looking to fulfill with your research. It could be a specific population that your center is focusing on. It could be the products or constituents you're taking a deeper dive into examining or it could be a scientific domain. And again, these are the scientific domains are what Cathy described in her presentation. Again, I'm not going to restate those scientific domains here but they include toxicity, addiction, health effects, behavior and communications and marketing, influence and impact analysis. Be sure to read the RFA. The scientific domains have additional scientific priorities that are listed as examples. Again, these scientific domains, the requirement is that your application must address no less than two of those seven domains across all three research projects. Now any single project could address one scientific domain, but collectively the application must address two or more and we'd like to you make those explicit in your application. So, keep in mind that even though there are seven listed, addressing many scientific domains or all scientific domains is not advantageous. We are really hoping that you have a focused center. And again, make explicit what you're going to be addressing both within each research project and in that overall component, describing collectively which domains your center will be addressing.

So each research project will have a separate component within the application. Again those are the components is what is described in part 2, section 4 of the application. It's required have you three or more multidisciplinary research projects within your application. We are looking for a fully developed R01-level projects. So again these are R01 comparable projects. Each project and each specific aim within the projects must fall within the regulatory authority of the FDA and CTP. I say that here to encourage you all to keep in mind that not only must your application address those seven scientific domains, two or more or each research project addressing one or more; each specific aim should be addressing something that falls within FDA’s regulatory authority. Many of you are very familiar with that what means. For those that aren’t familiar with what that means, that requirement for remaining within the regulatory authority, please speak with a program official—one of the scientific research contacts on the RFA. Your application could be deemed non-responsive if you fall outside of FDA’s
The next component is the administrative core. Another required component, and the objectives are to monitor and facilitate the center objectives, provide oversight and quality control, and promote a atmosphere of collaboration, and again, we require that there is a budget set aside for rapid response projects. And to talk a little bit more about that, beginning in year two, and all the way through to year 5, we ask the application set aside 200,000 dollars in direct costs per year in order to be able to respond to time-sensitive research topics. So these will be annual activities. The topics will be identified by the FDA, NIH, and the TCORS Steering Committee. That said, don’t—given those topics will be identified each year, please don't propose your research projects in the application. Because you won't know until year two what those first set of time-sensitive research topics are going to be. You're welcome to describe a process for soliciting the projects, assessing them, and prioritizing them within your center, or addressing the capacity that you have to respond to a broad set of scientific topics, or expertise that you have that might be brought to bear on time sensitive research projects. But, again, don't propose your specific rapid-response projects in the application.

Our next component is the career enhancement core. Another of our required components. And the objectives are to enhance the development of tobacco regulatory science research expertise of different—of investigators at different stages of their career. This could span from students, whether it is pre-doctoral, post-doctoral, new and early stage investigators. It could be more established investigators who are new to tobacco regulatory science. And the goal really is to enhance that research expertise. Within the career enhancement core is the inclusion of any career enhancement pilot project plans. Again these might be seed money to help establish research projects for the individuals who will be—whose careers might be enhanced. I'm going to take a moment to explain that this is one of the ways that the language is different from the previous TCORS program. If you'll recall we have a training component. That is one of the things that changed is that the NIH, given the way that the NIH tracks their training programs, they now use the word, “training program,” as well as “education program,” to define a very specific type of program. So that term, “training program” and “education program,” are really reserved for different grant mechanisms. So, what was in the previous TCORS and now what is in or being solicited in this application, does not rise to the level of what the NIH now calls a training program, and that's why we call it a career enhancement course. So be sure to look at the requirements in this RFA for this component and to make sure that what you're proposing really is consistent with the goals that we have for this component. If you have any other questions, feel free to reach out and talk with us about that.

