ATS/CDC/IDSA Clinical Practice Guidelines:
Treatment of Drug Susceptible Tuberculosis

Welcome, everyone, to the 2016 ATS/CDC/IDSA Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis webinar.

I'm Kelly Musoke, the Director of Education at the Curry International TB Center. We have over 900 participants that registered for today's webinar from across the United States, and we know that many of you are viewing in groups. This webinar is jointly sponsored by the Southeastern National Tuberculosis Center, the Curry International TB Center at UCSF, the Rutgers Global Tuberculosis Institute, the Heartland National Tuberculosis Center, and the Mayo Clinic Center for Tuberculosis.

We always like to ensure that everyone knows while all the RTMCC trainings and clinical consultation are divided by region, the products and the national webinars are available to a larger U.S. live audience. Since this training has many new participants listening in today, I'd like to highlight that each of the five RTMCC's provides free clinical and programmatic consultation to US-based clinicians; and the responses are generally provided within one to two business days. You can click on this website here to find out the contact information for those services.

All of today's faculty members have signed a Declaration of Disclosure, and please see the materials posted online for additional information. At the end of this webinar, these are the key points that we hope to touch on; but now we're going to move straight into our session.

It's my pleasure to introduce Dr. Lisa Chen, who is a Professor of Medicine at UCSF. Dr. Chen is also the Medical Director and Principal Investigator at the Curry Center.

Lisa?

Great, thank you, Kelly.

I'm going to get rid of my picture and put on the important ones right off the bat.

Welcome, everyone. Really the collective group of all five RTMCCs and the CDC are really excited to bring the first of what's going to be two webinars to highlight the great work of all the folks who are bringing us the new 2016 treatment guidelines for drug-susceptible TB.

In this first webinar, we really have the distinct pleasure to offer you guys a chance to hear straight from the folks who not only led the systematic reviews but also the primary co-chairsn at the end.

The second webinar -- which the date is not yet set, but you'll get a notice as soon as it is -- will really focus more on the programmatic issues. We're going to welcome any questions people have to help guide that session at the end.

So to start, we start with two presentations by Payam Nahid, who is a Professor of Pulmonary and Critical Care Medicine here at UCSF with the Curry Group. He is the Chair of the Guidelines Committee. He represented the lead in the American Thoracic Society. He's an investigator for the TB Trials Consortium; and, important to this data, is that he was the lead of one of the major groups that did the systematic groups here at UCSF.

The second presentation, Payam will lead straight into Dick Menzies' talk. Dick is well known to many people. He's a Professor of Medicine, Epidemiology and Biostats at McGill University. He's the lead of a highly productive group, who's contributed not only to the systematic reviews here for these guidelines but also key reviews that have influenced multiple global policies by the WHO.

Without further ado, Payam, I'm going to hand things off to you. Thank you.

Thanks, Lisa.

Thank you to the RTMCCs for giving us the opportunity to highlight the new treatment guidelines for TB. I'll be presenting, on behalf of the Writing Committee, the Guidelines that, as you can see, were sponsored by ATS, CDC and IDSA; and newly for this version, as compared to the prior version, co-endorsed by the European Respiratory Society and the U.S. NTCA.

The Guidelines are officially published in the *Clinical Infectious Diseases Journal* in October. I just want to make a note to all attendees that there's also an Executive Summary, so be mindful of that when accessing the guidelines. There's a shorter Executive Summary; but what you want to be accessing is the full guidelines, as shown here, which is comprehensive and covers all the topics.

I wanted to actually start with the acknowledgements rather than end with them. This was really a massive task; and I wanted to show you the Writing Committee members, who were carefully selected and screened for conflicts of interest. They included specialists in pulmonary medicine, infectious disease, pharmacokinetics, adult and pediatric TB, primary care, public health, and several members involved in systematic reviews. You can see that there were representatives from across the U.S., from Europe, from South Africa, as well as Writing Committee members from the World Health Organization. So it was really a broad, diverse group of experts that helped move this process along; and I wanted to acknowledge them.

I also wanted to acknowledge my Co-Chair, Susan Dorman, who represented the IDSA; GB Migliori, who represented the ERS; Andy Vernon of CDC, and I. I led the ATS effort and my colleagues are on the line here to contribute to the discussion.

The backbone of all the recommendations made in the new guidelines is based on GRADE methodology. This was also a separate but very large effort, and I wanted to acknowledge the Methodology Group for collectively synthesizing the data, doing the analysis. The key thing that comes out of these activities is a much deeper and clearer understanding of the quality of the studies that go behind the recommendations. The quality of those studies then impact, in many ways, both the strength of recommendations given and then our certainty in that recommendation as well. The certainty is driven, again, by the quality of the evidence.

There are some disclosures I think that are available to you elsewhere, but these are the disclosures that are in the Guidelines themselves. I show them only to illustrate that the majority of Guideline Committee Members report that they had no relevant commercial interest, and a handful reported interests that were managed by the ATS and Societies that were not deemed to be significant for the writing of this particular guideline. There may have been some disclosures that might be pertinent, for example, to drug-resistant TB; but these are shown for you here.

One of the key things to note about these Guidelines are these are intended for settings in which mycobacterial cultures, molecular and phenotypic drug susceptibility tests, radiographic studies, and other contemporary diagnostic tools are available on a routine basis. There is a WHO guideline, as you all know; in fact, a drug-susceptible guideline is currently in revision for the WHO, which we also contributed to at UCSF. But this guideline is intended for the settings in which these tasks and tools are routinely available.

I'll just break down for you very briefly the guideline content because this is going to be a very high-level overview of the content of the guidelines and really focusing on recommendations; but there's a lot more in the full text than just the recommendations made using GRADE. There are sections on patient-centered care and case management, techniques for ensuring adherence and treatment success. There are sections on treatment regimens, when to decide to initiate treatment, the preferred and alternative regimens. This is further expanded into treatment of special situations or special populations with a much larger section on HIV as compared to the original guidelines, expansion of language in pregnancy and

TB, an inclusion now of, again, more guidance on patients receiving anti-TNF drugs in advanced age, diabetics.

Then, in addition to that, all the other extrapulmonary manifestations of TB are also commented on with a very rigorously-researched bibliography. I think that's one of also the strengths of the Guidelines. The TB field is publishing at a very rapid clip, but we sort out really the quality references to help guide some of these special situations. Again, there have not been randomized controlled trials, per se; but there have been some cohort experiences, and we reference those.