So, the expected features of the TCORS. We really are looking for centers that are open to collaboration, both within a single TCORS, across the research projects, and across the different centers. Including the career enhancement activities. We would like to identify common measures and protocols where they are feasible, and we would like the centers to be open to addressing these ongoing scientific issues and time-sensitive research projects of the FDA Center for Tobacco Products. What is critical to keep in mind is that there are many pieces of your application that will determine whether or not it’s responsive. Applications that are not responsive will not be reviewed. So it’s very important that you ensure that you not only include all the required pieces, but you don't go beyond them. For example, what I was talking about, ensuring that your specific aims fall within FDA's regulatory authority. So here are some of those aspects of the application that contribute to a determination of responsiveness. Again,
identification of overall integrative theme, a program of research that addresses no less than two of the seven scientific domains that are listed in the RFA. All specific aims across all research projects must fall within scope of the regulatory authority of the FDA CTP. And no aim may address the non-responsive research topics that are outlined in the RFA and that Cathy outlined in her presentation. So, as such, strongly recommended and I can't say this enough, please discuss your research and your specific aims with the scientific and research contact from the Institute relevant to your research. Again, it is really important to have those conversations early. Don't wait until near the time of submission. We also ask that you make explicit the integrative theme and the scientific domains both within your letter of intent and within your application to ensure we can give you feedback in the letter of intent. And within your application, again to, make sure that we can determine its responsiveness. We encourage you to submit a letter of intent early to allow time for feedback. If not, please contact us early.

More information is available on our FAQ document. Please see our frequently asked questions. It's already up on the website, and we will continue to update it as new questions are asked. So be sure to check back regularly. And again, the letter of intent is not required but we strongly recommend it. There is the required information from the RFA, including the descriptive title, the names and institutions of key personnel. We also encourage you to include your specific aims, your integrative theme, and your scientific domains so we can give you any feedback if we think you might be going off course. Please again, give us a call. Feel free to contact more than one person on this list, but always start with the person whose research, the Institute matches the content of your research. They can give you the most targeted feedback. We are all happy to talk with you.

Meissner: Thank you, thank you, Kay. I see we are getting a lot of questions already coming in, but I'm going to hold them until we are finished with all the presentations. So now I'm going to turn it over to Dr. Boris Sokolov, who is the scientific review officer for the FOA.

Boris Sokolov: Good afternoon and I like to touch on a few issues which are important to keep in mind when you prepare and submit the application and may be significant on the results of the reviewer. The first applications are due on July 19, 2017, and scientific merit review is January 2018 and Advisory Council review may be in May and some probably in June. Again, applications are due on July 19. Make sure that you make all effort to submit before July 19, because if, for example, we have continuous submission privileges, these privileges do not apply for this RFA. So if you are eligible for continuous submission and you are able to submit normally, most of your R01s, any time you want to submit them, this doesn't apply for the current RFA. You are only eligible for two-week extension beyond the July 19 submission date. Two-week window of consideration for late submission might be applied in some other cases, such as death or severe illness or of the PI or recent study section service. However, even in these cases no advanced permission may be given for late applications. It will be decided at the time when they are submitted. [Inaudible] And if you show within two months of the application due date, two months before that or after that, you will be eligible for two-week submission. It's not guaranteed, but it never happened before the request would not be honored. And please keep in mind that it is best to submit applications not at the last day of the submission date but one or two days before, because problems such as problems with your computer system, the computer system in your institution, or system-to-system, or illness of the person supposed to submit the application will not be considered for late submission. And applications must be completed at the time of submission. No changes can be made after submission. No errors can be corrected, and we cannot accept post-submissions supplemental materials except for those that derive from unforeseen circumstances such as a death or
departure of investigator, and in that case, we may accept modified budget pages or sketches but no changes to the scientific content of application can be made, and no other kind of errors can be corrected. We can also accept notes of acceptance of—any allowable post-submission supplemental materials must be submitted not later than 30 days prior to the meeting, and they must be submitted or approved in writing by your grant signing official. Otherwise will you not be accepted. And also to keep in mind that reviewers, although we ask reviewers to read supplemental materials, the reviewers are not obligated to read them, and sometimes it is technically almost impossible.

We make all efforts to avoid any real or perceived conflicts, and you may be aware of some conflicts we cannot identify by ourselves. Those may be personal conflicts or long-standing scientific differences. And if you have any of those, we ask you to inform us at the time of submission in your cover letter. So when the application arise, you have a chance to take a look at your request and take appropriate actions if it's needed, and please do not wait until you see the roster because it may be way too late to make any reasonable actions.

We will exclude from the review process anyone who is involved in any of the applications and any significant role including consultants. We will exclude also people from the tobacco industry. And from the review of a specific application, not from entire review process, but from review of a specific application, we will exclude all collaborators and former collaborators within the last three years, all investigators who are involved in their particular application. We will also exclude all mentors and mentees in the 10 last years and sometimes forever, of anybody who is involved in your application, including consultants. And if you have collaborators and consultants from 10 different institutions, nobody from those 10 institutions will be allowed to review your application. So please make sure that when you include collaborators in your applications, they have very well justified role, and it would not create later problems with finding appropriate reviewers.

We have five score review criteria and they are the same as for all other, most other NIH applications: significance, investigator, innovation, approach and environment. But this may be confusing, and please read the RFA very carefully, because what is meant by significance and innovation in the RFA is slightly different from standard definition of significance and innovation. For example, significance, the reviewers of the questions, how will successful completion of the aims affect the concepts, methods and technologies related to the manufacture, distribution, and marketing of tobacco products? And when they read innovation, they will ask the question, does the application challenge and seek to shift current research in the field of tobacco science as it relates to the manufacture, distribution, and marketing of tobacco products? And whether it advances the knowledge base that informs the manufacture, distribution, and marketing of tobacco products in order to protect public health. So please keep that in mind and we will make significant efforts to train the reviewers and provide them with appropriate guidance and to make sure that they apply these criteria exactly as written in the RFA. So, if your application helps the reviewers to answer situations in RFA, it is very helpful for reviewer and at the end of the day to your outcome of your application.

We have some additional review criteria for this RFA. These review criteria will not be given individual scores, but they will be considered in the review, and they will influence the overall collaboration of the application and the overall impact score assigned to your application. And the reviewers will be asked to rate synergy and the research potential to inform regulatory decision-making and career enhancement plan. And besides this RFA-specific situations, the reviewers will raise standard aspects of all NIH
applications including protections of human subjects, vertebrate animals, biohazards, resource sharing plans, and authentication of key biological and/or chemical resources. And please do not estimate the significance of these criteria because, particularly protection for human subjects and vertebrate animals, may dramatically influence the overall impact of your application. And a disclosure, I touch on just a few issues and you may find the whole set of the policies which are applicable for this RFA or those policies and see all the aspects of those policies. I didn't have time to discuss them, all of them. So if you have any difficulties in interpretation of policies, please feel free to contact me anytime. My contact information is on the RFA. And it is better to start with e-mail so I will start there with what your question is, and then we will discuss over the phone. Thank you.

Meissner: Thank you Boris. And now we'll be hearing from Carol Perry and Tawana McKeither at the Office of Grants Management.

Carol Perry: Hello, everyone. We are down to the award information. Good stuff. So, with this particular RFA, we are going to fund up to 10 TCORS from CTP. It's going to total 40 million dollars from fiscal year 2018. The U54 center will not exceed 4 million dollars in total costs per year. That total cost per year. Applicants may request a project period up to five years. And this piece right here with the foreign institution gets a little tricky, but the non-domestic entities, non-U.S. or foreign institutions are not eligible to apply. Also, non-domestic components of U.S. organizations are not eligible to apply. But foreign components are eligible to apply. So, it's really nice, when you actually press on the link that is in this particular slide, you're able to go to where it breaks out foreign components, foreign organizations and foreign public entities and if gives you exactly what it is that I'm sure you're going to need to understand if you have this particular piece, if you have a foreign component piece.

As Dr. Wanke said, the letter of intent is due 60 days prior to the application due date, which is May 19th. Electronic application submissions are required. All submissions will be through NIH Assist, and no paper applications will be accepted. The earliest possible start date is July 2018, and awards will include a term and condition requiring a separate interim progress report every six months, and this is even during the no-cost extension period. If your application is approved.

I'm just going to continue with some things to remember and I do want to reiterate that please, please, please, read through the entire FOA or this RFA. Please read through it so you are mindful of the dates and all of the requirements that are included in the announcement. And just please be reminded that applications are due by July 19. However, early submission will begin on June 19th of this year. Again, the funding instrument that we are using is the U54 is a Cooperative Agreement so that involves a process that has programmatic involvement and you will not have automatic carryover authority. And it will not be a part of the snap population. Also, if your application is selected for funding, please submit that just-in-time information as early as possible. IRB, ISO approvals, these are types of things that will delay or hold up an award. And being that the we are looking to award these in July of 2018, that is in our fourth quarter, which is a critical time of the year for us in the Office of Grants Administration. We do 50% of our work during that time, and so it's critical that we get these documents in early or on time if your application is selected for funding, so that we can issue the awards as soon as possible. Also, if you have any questions, you have our contact information. You may feel free to contact me or Tawana, and I think the next slide shows our e-mail and our phone numbers. And that is all we have.