There's also a Practical Aspects of Treatment section on managing common side effects, drug/drug interactions. There was a call and request for more language on therapeutic drug monitoring, and that has been expanded. Then we have some closing information in TB treatments regarding recurrent TB, treatment failure, drug resistance. Essentially, drug resistance in this regard is about how to be mindful of it, to have a suspicion for it in the right settings and, if empirical treatment is needed, how to manage that. Again, drug resistance is not a focus of this Guideline; there's a separate guideline under development by the same Societies and including the CDC that will provide, as a companion document to this document, guidance on drug resistance hopefully sometime next year.

When one does these kinds of activities, it becomes much more clear what areas are missing adequate evidence. There are certainly areas of research that will improve our understanding of the optimal ways to manage TB. So there's a section on the Research Agenda for TB Treatment; and I think that this in particular highlighted the paucity of data, for example, on TB in children and TB in pregnancy, breastfeeding women. It's very hard to make recommendations in those settings without high-quality published studies.

A very brief comment about the GRADE methodology, which you'll hear more examples of through Dick's presentation to follow mine -- the GRADE methodology, or GRADE itself, stands for grading of recommendations, assessments, developments and evaluations. This is now the standard technique by which practice guidelines are being developed. It's a standardized approach. It allows one to make recommendations based on the certainty in the evidence, which historically has also been the quality of the evidence.

These PICO questions – population, intervention, comparison, outcome, or PICO – are very directed, very clear questions that then get addressed through these meta-analyses and systematic reviews. For our work, we use the method of the Cochrane collaboration, assess the risk of bias at the outcome level using risk of bias tools – so really implemented the state of the art in analytic techniques to understand best what the level of evidence is.

So based on the certainty in the evidence, you can either make a strong recommendation or a conditional recommendation. I'll pause here; this is an important distinction that you should look for in the recommendations and the Guidelines. They are specifically marked as either being strong or conditional, and then they're followed with a level of certainty: high certainty, moderate certainty, low certainty, or very low certainty.

At the end of the day, just to focus here for a second on the Conditional Recommendations section, this basically means that when something is conditionally recommended, the majority of individuals in this situation would want the suggested course of action, but many would not. This also takes into account that for clinicians, they would recognize that different choices may be appropriate for individual patients. You'll have to work to make that management decision in concert with the patient. For policymakers, conditional recommendations will often require substantial debate and involvement of various stakeholders and to know how best to implement this recommendation.

Strong recommendations, I think, are somewhat more straightforward. This usually is based on high-quality evidence or high certainty of the evidence, which is born out of multiple randomized trials, very

well-designed, having a consistent signal of benefit or harm, whichever direction. Then in this scenario, as you can see, most individuals in this situation would want the recommended course; and only a very small proportion would not. So there's less debate here by policymakers and clinicians. Those are the key language vocabulary, if you will, for interpreting the various recommendations and why some say strong, some say conditional.

Let's start with the treatment for drug-susceptible TB, which hasn't changed. As many of you know, the fluoroquinolone-based treatment shortening trials were unable to show non-inferiority to the standard six-month regimen that is being used worldwide. So the preferred regimen is one that uses the standard four first-line drugs during the intensive phase of two months, and followed by a continuation phase of four months of isoniazid and rifampin. We will go into the intermittency dosing in much greater detail in Dick's talk, but this remains the recommended regimen until future trials find an alternative regimen.

We took on nine PICO questions for this guideline. We were actually counseled against taking on so many because each PICO does require a systematic review, but we felt that these were nine that we could manage and expanded our team of GRADE methodologies to make it happen. What I'll do here is I will stage each PICO question and then show you the recommendation and then provide some context, but this will be a very high-level overview again.

The first question was: Should case management be provided to patients receiving curative TB therapy to improve outcomes?

By case management, we meant patient education/counseling, field/home visits, integration/coordination of care with specialists and medical home, patient reminders, incentives/enablers – really a whole span of case management techniques. In fact, each one of these ends up having its own assessment as a PICO question and its own evidence profile.

Based on the data that was reviewed and synthesized through meta-analyses, we suggest using case management interventions during treatment of TB patients. This is a conditional recommendation with low certainty in the evidence. In particular, of note was the impact of patient education and counseling, as well as incentives and enablers, in improving outcomes. So there was a real impact there.

The second question we handled somewhat separately, which related to SAT and DOT: Does SAT of medications have similar outcomes compared to directly-observed therapy in patients with TB?

We took the position in answering this question that DOT was essentially the standard of care worldwide at this stage across many programs in the U.S. and Europe in particular. So we were looking from that perspective, with DOT being the standard of care, is there enough evidence to suggest that SAT should replace DOT going forward?

Based on – let's see, this is one of the GRADE profiles, one of the evidence profiles, that I wanted to bring to your attention. I apologize; they're small. I was told to note for you that at the top of your screen, there's a way to expand your slide so you can see this in full screen. Here you can see – I'll just draw your attention. Here you have the quality assessment; and the quality assessments used for this GRADE methodology include an evaluation of risk of bias, inconsistency, indirectness and precision, other considerations such as publication bias, for example.

Then you have your interventions here. So just to reorient you that you have SAT/DOT listed here in these columns. What we see with DOT is that in particular for treatment success, there's an improvement with moderate level of evidence in DOT as compared to SAT. Time to smear conversion at eight weeks, which was what was available in the literature, that's also improved with DOT. So there was no evidence to suggest that SAT was superior or even equivalent to DOT to suggest that we should change the current standard of practice or make a recommendation that would change it. So we suggest using DOT

rather than SAT for routine treatment of patients with all forms of TB. This is a conditional recommendation, low certainty in the evidence.

The next question we asked was: Should tuberculosis medications be dosed daily or intermittently in the intensive phase of treatment?

Should tuberculosis medications be dosed daily or intermittently in the continuation phase of treatment was handled separately. These will be discussed in great detail by Dick Menzies to follow my talk.

The fifth question we asked was around the initiation of antiretroviral therapy during TB treatment compared to the end of tuberculosis treatment; does that improve outcomes among TB patients co-infected with HIV?

As you might recall, this was an area for which the 2003 Guidelines essentially said you could start antiretroviral therapy at the end of TB treatment. So this is one of the areas in which there's a substantial change. This change is driven by very high-quality randomized clinical trials, and several of them that showed that there are advantages to early – again, I'm going to draw your attention to – so you have pooled estimates provided here, as well as the events per number of patients for early initiation of ALT, which is during treatment for TB. There was some range of days or weeks from initiation of TB treatment in the various studies; I'll touch on that in a bit, but certainly early versus late.