Meissner: Great. Thank you very much. Okay, so now we will go into our question-and-answer period. We have already received a lot of questions, and if you keep them coming hopefully we'll have enough
time to answer all of them. So the first question is, the RFA requires plans for career enhancement pilot projects for trainees. So the question is, do we need separate screening evaluation mechanism for these training pilots and career enhancement cores, or can this be a separate component alongside the rapid response projects and the administrative core? We anticipate similar screening mechanisms for the rapid response projects and the training pilots and feel that it will fit better into the administrative core. Additionally due to budgets do these training pilots need to go into the career enhancement core or can they be a part of the administrative core? So that's a long question about basically trying to distinguish between what we are talking about, which is new in this RFA, about rapid response projects versus pilot projects that are in the career enhancement core. So rapid response projects are new and they will be from year 2 to year 5 and require set aside. However, the topics and how those pilot projects or rapid response projects evolve really is going to be involving input from FDA and NIH, whereas before the pilot project that the TCORS were conducting were pretty much the ideas were generated from the TCORS. This allows a mechanism where FDA, in fact, can get a quicker response for some time-sensitive projects. That's what the rapid response projects are intended for. As said in the RFA, those need to be budgeted in the administrative core. The pilot projects—and there is more leeway for this because each center may develop their career enhancement activities differently, but this still allows for some center-generated types of pilots connected with career enhancement activity. So, I would recommend even though it doesn't say in the RFA you have to budget those within the career enhancement core, I would guess that reviewers when they are looking at—because you're going to be describing that pilot project program in that core according to the RFA, I would expect that the budget—it would make sense for the budget to be there. Hopefully that answers that question. Next question.

**Wanke:** I'm going to jump in and just clarify that. The review process will be different. I think that was an element of that question. So the review process for proposed rapid response projects and pilot projects will be different. So I would not recommend you describe them together in the application.

**Meissner:** That's a good point, Kay. The rapid response projects are going to be reviewed in conjunction with the FDA, NIH, and the Steering Committee. However, the pilot projects for career enhancement activities each center again, will have its own way of deciding on which projects they want to put forward, but, as stated in the RFA, those projects will still need to be vetted by NIH and CTP to make sure that they are still responsive to FDA regulatory authorities. So just in case you did not get to this information, please clarify limits for sections—is it 12 plus 1 for projects and 6 plus 1 for cores, where the plus 1 is a specific aims page or is there no plus 1 for specific aim? No, it's 12 total. It's 12 total. And I think there was another question related to the page limit, apparently there is an error in the FAQ. Please follow the page limits that are outlined in the RFA, so the projects overall is 12 pages. The projects. So each research project gets 12, but the cores get 6. That's total, not plus one. Next question. Do the rulings that relate to the type of products submitted for authorization affect the research question FDA wishes to explore? I'm going to turn that over to FDA to answer.

**Backinger:** Okay. I don't know how to answer that question, honestly, without more information, because to be honest, I'm not sure what the question is trying to ask. I mean, obviously, there is a lot of litigation that goes on around tobacco products, and so I'm speaking generally. And, you know, I would just say, if it's a product that would meet our definition of a tobacco product and would therefore fall within our jurisdiction regardless of where things are at a court proceeding, until there is an actual court ruling, I would say it would fall within a product that we would be interested in studying. That would be relevant and appropriate for the RFA. And without any more information, they think is all I can say.
**Meissner:** Okay. Next question. How does FDA balance questions of toxicity versus population effects that may relate to abuse liability?

**Backinger:** I think, well, partly depends on the pathway the product would come in, and I did go through that quickly meaning substantial equivalents, which asks a different question. Does it raise a different question or a new question of public health versus premarket tobacco product application, which asks, is it appropriate for the protection of public health? So I think the answer is, it depends. I mean, we look at all of those aspects in total when we review a product application. And again, without more specificity in the question, I think that is all I can say other than it depends on which mechanism or which pathway, and then it depends on the weight of the evidence in that product application when we are reviewing it.

**Meissner:** Characteristics for substantial equivalence and prepackaging.

**Backinger:** Yes. So that is the short answer. Obviously, packaging of a tobacco product would be considered a component and a characteristic. So, for example, what material is in the packaging could leach into the actual tobacco product that is used. So, packaging is considered part of the tobacco product and we reviewed that. I'm not sure exactly where the question is—what angle the question is coming from, but when you look at marketing and labeling, as I mentioned in my talk, that's also something that we look at and that could be on the packaging. I would just point whomever asked the question we did put out a guidance around FAQs around SE and that was the latest edition which we've updated it a couple of times. I want to say that's addition number 3 that was just put out in December 2016. So you can look on our website for that and it talks about what changes constitute a new tobacco product that would require SE to come in. So for example, if you change the quantity, if you change from 20 cigarettes to a pack, to like 6 cigarettes, I'm just making that up, that would be considered a new tobacco product. So obviously that is a packaging question as well. So I would point to you that SE guidance on our website. Just Google probably FDA CTP SE guidance and find that.