There are clear advantages in AIDS-defining illness or death outcomes in mortality, so early initiation of antiretroviral therapy certainly improved outcomes for the patient. There was, as you note, an increase in IRIS, so 15%versus 9% for those who started late. That's not perhaps surprising. What was informative is to look carefully at these events of IRIS and note that they are predominantly manageable episodes of IRIS, so they're not representing major issues. Again, the DOT is suggested rather than SAT based on low certainty in the evidence but conditional recommendation.

We talked about daily versus intermittent will be covered by Dick. This was the slide that I was showing you in regard the early versus late initiation of antiretroviral therapy. So for these evidence profiles, we have the quality assessment, as I noted. For each outcome of interest, we have the pooled estimates. So IRIS is one endpoint, mortality another, AIDS-defining illness another, treatment success, and so on and so forth. And then you grade the certainty in the evidence, as shown here, from very low to high.

So here, just to draw your attention again, for mortality and for AIDS-defining illness, there are clear benefits for starting antiretroviral therapy early. There is some increase in the proportion of the patients experiencing IRIS, the majority of which were reported as being mild and manageable. So based on that evidence, to answer the question does initiation of antiretroviral therapy during TB treatment compared to the end of TB treatment improve outcomes, we recommend initiating antiretroviral therapy during TB treatment, optimally by 8 to 12 weeks of TB treatment initiation for patients with CD4 counts greater than 50 and then within the first 2 weeks of TB treatment for patients with a CD4 count of less than 50. This is a strong recommendation based on high certainty in the evidence.

There is one exception that is raised in the Guidelines in reference to a specific randomized trial in which patients with HIV infection and TB meningitis, this early initiation within the first two weeks was linked to worse outcomes, presumably because of the IRIS and related to TB meningitis. So this is an area of caution and interpretation, but this matches up with the international community now and their timing of antiretroviral therapy being as early as feasible taking all things into consideration.

Now, we just made a recommendation saying that antiretroviral therapy should be used in all TB HIV patients during TB treatment; but the Committee recognized that there may be times and extenuating circumstances in which the antiretroviral therapy may not be available or initiated during TB treatment. We asked the question, linked to that query: Does extending treatment beyond six months improve outcomes compared to standard six-month regimens among TB patients co-infected with HIV?

As you recall, the 2003 Guidelines recommended a six-month regimen for TB regardless of HIV serostatus. We recommend, based on our meta-analyses that Dick ran, that for HIV-infected patients receiving antiretroviral therapy, we suggest using the standard six-month regimen. That's in concert with the guidance before.

In uncommon situations in which HIV-infected patients do not receive antiretroviral therapy during tuberculosis treatment, we suggest extending the continuation phase to seven months in duration, corresponding to a total of nine months of therapy. It's a conditional recommendation with very low certainty in the evidence. I think this is something that operationally would be a decision that one would make, for example, at the end of TB treatment is that HIV TB patient has not received antiretroviral therapy for whatever reason, that some consideration should be given for extending treatment.

The basis for this is this GRADE profile, evidence profile, that I'm showing you now – that hopefully you can see -- again, quality assessment, pooled estimates, shown here for six-month regimen and eight months or longer regimen, and then the outcomes and interest shown in these here and failure/relapse. So when you look at relapse in patients not taking antiretroviral therapy, the subset of population, you will note that the risk of relapse is 18% in those who received six month regimen as compared to 5% in those receiving eight months or longer and with an adjusted odds ratio of 3.1. This is a very low certainty in the evidence because these are – predominantly, many of them are observational trials and there are some questions about the designs but with serious issues around inconsistency; but it is a conditional recommendation.

The seventh question we addressed was the use of adjuvant corticosteroids in TB pericarditis. Does it provide a mortality or morbidity benefit?

As you recall in the prior Guidelines, adjuvant corticosteroids were routinely recommended for TB pericarditis. However, based on a large randomized trial published in the *New England Journal*, the largest to date with somewhat of a unique trial design – it was a factorial design, with an immune-modulating agent as the other intervention – we did not find any routine benefit from adjuvant corticosteroids. So we suggest that initial adjunctive corticosteroid therapy not be routinely used in patients with TB pericarditis. This is a conditional recommendation. The clinical trial found the same result essentially. The one stipulation would be corticosteroids could be used in patients who appear to be at high risk for constrictive pericarditis, but it shouldn't be used routinely.

The next question was about adjuvant corticosteroids: Does the use of adjuvant corticosteroids in TB meningitis provide mortality and morbidity benefits?

There's clear evidence here across several trials that there are benefits related to adjunctive corticosteroids. So we recommend initial adjunctive corticosteroid therapy with dexamethasone or prednisolone given for six weeks for patients with TB meningitis. It's a strong recommendation with moderate certainty in the evidence. There are sources on the Web that provide guidance on how to administer the steroids with some direction on tapering. Those are not in this particular guideline, but available through other Society guidelines.

The final question we addressed was: Among HIV-negative patients – the original question was to include adults and children – with paucibacillary TB (i.e., confirmed to be smear negative, culture negative), does a shorter duration of treatment have similar outcomes compared to the standard six-month treatment duration?

The reason "confirmed" is bolded there is because we wanted to underscore, and did so in the text, the importance of having a certainty in the quality of the sputum that you are obtaining or the samples that you're obtaining, and that these individuals are indeed smear and culture negative; and these are not false negatives because of laboratory contamination or laboratory handling or sputum quality.

So with that said, if a patient is confirmed to be smear negative/culture negative, we suggest that a four-month treatment regimen is adequate for treatment of HIV-negative adult patients with smear negative and culture negative pulmonary TB. This is a conditional recommendation with very low certainty in the evidence. We were unable to address the children because there are no studies in children.

So just to wrap up, some of the key changes and updates from the 2003 edition are that, as compared to that prior edition, we now recommend early initiation of antiretroviral therapy in all HIV/TB patients.

We suggest that the duration of TB treatment in HIV patients who do not receive antiretroviral therapy during their TB therapy should be extended.

In the Guidelines, we have provided a much greater evidence base for the intermittent therapies, and those will be covered next; but this is jumping a little bit to the gun, but once-weekly treatment in the continuation phase is no longer recommended.

We also expanded the evidence base and bibliography for case management strategies: patient education in particular, incentives, enablers, DOT. That's been enhanced in the latest Guidelines.

We've expanded the language around TB treatment in pregnancy and updated it for PZA, highlighting that in certain settings in pregnancy pyrazinamide use may be warranted, in particular for patients with HIV or severe disease, and that it not necessarily always should be avoided.

Then steroids are no longer routinely recommended for TB pericarditis, but could be used for selected case in which constricted pericarditis is a concern.

I'll just close by thanking again leadership from the Societies, from CDC. I wanted to particularly recognize Kevin Wilson from ATS, who is the document editor who worked with us very closely, and Jan Brozek, who guided us in our GRADE methodology work.

This was reviewed by three to four, sometimes six, members for each one of these Societies; and over 350, possibly close to 400, reviewer comments were individually addressed in the writing of this.

We also sought out input on language used, the patient-centered aspects, from the Community Research Advisory Group of the CDC-TBTC and the Treatment Action Group.

Again, I wanted to just thank the Writing Committee members who persisted through the many versions and revisions and questions, and my Co-Chairs: Susan, GB and Andy.

Hi, everybody, Dick Menzies here. I hope that everyone can hear me. I'll jump in and talk about the evidence review for intermittent therapy, as that is one area that is both some important changes perhaps in the recommendations but also has fairly substantial programmatic implications.

I'd like to also thank Lisa and the many sponsoring groups and Societies that have participated both in the production of the Guidelines but also in today's webinar production, and I'd certainly like to acknowledge Payam for his leadership in the Guidelines and providing me with the opportunity to not only provide evidence and give this talk, but to participate in the numerous revisions.

Let me move on and hopefully I'm able to skillfully negotiate the moving of slides.

The two questions were, again, as Payam said, the intermittent dosing in the intensive phase, so in the first two months generally speaking; and then what about intermittent dosing in the continuation phase meaning, again, for the standard six-month regimen, the last four months. Hopefully I'm using definitions that everybody is familiar with.

Very briefly, I'm going to run through quite a bit of evidence. These are not in the form of GRADE tables. For those of you who were looking at those GRADE tables in some degree of bafflement, hopefully this will be a bit more like a talk you might hear at a symposium.

There are a number of other reviews. This is going to be, if you will, a bit of a review of reviews. I'm going to end with an updated review that is not yet published that I've been part of, which I think also helps to answer some questions I've heard already.

One point to make is that we consider the best evidence to be a randomized trial where in that trial the primary question is intermittent versus daily. A systematic review was done really back in 2001; and in that Cochrane review, which tend to be very high-quality reviews, only a single trial was found with a total of just under 400 patients – that should be 399 patients – so about 200 people per arm. There was a small difference in relapse rates with the three times weekly throughout; but, as you see, the rates were all small, were all low, and so the differences were not significant. So they concluded there was no evidence of significant difference, but there were also very few trials where the schedule of intermittent versus daily was actually the question. There was really only one trial.

Again, I'm relying on the people who type to let me know if ever I'm not progressing -- so, moving to the next slide: Dosing schedules of 6-month regimens and relapse.

This was a review published in the *Blue Journal* about a decade ago, 17 studies, about 5,000 patients. So here you have different – it's a relative risk, so the daily throughout had the lowest rate of relapse. Then you see that when it was daily in the first two months, then three times weekly, it was a bit higher – 1.6 times higher. So typically relapse rates in these large meta-analyses average with a six-month regimen, 3% to 4%. So if 3% to 4% is for daily, then 1.6 would be around 6% relapse rate. Then daily, followed by twice a week in the continuation phase, this would be 2.8 times higher. Then three times weekly throughout, now this is five times higher, so really substantially higher; this is relapse only.

The same study, they noted that the risk was greater if there was cavitation or the two months was culture positive, which again are well-known as risk factors for relapse. So this might be for later discussion of a particular group to be concerned about when you're using the intermittent regimen. Also, they noted that the very highest rates were of once weekly rifapentine; again, I've not shown those specific results.

Then there's a review, which I have immodestly called Menzies' Review; but I was the first author. This was a review of older studies up to 2008, published in *PLOS Medicine* in 2009. Again, this particular review we only considered randomized trials and only bacteriologically confirmed cases of course, so no clinical cases, and also bacteriologically confirmed failure or relapse and acquired drug resistance, only studies with six months at least of therapy, and that included of course INH and Rifampin – so reasonably close to the current regimen that is in standard use.

So in this, again, it's kind of the typical schematic; but essentially, a lot of titles reviewed. We came down to 57 randomized trials that had been done in TB in this interval from 1970 up till 2008, which tells you just as a side note, just how many trials sometimes are needed to get to where we finally have the regimen we have today, which is the six-month regimen with two months of INH, rifampin, pyrazinamide and so on. It takes really a lot of work to kind of hammer out the best regimen.

Okay, so what did this review show?

First of all, one kind of striking point was that in all 57 trials, there was no trial that looked at the so-called Denver regimen in a randomized trial. So there was no trial where they either started from Day 1 or after two weeks and then went to twice weekly for the rest of the treatment. So that was kind of striking.

Three times a week, though, there were trials; and three times a week could be from Day 1 -- from, in other words, the first dose -- or after two weeks or one week, as sometimes occurred. All of these were

considered three times a week throughout. As you see, there was some slight increase, significant though, in failure rates and quite a substantial increase in acquired drug resistance – that's what ADR stands for – quite significant, although the absolute rates were quite low; and I'll come back to that point later.

Moving on, then there was another review just of children, intermittent versus daily. This was again a meta-analysis. They identified four trials with 466 children; and in these trials, children received either twice weekly or daily. Basically they found that the twice weekly was not as good, so 0.27 means the odds of treatment success was quite a bit lower than in children who had daily therapy. They analyzed it different ways. One way it was clearly significant, so-called per protocol; and intention to treat was not significant, although still the intermittent regimen was worse.

Then again, HIV infected – so I'm sort of running through a variety of populations, if you will, where the same question has been addressed. This particular one is a review of treatment of active TB in HIV co-infected, led by my colleague here at McGill, Faiz Khan. Again, pretty standard – but in this particular review, we included cohort studies, or observational studies, as well as randomized trials primarily because there simply were not that many randomized trials.

Again, a lot of titles reviewed; we ended up with 27 studies. In fact, we did a first review; and then we updated it a few years later. This slide doesn't seem to come out quite as clearly, but let me just say we added another 7 studies, so a total of about 30 studies included in this review.