[UNKNOWN SPEAKER] Google can find anything. Just saying. [Laughs]

**Meissner:** [Low audio] Does the President's budget raise issues of funding for this RFA or for this time period? Not that we're aware of.

[UNKNOWN SPEAKER] Good answer, Helen.

**Meissner:** So, for PIs for the overall TCORS and also for each individual study, do all need to have current R01s?

**Sokolov:** Is this not a question?

**Meissner:** I don't think it's required. Question, can everyone mute their mic. I'm hearing a lot of background, papers moving around.

[UNKNOWN SPEAKER] Is that us?

[UNKNOWN SPEAKER] I guess. Is it us?

**Meissner:** We just turned the air-conditioner back on because it was stifling hot in here but I guess text us if it is interfering with your ability to hear the answers to these questions.
With the new administration's priorities on cutting federal research and being anti-regulation, is the funding for this U54 at risk and the CTP at risk? Again, same answer. Not to our knowledge. This FOA cleared the department, and as far as we are concerned it is moving forward. Given that, we must set aside $200K for rapid response projects, does that mean each center will be assigned rapid response projects each year? If not, is the $200K then freed up for other center research? We are hoping that all of the centers will be able to use that money, but I would say that in cases that it doesn't happen, that there would be consideration for other ways to expend funds. Is that correct?

[UNKNOWN SPEAKER] I mean --

Meissner: Or is it earmarked? Does it have to go through the specific rules?

[UNKNOWN SPEAKER] Usually what is in the RFA, that's what we try and keep the money to. We don't want to have everyone—“I have 200,000 extra dollars, let me just now figure out a piece of equipment or something to buy with it.” So, no, we want them to try and keep to what the RFA -- the purpose of the RFA.

Meissner: And every effort will be made to have that happen. There is a very big overlap between toxicity and health effects. Most people who are addressing one are automatically addressing the other. Is it a concern given that addressing too many priorities is considered non-advantage us and maybe confined?

Backinger: I would say that this isn't something for you to consider as you're framing your application. I wouldn't say to shy away from having both be included and making explicit that your research can include both. You're going to be the one framing your application to show that it is tightly focused and that you are proposing a program of research that is really going to be addressing the priorities that are set forth in the RFA. So, we are not going to be counting it like a bean counter in essence. We are really going to be looking at the unitary proposal that you put forth. So I wouldn't worry too much about can we combine it and call it one. I don't think that would be advantageous. You can emphasize that you are looking primarily, say, at toxicology versus health effects. And really call that your focus. Again, this will be something to discuss with the scientific and research context. I think that that is really a good place to start.

[Not sure who is speaking] I think it's a matter of framing and integrated center with the logical focus. I mean, these categories are kind of arbitrary in a sense that there is a lot of overlap between what you can call one category versus the other. That's not the point. I think the point that Kay tried to make earlier about it not being advantageous to address all or too many is just that you don't want to have sort of a kitchen sink approach to your center. So that is really what that is intended to impress on that.

Meissner: So on all other NIH proposals, the page limitations apply to the research strategy component and does not approve a one-page specific aims document. Please confirm that the 6-page limits only applies to the research strategy. Boris?

Sokolov: So I cannot answer because... it says nothing else. At best I could double check... [Inaudible]

Backinger: We'll have to look into that. For now, I would say count on following the RFA, and if we find out any information to the contrary, we will—I think if we find out anything to the contrary regarding
that, we'll put a notice in the guide so that all of the investigators will be able to see if they are given an additional page beyond what is listed in the RFA.

**Meissner:** Can a single scientist serve as an investigator more than one U54 application? I don't see why not. I mean there is nothing, no requirement that says they can't. As long as it's not castle and –

[UNKNOWN SPEAKER] Right.

[UNKNOWN SPEAKER] We will note in both the castle and TCORS the key personnel of the castle cannot be the same investigators who are on TCORS. I mean, the idea here is that there is a level of objectivity and distance between coordinating center and the TCORS. So that is stipulated in the RFA, however, if you're talking about someone who wants to be on a U54 for one university and another, I don't think there is any restriction on that.