Rushing on, when we look at all studies all together – and here perhaps I'll pull a pointer – so when we looked at all studies all together, we basically divided studies into daily in the initial phase. They could have been any regimen after the initial phase, or they were three times a week from the beginning. In the three times a week you can see quite a bit higher rates of failure and relapse and acquired drug resistance -- so quite, we thought, important differences. The Constance intervals are very wide, so I've only highlighted the absolute estimates; but again, you'll see that it's two to three times higher rates of failure, relapse and acquired drug resistance. Mortality was not the difference. Again, mortality was quite high; some of these are older studies.

Going on to the next, when we adjusted for various confounded factors, we still see that now instead of these are not percentages, so not rates; these are odds relative to daily. So daily is the reference group. So three times a week would have twice as high rates of failure; relapse would have, again, about twice as high; acquired drug resistance about three-and-a-half times higher. Again, these are with all studies, so some patients not on antiretroviral therapy.

So now we tried to stratify; and again, I've just highlighted sort of the rates. The left-hand column is always not on antiretroviral; and the right-hand column would be on antiretroviral, not on insulin. This is, again, the 30 studies split into – you know, it's basically the years when the studies were done of course. So here you see not on antiretroviral, much higher rates of failure and relapse; but on antiretroviral, only relapse looked different. Again, this is just one way of analyzing the data. You've also seen the same information presented to you by Payam, where the absolute numbers were quite different.

The final review was led by Jay Johnston at UBC, and I was a distant reviewer. Again, the first strategy I showed you; this was the one that I claimed authorship of up to 2008. Then the second review just overlapped a little bit, up until really March of this year – so pretty up-to-date. Again, what we ended up with – just to kind of show you – the first review we had 57 studies; up-to-date review, we have another 7 studies. So we ended up with a total, when we cleaned it up and took things out, where they were drug-sensitive TB or DST was not done but they were new cases, which happens in some settings and at least six months of rifampin use. So then you see these numbers: 108 arms, one study could have several arms of course, but 13,000 patients – so large numbers of patients when you pool all of these studies together.

As I said, the primary analysis – drug-sensitive TB or DST not done, but they were new cases, at least six months of rifampin. Again, we compared; we grouped everything into daily, which we considered five days a week or more: daily intensive, so the first two months, then twice a week; daily for the first two months, then three times a week; and then three times a week throughout, meaning either from Day 1 of after one week or two weeks of daily. Again, just to reiterate, even in the update date we have not found any randomized trials where twice a week was given throughout, from the beginning to the end. The so-called Denver regimen has not been included in any randomized trials that we've been able to find.

Okay, so I think actually I will perhaps jump forward.

These are the absolute, if you will, event rates -- daily versus intermittent. So here's daily versus three times a week, so this is initial phase -- so from the beginning, daily in the initial no matter what happened after or three times a week from the beginning. You see that the failure rate is a bit higher, not significant. The relapse rate is quite a bit higher and significantly different. The acquired drug resistance is higher; but, again, the absolute numbers are small but not a significant difference in this analysis.

Dick, can you hold the phone closer to your mouth?

Oh, sorry.

The Continuation Phase – and I need to get the pointer here. The Continuation Phase – so you either have daily from the beginning and right through, or daily for the first two months and then three times a week, or daily then twice a week. Again, what you see is a bit of a trend in failure. It gets higher with the more intermittent regimens.

Relapse, there's clearly a difference again when you start with daily and then twice a week; and acquired drug resistance, just very low rates in total. When we do adjusted analysis, so-called meta-regression, here now these are odds ratios. So daily throughout becomes the reference group, then we have daily, then three times a week. So you see maybe a slight increase but not significantly different. Daily then twice a week, we see that the failure rates are significantly higher. Then three times a week throughout – failure, relapse and acquired drug resistance are all higher in terms of these adjusted odds ratios relative to daily throughout. There are details at the bottom of the slide as to what it's adjusted for.

Again, I must mention that although it's been submitted for publication, this is not yet been published. It was submitted at WHO Guidelines last summer, and so it's sort of been in the public domain since then but not yet published – last summer meaning July of this year.

Sensitivity Analysis – basically because questions are raised and so on, we tried the analysis a variety of ways. First of all, we tried only drug sensitive; so if they didn't have a DST, even though they were new cases, very unlikely to be resistant, we dropped them – didn't matter. We tried all studies, like my own analysis, earlier – no difference. There were some studies where there was streptomycin included; we took them out, nothing changed. We looked at drug-resistant strains only, similar findings. We looked at purely the standard regimen everyone uses now and, again, no difference in findings. Finally, we took out a few studies where it was only HIV-infected – again, nothing happened. So all of these different sensitivity analyses were tried, and the findings were basically the same. I'm not going to show all those results, obviously.

We just had a few other issues that have come up along the way: how many studies used DOT. The majority of studies, and virtually all of the studies using intermittent regimens, used DOT. Some of them used them only in part, so again it depended on the regimen. Did not use, 29%, and these were mostly the daily regimens that did not use DOT.

One issue for quality is how many studies had less than 10% total loss to follow-up default and transfer out, unknown, et cetera. So two-thirds of the studies had less than 10% of these all-in, no one knows

what's going on; although one-third of studies did have more than 10%, so we judged those of lower quality.

HIV-infected – 11% of all patients were HIV-infected in this review.

How many were older studies? Prior to 1990, 69% of the studies, so you see that really most of these studies are older even though the regimens are familiar. Again, this reflects the evidence base for the regimens we use nowadays and the drugs we use nowadays.

Finally, conclusions – so intermittent, three times a week from the beginning or after two weeks, have higher rates of failure, relapse and acquired drug resistance in multiple reviews. Then I've just kind of listed again as a reminder which studies – so the Cochrane review it was higher, not significant. In the Chang review, relapse was significantly higher; the children, again, significantly higher. My own review in 2009, failure and acquired drug resistance. HIV-TB, only if ARB is not given; and then the 2016 updated review, again, all outcomes. Very little published evidence in terms of randomized trials from the Denver regimen; and finally, daily initially, then twice weekly intermittent, higher rates of relapse. Daily initially followed by three times a week seems to be as good as daily in at least the three reviews where it's been looked at carefully.

Finally, just a few limitations – again, as mentioned, very few large-scale randomized trials with direct comparisons. Most studies have been conducted in low- and middle-income countries; however, I think the quality of these, at least during the studies, was high. Dropout rates and non-adherence was low. Some studies did not use PZA; but when we sensitivity analyses arms with PZA only, we found the same findings.