[UNKNOWN SPEAKER] I just want them to be mindful of the effort because when we are starting to look at these particular grants and see where they are starting to spread themselves thin, that is where we start to get concerned. So I just want everyone to be mindful of the effort they are carrying on these large awards. Because they need to really be engaged.

**Meissner:** Right. Thank you. Is a subcontract or collaboration with a foreign entity to study a new tobacco expected to be reviewed by FDA in test marketing in their country eligible for funding set or collaborator? I think there is some words missing from this question. So is a subcontractor or collaboration with a foreign entity to study a new tobacco product expected to be reviewed by FDA in a test market... [Reading ]

**Backinger:** I think the question is actually may be asking two things, and I think the first part is probably the most relevant. I think you just basically are asking, can you or can someone have a subcontract way foreign entity to do research in the TCORS, and I would say the answer is yes. And then the second part, I think, is that you're asking, does the product matter? And I would just say again, if the product is one that meets our definition, then the answer would be yes because, regardless of whether it would come to market in the U.S. or not, but I think the question is assuming that it is, then we need to understand, that is why part of the RFA or the RFA is eligible to foreign entities because we know that there is research in other countries that would be informative for us in the U.S. So, I think its answer is yes, and I'm not sure what the second question was but if it's a product that meets our regulatory authority, then I would say, yes.

[UNKNOWN SPEAKER] Did you want to say something?

**Tawana McKeither:** Just really quick. Just for foreign institutions by themselves, are not eligible for this. But, the foreign component, yes.

**Backinger:** I think that's what they were asking.

**McKeither:** Oh, my gosh, yes. So if they could just read the RFA there it tells you and it breaks it out for you exactly what the foreign component is and what we will accept.

**Meissner:** For existing TCORS, how should progress be recorded? How will it be used in the review process? Do you want me to answer?
**Sokolov**: So we tried to discuss that question. So as long as you are [inaudible] 12 pages for project and 6 pages for cores, you can describe your progress within those limits and if you collaborate appropriately as needed by the review.

[UNKNOWN SPEAKER] Especially if you’re basing your next project on results that you got from the current TCORS, I mean you could structure it like a preliminary study or preliminary results. But it still does need to stay within the page limits.

**Meissner**: Do all current TCORS have to go in as renewal? If the TCORS is submitted as renewal do the title and aims have to be the same of the original submission? So, the answer to that is, no. They do not. It is up to the investigators, and you might want to talk to your program official about what you think would be more advantageous, whether you want it to be the renewal or whether you want it to be a new application. You can do either. And my guess is a lot depends on the productivity that you could demonstrate from your current TCORS and the directions that you think the research should be taking.

The previously funded TCORS, is it expected to have section on progress, accomplishments made during the funding cycle of the research plan? Again, I think this is kind of left to your discretion in terms of how strong a case you can build. And yes, if you have progress and a lot of productivity, I would want regulators to know that. So, you know, I don't think there is a set standard here. It's more of the type of case that you can make. I want to switch to the questions here. Hopefully we'll get to all of these. More questions, by the way, that we don't address today during the webinar... [Inaudible]

[UNKNOWN SPEAKER] We are also talking about the title.

[UNKNOWN SPEAKER] The question was, can they change the name?

**Meissner**: Yes.

[UNKNOWN SPEAKER] Yes. They are welcome to. And actually we would encourage you to change the title of your TCORS to something that is more descriptive or aligned with your integrative theme. I think that would be useful rather than calling it the X University TCORS. I would recommend that. But again it will be up to you.

**Meissner**: Okay, so, here is another question. Will NIDA research cigarettes, e.g. spectrum, be available for TCORS to research on similar basis as it is currently? Do you want to answer that?

**Felicia Porter**: Yes, nicotine research cigarettes will be available for TCORS 2.0. However, I should caution you that a new letter of authorization will be needed for your project. It is grant-specific and also institution-specific. With the newly formed letter of authorization, project duration and quantity requested will be explicitly stated in the letter of authorization. And also just checking with the drug supply program for inventory, making sure we have enough inventory for your request. And checking with myself or the FDA for new investigational tobacco product applications because they are grant-specific and institution-specific. They may need to be updated as well. I'm Felicia Porter, and on the website. So just Google NIDA drug supply program, I'm the first point of contact, and if you have any questions, feel free to give me a call or e-mail me.

**Meissner**: Might it be possible to obtain other research tobacco products, for example, cigars, roll your own tobacco, or e-cigarettes with no nicotine concentrations for use in TCORS 2.0 research projects? I see shaking heads. The answer to that is no.
How about just research e-cigarettes?

**Backinger:** The only thing, this is Cathy, there aren't any other—I'm using air quotes. You can't see me, but research products other than the e-cigarettes that NIDA are working on. However, I should mention that we, FDA, have had a cooperative agreement to manufacture reference cigarettes so those are for testing not for human use. But those have the known constituents, HPTs, nicotine content, so those are available for testing, again not human use. And then also we are working on a reference product for smokeless tobacco. So again, a reference product for testing not for human use, per se, but I'm not aware of other research or reference products that are available beyond the ones we just mentioned.

**Meissner:** Might it be possible—I just read that one. Will applications that propose the study of products not yet available in the U.S. be considered responsive?

**Backinger:** I think I kind of sort of answered that previously, meaning that if it meets the definition of a tobacco product and would fall within our jurisdiction, then I think that it's relevant and could be included as a product to be studied. So yes, I think if that was, if that's what I understood the question to be.

**Kay Wanke:** Since Cathy is saying she thinks, this sudden one of the points where I would say I really strongly encourage you to contact a scientific contact from the RFA and have that discussion to make it explicit what you're thinking about. Because make sure that your application is responsive that it falls within the regulatory authority, and it is also important to note that it should also be a priority. And so when you're looking at products that aren't already marketed in the U.S. or if you're conducting research outside of the U.S. as well, you need to make sure your research is relevant to U.S. product standards or potentially U.S. actions, and so you're going to have to make that face your application. So I would say this is really worth talking with the scientific research contact.

**Backinger:** And I can understand why whoever is asking the question doesn't want to specify the product, so I think that is a really good point. You can get more specific with your program person and have a discussion about relevancy and priority.

**Meissner:** There is a second part of that question: in particular, would an application that proposed to study a burn product that is already included in an MRTP application be considered responsive?

**Backinger:** I would say, yes. Again, for the reasons we already talked about.

**Meissner:** The RFA states that short-term studies of the acute effects of reduced nicotine cigarettes are not required. What does the RFA consider short-term? Dana will you answer that.

**van Bemmel:** This is Dana van Bemmel with Center for Tobacco products. So, I think that the thinking around acute or short-term was really looking what is already in our current research portfolio and then the research program. So most of that funding if not all, I think, is through the Tobacco Regulatory Science Program, or TRSP, so I encourage you to go to their website and look what the we are already funding around the research cigarettes. Currently, the majority of those projects are looking at short-term. So 6–8 week research projects, in-lab studies looking at specific populations, looking at short-term or immediate biomarkers and changes in biomarkers within that short window of time. I think that we are interested. I don’t think—I know. I know that we are interested in looking beyond those studies, so...
that's why we highlight what we weren't interested in this RFA in the hopes folks could take it to the next step because we are interested in looking beyond that, is it 6 months or a year? I don't know if anyone knows exactly what that would be but we are interested in looking at behavior and use of those research cigarettes, those low nicotine research cigarettes beyond that short-term.

**Meissner:** Thank you. If an applicant sends an LOI early in May and obtains feedback that part of it is off target and non-responsive, can they resubmit or revise the LOI? The answer is, yes. But again, like Kay said, I encourage you sooner rather than later to talk to the appropriate scientific contact listed in the RFA to get feedback to see if you're on the right track. The RFA is out now so we can give you feedback and are happy to do that.

**Wanke:** And this is Kay and I'll add that even if you're LOI comes in on May 19, and you get feedback that it's not responsive, you aren't tied to what is in your LOI. You still can modify your proposal and aims based on feedback that you get. So that is not binding. The LOI is not binding.

**Meissner:** This is it a good question. We offer pilot money for our postdocs but also an RFA for others. It's been very productive to new ideas. Are we now restricted to only our postdocs and rapid response?

**Wanke:** Within the career enhancement core, the pilot projects aren't restricted to postdocs. Your career enhancement core, the activities within your career enhancement core are meant to enhance the tobacco regulatory science expertise of investigators across levels of expertise. It could be predocs, postdocs, early stage investigators, it could be more senior investigators who are retraining within tobacco regulatory science. So I would say it's not limited to a type of investigator.