I think probably the other is that the absolutely effect size is small. When we're talking typically of a difference in relapse rates, even if the odds are two or three times higher, the absolute difference might be 4%. Acquired drug resistance, the absolute difference is only 1%; acquired drug resistance is very, very uncommon with the regimen we are using in drug-sensitive patients. So again, the absolute effect is small; and, at least in one review, the majority of relapses occurred in people with known risk factors for relapse – so cavitary disease, smear positive or culture positive at two months.

Strengths – so this is a large number of studies and large numbers of patients. No patients with clinically-diagnosed TB were included in these reviews. Pretty consistent results from multiple reviews in adults, children, HIV-infected, and again, not always significant but the trends were quite consistent. In three reviews, multivariate analysis was used to adjust; findings, if anything, were strengthened. The findings are from many countries, which might make things more real-life.

Just to acknowledge the people who participated in the different reviews: Jay Johnston, Jonathon Campbell from UBC; in 2008, a bigger crew, and the HIV Review as well. Large numbers of people have helped by contributing data, thoughts, comments, et cetera.

I think that's it for me, so I'll stop there.

Hi, it's Lisa. I think we're back on. Can you advance the slides?

Thank you, Dick. Thank you, Payam. There are additional slides from Dick Menzies' sets in not areas that we're covering this time around.

We thought we'd include those in case questions came up only.

Yeah, it's a freebie from Dick Menzies.

So what I'd like to do is queue the slide set-up for our panelists. For the rest of you, this is where we get to open up for about a half hour your opportunity to throw some questions our way via the Chat. Of course, we can't get to all of these questions; and I'm really hoping that either through the Chat or through an additional link that we're going to give you, a person to e-mail with other programmatic questions, we'll be able to inform the second webinar that's led by the RTMCCs to really address more of the nuts and bolts and practical issues that these new Guidelines might mean to programs.

What I'd like to do is welcome to join --both Payam and Dick will stay on the line, but we're going to add for your listening pleasure, of course, always Dave Ashkin, who's the Medical Director and Co-Principal Investigator for the Southeastern National TB Center in Florida. He's also the Medical Director of the Florida Department of Health's TB Program.

Susan Dorman, we're very fortunate to have as well. She was the Co-Chair from IDSA for the Guideline development. She's a Professor of Medicine in International Health at Johns Hopkins.

Last, but not least, Andrew Vernon from the CDC, the Chief of the Clinical Research Branch at DTBE and, as well, the Co-Chair of the Guideline development for CDC.

Let's make sure we unmute you all. Go ahead and do hash six (#6) to unmute. I know David's also kind of fielding the Chat questions a bit, but we've got a starter set of a couple of questions just to get people going.

So we've had preliminary calls, of course, between the panel group here; and one of the issues that came up is the question of when we look at these large systematic reviews, meta-analyses that look at often data that's not from randomized controlled trials, people will also question. Boy, there's a lot of data from international studies or from a long time period maybe when treatment was a little bit different, maybe the populations are a little bit different or the regimens may be different than we're currently using. Really, the question that comes up to people's minds: Are these really applicable to our current day process?

So the question really is: "From a practical standpoint, panel members, how would you advise program people listening who may have these questions about whether or not the data that guided the recommendations are truly relevant to our process in the states now?"

Let me start with Andy from the CDC. Any advice you have for folks? Again, hash six (#6) to unmute your phone.

This is Andy Vernon.

Great, we can hear you, Andy.

We consider this, as Payam noted in his presentation, perhaps the strongest form of evidence that we can consider in the process of developing recommendations. Practices are, of course, also influenced by practical considerations, including cost and acceptability among others. With regard to the expected efficacy of specific practices, we consider this to be very strong evidence.

Great. Payam, Dick, would either one of you want to weigh in on this issue?

I would just add that within the quality assessments that are done in these evidence profiles – admittedly, these are the profiles we worked with in making our recommendations – you'll note that these quality assessments are standard assessments around risk of bias, inconsistency. For example, inconsistency between studies would downgrade our view of the quality of the evidence. Indirectness happens to be one of those quality assessments as well, and indirectness can be something as, I suppose, plain as this is a study in adults so it would be indirect to a question on children. It also incorporates potentially

indirectness as it relates to, let's say, studies done in a very high-incidence, low- resource setting in relation to potentially another setting which has low incidence of TB but is well-resourced.

So those things are all factored into the final scoring, if you will, of the certainty and the evidence. So I think it's a good question. It is, as Andy said, the best available evidence out there in the world. So until there's more published from low incidence, well-resourced settings, these are the data that we have to work with.

Well, I think, in fact, Andy, in previous calls, you had mentioned that there is a large effort underway by CDC to look more closely at U.S. data – maybe you can expound on that a bit?

The report of a verified case of tuberculosis, the official report form that's used for surveillance purposes, has undergone several modifications over the past two decades. Coupled with our ability currently to genotype the vast majority of positive pulmonary cultures of TB, we are increasingly here at CDC able to assess treatment outcomes. So I think in the future, we will be looking carefully at outcomes in association with various aspects of individual patients, including the regimens or modalities that were employed in their treatment.

In order to be practical, those forms do not collect substantial detail regarding individual patients. So our ability to use surveillance data in this regard will have some limitations. We're very interested in investigating ways to combine the advantages of the ongoing collection of surveillance information with the strength of data that are generated by clinical trial approaches, such as randomization, perhaps in the future to allow us to generate even stronger information from the activities in which all programs are engaged on an ongoing basis.

Andy, this is Dave Ashkin. I just wanted to ask a question kind of that is on the Chat and we said we would discuss. I think this question really is for Payam and Dick and Susan too. We hear terms like – Andy, you used the term before that this is a "strong recommendation." Or we heard before Dick talk about that this is "significantly higher." I think some of the confusion comes down to the definition of the terms we use.

Usually, if we use the term "significantly," many of us in the medical community will think about statistically significant. Or sometimes when we're hearing "strong recommendation," well, I think you'd agree, Andy, I guess you're saying, hey, this is based on the best information we have. Then "strong recommendation" is different than what we'd say "conditional" based on the GRADE system. I was just wondering if we could – like one of the questions that was asked is, "Please explain conditional recommendations in certainty again."

I would think DOT would be higher than conditional and below certainty. I think in our everyday language as we're speaking, we use terms that are getting confused back and forth by their definitions, the way we use them in everyday language versus how they're sometimes used in statistics or in recommendation language.

First, before we even go there, I have to make this statement. I want to thank you guys for I think one of the most amazing documents that TB has had if not ever, in a long time. It is – and I'm just making this recommendation for everybody out there, I highly recommend you take a look at it. It has over 500 citations, such great practical information and, again, really reviews the literature. I can't not thank you guys for doing this.

So, Payam or whoever, I'd like to go back to that question about to the language and statements such as we were asked, would DOT be considered higher than conditional and how you would answer that.

Sure, this process of GRADE methodology is actually not new; it probably feels new to many of us in the TB field, but it's been around for many years now and it's used across all practice guidelines essentially

as the standard in other diseases as well. In fact, there's a movement to not allow guidelines that don't use GRADE methodology to proceed to publication as practice guidelines. There's a strong movement towards this, and we're coming to it a little bit late; but it is a good system.

The way the system works is, as I noted, you collect all the data that addresses the question that has been posed, the PICO question; and then you look at the outcomes of interest the Committee panel members feel clinicians and end users and providers and patients want to know about. That would usually include things like what's my risk of mortality on this? What's my chance of cure? What about relapse, or what about acquiring drug resistance? So those are the outcomes that we select.

Then the intervention and the comparison in the PICO kind of acronym there are compared to each other, and pooled estimates are made. Now, there is a whole variety of study types that go into this. As a Committee, we decided that we would only include randomized clinical trials if we could include only randomized clinical trials; but if there were questions that just frankly didn't have randomized clinical trials but were still important to clinicians and providers that we would then sort of look at in some ways the lower level of quality of studies, like cohort studies or observational studies, that don't have the randomization to them to take into account residual confounding.

With these quality assessments, we then are able to determine whether the certainty we have in the evidence that has been gathered for that particular outcome, that same mortality – or let's do the SAT/DOT one. The SAT/DOT one, I told you treatment success was shown to be better in DOT in the arms that used DOT versus SAT. We assess the quality of evidence and give it a score. That's the certainty in the evidence; so it goes from very low to high.

The reason why there might be some confusion to the readers about why DOT versus SAT, for example, isn't a higher certainty in the evidence because by convention, you score the overall certainty in the evidence for the PICO question according to the lowest level of evidence for a given outcome, for any outcome that you've selected. So mortality happened to have very little information, very few trials that were helpful in mortality, as it related to DOT and SAT; and the certainty in the evidence of that was very low. So that becomes the lowest level across all the outcomes assessed. Even if treatment success had moderate quality of evidence, we are, by convention, conveying to the reader that this particular PICO question that incorporates all these things, including patient values, has in general at its lowest level a very low quality of evidence or very low certainty. That's why you get that kind of information.

This is Susan Dorman.

Go ahead, Susan.

Thanks, Lisa.

I'd also like to add that while the PICO and the GRADE process really does add rigor to the Guidelines and to the process of formulating the Guidelines, the conventions of language that Payam talked about do include some constraints. So with that in mind, the Writing Committee really endeavored to – in the fuller version of the text, so not the Executive Summary, but the fuller version – the Committee really endeavored to explain some of the rationale and the evidence insofar as permitted by page limitations and whatnot, but really tried to give the reader, give you guys, a sense of where the recommendations were coming from and some of the nuances around them. So I would encourage folks to also have a look at the fuller text.

I think that is really true. It's well-written. There are a lot of practical issues addressed in there. So there's a link to the Guidelines listed around this webinar. I think everyone might want to have that link on their desktop computers in their clinics.

So I think what we can appreciate is this is an extensive process. A lot of the concerns we have -- like does this data really relate to what I do – actually those kind of considerations are built into how you're making these recommendations according to a standardized protocol that you apply to everything. So I think that where we like to think we could do that in our heads when we just are seeing a patient in front of us and we know we've read some of the literature, you guys have done that in a very rigorous way in order to give us these recommendations. The care that has to be taken is how we read this. When we see "strong" versus "conditional," we just have to remember how those terms are being presented.

So that really helps, you guys. I hope it helps people who are listening. I want to go to another question before I hit some from the Chat because I know this is something that came up in many of the planning calls. We just want to dig in a little here because we have these folks on the panel. Again, this is probably an issue that will come up in the second webinar for sure.

A lot of programs who are listening use intermittent treatment, in whatever fashion, as their standard protocol; and many people will say that they have great experience and great outcomes with it. So I'm sure in the background when you guys were developing those recommendations, there was a lot of internal debate and careful wording because you knew what kind of impact this would have on programs. So if you were going to give some kind of practical guidance to programs of how to look at these new recommendations for use of intermittent treatments, what would be your take-home message?

Susan, you've got a practical voice. I'm going to pull you into this first if that's all right.

Sure, thanks, Lisa.

I think it's fair to say that many of us do come from programs where intermittent, or even highly intermittent, therapy is regularly used. Our charge though, as a Guidelines Writing Committee, was to review the data and use the published data to formulate guidance. Really, as Dick described, the data around intermittent versus daily treatment were really thoroughly and very formally reviewed and then were discussed by the Committee in great depth and on a number of occasions.

Perhaps a couple of key points that I took from this that might be helpful – first, with regard to daily versus intermittent therapy, the results around outcomes really are consistent across multiple reviews and in multiple populations. I think as Dick mentioned, the differences are not always statistically significant; but the trends are quite consistent, and he presented that information. I think those trends are important in thinking about guidelines, although when we work with individual patients, we also need to think about the individual details of the circumstance. I think the data in the reviews also point towards a couple of factors that increase the risk of poor outcomes with intermittent treatment, and those being untreated HIV as well as cavitation and other measures of high bacillary burden before treatment.

So even acknowledging the limitations of the data, we thought that the trends were quite telling. So we sought to provide recommendations that were clear but also provided programs with some flexibility in their interpretation. Then in the narrative text, we tried to provide information to help guide clinicians and programs as to circumstances in which intermittent therapy may or may not be a good option, at least from an efficacy point of view.

I think a final point is that the Committee definitely discussed and did appreciate that there are many programs that have historically good outcomes with intermittent therapy, and really underscores the importance of getting that information out there and understanding program performance.

I have to say, that was one of the things that really hit me about all of this. We need to publish our data so that they're actually included in these kinds of systematic reviews.

Dave Ashkin, I'm going to pull you into this because I know that this is a topic that you've been very thoughtful on and engaged in. Any additional thoughts from you?

Well, I think the discussion is very, very important. To me, what I think all the data really points to is the importance of what Payam said earlier when he was talking about the idea of conditional. He said that when you look at conditional recommendations, it's really about taking a lot into consideration and making the best choices, understanding the pitfalls -- meaning in certain populations, those that may be smear positive, those that have cavities -- that you may not want to go to intermittent. But taking into consideration the patient, the intervention – everything – what is best for not only your patient but also for the program.