**Tawana McKeither:** And in addition, tell me if I'm wrong on this, I apologize if I cause confusion, but I think the rapid response aren't necessarily tied just to TCORS either, right? So, the rapid response topics and how that information is coming to the individual centers is different, but how you choose to award and respond to those is up to you. So you could envision having someone not directly affiliated with the TCORS who might be part of that.

**Wanke:** Then it becomes a new collaborator.

**Backinger:** And I would say that with the current program, that these types of activities vary substantially from center to center in how they are solicited and how they are reviewed, how topics are chosen, and who the awardees are. And there is still that flexibility here. It's just that we are now also having more directed research through the rapid response projects. So hopefully that answers your question.

**Meissner:** In the career enhancement core, are the two plans listed in the RFA supervised research and career enhancement pilot projects separately evaluated? I'm not sure I understand.

**Backinger:** Read it again.

**Meissner:** In the career enhancement core, are the two plans listed in the RFA supervised research and career enhancement pilot project separated? I'm wondering if they are choosing supervised research with rapid response projects... Confusing...

**Wanke:** Or assuming that supervised research and pilot projects are two different things.
Backinger: Again, it's up to the center to propose a career enhancement for instruction as the centers sees fit.

Wanke: And I would add this, that any new program of research that isn't already a component of say one of your three or more primary research projects, or the rapid response program, any time you're proposing something new, it has to be approved by the NIH and the FDA Center for Tobacco Products to ensure it's responsive, and by default that would be called a pilot project. So you can think of it that way. Anything that you're going to be proposing new would go through that pilot project approval process.

Meissner: Okay. Next question. What view would FDA and NIH take of an application in which study products, for example, were provided directly by private tobacco company? For example, would that be perceived as creating a conflict of interest?

Backinger: So, this is Cathy. And I can't speak for NIH but I guess I'm going to pretend that I am—kidding. And maybe you want to jump in. But my understanding of the COI policy at NIH is that is a question for NIH and as anyone that gets a grant or a funded award from NIH, there is a conflict of interest process and so that would be dealt with at the time of award. I understand it's around, I believe there is a dollar limit and it's $5,000. And it's around research objectivity. But that would be an assessment that NIH would have to make at the time. So I think that is all I know that I can say. I don't know if Carol or Tawana you had anything to add to that.

McKeither: When you said—what was the dollar limit?

Backinger: $5,000, I thought. Maybe—that's what I recall reading. I have read the NIH COI policy.

McKeither: I'm not as familiar.

Perry: But the point is that if there is any potential conflict of interest, the investigator, it is incumbent on the investigator and the institution to report that to the NIH and to detail plans for mitigating the conflict of interest. So, that is pretty much without having specifics, that's pretty much all we can tell you. That is the NIH policy.

Backinger: And it is around having the person or the institution that gets the award, it's around research objectivity. So that is what the assessment is about.

Perry: I would say that also, the reviewers see them and they will want to see studies and objective maps. So, there is a perception here and it's kind of incumbent on you to clarify that.

Meissner: Are studies of the acute topography effects of second generation nonresponsive, i.e., first generation studies, nonresponsive?

Backinger: I would say, yes. This is Cathy again. I think the reason that we had what we weren't interested in as far as first generation products is that one, there has been quite a bit of research done on those products and two, I think based on surveys and other research we seen people kind of move away from those products, and so having research more on the products that people are actually using, much of the population and again, that was part of my presentation, my point, that it's one thing to say you're studying e-cigarettes but useful to understand exactly what kinds of e-cigarettes and what kinds of populations because, again, having specificity is most informative to FDA. But the short answer is, yes.
Having studies of topography on generations of e-cigarettes beyond first generation would be responsive.

**Meissner:** I think this may be one of the last questions. We are supposed to end at 4:30 I believe. So if an additional statistic report is included in the proposal, are the additional cores evaluated separately as a whole?

**Sokolov:** Separately and then -- [Inaudible]

**Meissner:** So, yes, they will be evaluated separately and incorporated into the overall evaluation. I think that’s all we have time for. I know there were other questions. We will get the answers to those and post them on the FAQ website. And again, if you don’t feel your questions have been answered here today, please, and even if you do, we still encourage to you contact us or the scientific contacts in the FOA to get answers. So thank you very much for your participation.

[UNKNOWN SPEAKER] Thank you.

[UNKNOWN SPEAKER] Thank you, everyone.