You're right, Lisa; I totally agree with you. What we really lack – it's really sad – is a lot more very, very good data to make "strong" recommendations. Based on what we have, I think first of all, again and again, it's an excellent, excellent job. But I think for us as clinicians, for us as program managers, I think it's going to become very, very important to make decisions based on the individual patients, based on the resources that we have and making sure, obviously, that we keep an eye on what's going on.

I think ultimately it becomes very, very important that we as programs continue to monitor our success, our weaknesses, and be able to understand early on. One of the statements that is made over and over again, if you have somebody on intermittent therapy, if they're missing doses, it becomes important to recognize that early and obviously switch them onto a regimen that guarantees the highest chance of success, meaning potentially taking more intermittency.

I think the messages are if you have the option, obviously, daily is better, at least when it comes to intermittency. Again, when you have the option, obviously things like starting antiretroviral is better; and that, I think, is made clear by this document.

Well, we have just a few more minutes. Dave, I know you've been scanning all the different Chat questions, again, that we're going to forward on to the second webinar. But you had one in particular that you wanted—

You know, it's kind of an interesting question because one of the things that's being brought up over and over again is if you look at one of the rationales for why you may not want to use biweekly therapy is the concept that if you miss one dose, then you're really only giving it once a week; and studies have shown that once a week, at least with INH or rifapentine, in a continuation phase fails. Charlie Crane was asking if somebody could maybe summarize the results of that study and why they think maybe once-a-week therapy failed and why it becomes important to be very careful with intermittent therapy.

I'm wondering if maybe Dick or Andy – I know, Andy, you were involved in the study – would like to maybe comment on that.

I'll let Andy comment on the rifapentine study because he's much more familiar than I, but I definitely know there were some older studies where they tried once weekly INH with rifampin; and results were very poor, and that approach was abandoned quickly. Not only was it very poor, but also there was a higher rate of serious adverse events in the so-called hypersensitivity reactions with rifampin occurred with people on once-a-week therapy. So there's not only poorer efficacy of treatments when you go to once a week, but you actually substantially increase the risk of adverse events.

In our rifapentine study, which was begun about 20 years ago to deal with adverse events, first, we did not see an elevated rate of hypersensitivity reactions or other adverse events; but we were not using high doses. We were using a 600 milligram dose, with is less even than the 3HP regimen for LTBI uses.

With regard to your comment, Dave, that once weekly failed, it failed to demonstrate equivalent outcomes with twice-weekly therapy. It was a little bit weaker. I think the conclusions that the panel drew from the multiple reviews that Professor Menzies presented is that fewer doses is a little bit weaker than more; and the binary thinking of it works or doesn't into which we've fallen for some years, doesn't really do justice to the evidence, which is rather more quantitative and graded.

Andy, you're exactly right; I didn't mean to mean fail.

No, it's all right. It gets back to the question of wording and the words we use.

You are so, so right; and I appreciate that over and over again. Let me ask this question because it's being asked, and I think Pete Davidson really brings it to bear. This is what the programs are asking: If a TB program doesn't have the staffing or the capacity to provide daily doses throughout the regimen, do the panelists feel that intermittent therapy is accessible?

One of the big issues I think that some people feel that the capacity of our health departments, especially future capacity, at least to some readers, may not have been taken into account enough when these Guidelines were written. Any comments on that?

This is Payam. I'm going to respond to it by referring everyone back to the document. The full-text document very clearly states that the preferred regimen – and notice the word "preferred" – is a daily regimen; and the effectiveness of the data regimen has been shown, through the analyses today and in the document, as having the highest effectiveness of all of them.

Now, we note though that alternative regimens may be acceptable in certain public health situations. It's in that context that we talk about the thrice-weekly, twice-weekly, and once-weekly regimens. In general, we feel that the data show, with consistency, that a daily intensive phase is preferred and that anything less than daily in the intensive phase is generally not preferred. Then from there on, it's almost, frankly, stepwise. We say thrice weekly is the next best, if you will, followed by twice weekly if you don't have the infrastructure or if for whatever reason you can't do thrice weekly. Then it follows down to once weekly, which we, contrary to 2003 Guidelines, actually suggest it not be used. So it has already in there the stepwise interpretation as it relates to public health infrastructure and local situations.

I'll add a little bit to that. In Study No. 22, to which I alluded earlier, the failure and relapse rate in the twice-weekly arm was about 5.5%. In most of the published trials where DOT is used with daily therapy, it appears you can usually get the relapse rates certainly below 2% and often below 1%.

From a patient perspective, I think a 1 in 100 risk of an adverse outcome is highly preferable to a 1 in 20 risk. From a program perspective, there are challenges with regard to cost and infrastructure; and, again, I don't think our choice is simply binary. There are creative solutions, creative compromises, that we have only begun to think about.

I'll just suggest one of them, which could be a regimen in which patients are given twice weekly DOT, and three times a week they receive self-administered therapy. That's an untested regimen, but one that would address a lot of the program concern about costs and provide patients the opportunity to receive stronger rather than weaker therapy. That, of course, is not something that this guideline address in any way; but it points out that we have potential to investigate many ways to address the findings and these recommendations other than saying simply, "It costs too much; we can't do it."

Thank you, all of you, for chiming in on that. I know that this is really an area where at least we've had a small chance to hear directly from the folks involved in writing this. I know particularly this topic is something that there is a lot more discussion to come. I just want to remind folks. I know I let things go a little over because I do really think it's important for folks to hear from you all, especially on the topics of intermittency.

Join us for the second webinar. The dates and speakers have yet to be determined, but they'll come up. Submit any of the questions that you have to the e-mail that you see on the screen for ideas that you want them to address doing this. Since we're running over, I wanted to say a really big thank you to everyone who was involved in the development of these Guidelines. Particularly, thank you to the faculty who joined on this webinar to present it and share it with all of us and Dave, my Co-Chair over there,

There's CME information. I'm getting the signal that we don't need to review it again. Just make sure if you want the CMEs to follow the directions. Otherwise, thank you all for joining us here and stay tuned for the second webinar in the series. Bye-bye.

This is Andy. I'd just like thank all of the folks who worked on the Guidelines and the staff and leaders at the RTMCC who helped make this possible. CDC is quite grateful.

Thank you.

Thanks, guys, bye.