Thank you. I was a little worried that Dr. Senior was going to say that I met him in 1974. I’m trying to remember how old I was then. (Laughter.) But I want to thank him for inviting me to participate in this meeting.

I am a medical oncologist. And so, my whole world kind of revolves around, when you talk about drugs, it is always oncology drugs. I just want you to have some perspective of where I am coming from.

How many people here actually know what CTCAE is? (Show of hands.) So, I will probably go through a little more in detail. CTCAE is a document that primarily is used to assess adverse events in terms of drug development. The Cancer Therapy Evaluation Program of the NCI in 1983 developed this in order to kind of cross the multiple trials that they were supporting to have more uniformity in terms of adverse events that were coming in.

Because if we just left it up to everybody, somebody who is bleeding, could come in as low platelet counts, thrombocytopenia, molar suppression, different terms. And so, in order to have some uniformity, we developed a guide in terms of the common nomenclature and how these adverse events need to be reported. That has been revised three times now. Version 4 was released in 2009. With that there was a huge change in the CTCAE. Up until then, our adverse event terms were done independent of any documents. From what we have seen in our reporting by our investigators, we have picked up those terms and have listed them under categories.
But we then realized that a lot of the pharmaceutical companies were doing their adverse event reporting to both the EMA and the FDA using MedDRA. So, we got involved with MedDRA around 2008 and started to change all the CTCAE terms to MedDRA terms. We are hoping that that allows it to be a document that is easier for people to use, especially as everything becomes more electronic. The categories become System Organ Classes (SOCs), so that where these AE terms come in is determined by MedDRA to some extent. And I have to admit that we have gotten some of the comments since the release of 4 wanting to know where to find these terms from people who were not accustomed to MedDRA and didn't understand why certain terms are put under various SOCs.

Also, when we released in May of 2009 CTEP, then, systematically, they support thousands of trials. They systematically start to convert all our trial reporting to CTCAE Version 4. Now this is not true for all the trials out there because some of the PhRMA-sponsored trials continue to use older versions, but we couldn't support Version 2, 3, and 4. So, we have just made a decision to actually convert all the trials, as of September of 2010, to use CTCAE Version 4.

There was also a core group that was developed at that time to allow us to continue to look at the comments that came in for CTCAE Version 4 to see if there were any mistakes that were made or in terms of when we need to come up with a new revision.
So, these are the SOCs, the System Organ Classes of the MedDRA terms in which we have placed the CTCAE adverse events for Version 4. This is kind of what the document looks like.
I just selected the hepatobiliary disorders. You have the adverse event, and then, there are five grades. That is one of the reasons both companies used the MedDRA term for reporting as well as CTCAE, because this does provide grading.

<table>
<thead>
<tr>
<th>Hepatobiliary disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>1</td>
</tr>
<tr>
<td>Bile duct stenosis</td>
<td>Asymptomatic; clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Definition</td>
<td>A disorder characterized by a narrowing of the lumen of the bile duct.</td>
</tr>
<tr>
<td>Biliary fistula</td>
<td>-</td>
</tr>
<tr>
<td>Definition</td>
<td>A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.</td>
</tr>
<tr>
<td>Cholezystitis</td>
<td>-</td>
</tr>
<tr>
<td>Definition</td>
<td>A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.</td>
</tr>
<tr>
<td>Gallbladder fistula</td>
<td>Asymptomatic clinical or diagnostic observations only; intervention not indicated</td>
</tr>
<tr>
<td>Definition</td>
<td>A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site.</td>
</tr>
</tbody>
</table>
How the grading occurs, Grade 1 is usually asymptomatic, something that is just found because you did a test. Usually no intervention is required.

Grade 2 is usually there is some intervention that is required, does not require hospitalization. Usually, Grade 2 in most of the trials for therapeutic, not so much in the prevention setting, for Grade 2 we do not change the doses.

Grade 3, the big difference between Grade 2 and Grade 3 is that for Grade 3 a lot of times it requires stopping the drug or clinical trial. And so, when we did 4, we try to keep that in mind as we come up with the criteria for Grade 2 and Grade 3 toxicity. Grade 3 usually requires hospitalization, IV, or some type of surgical intervention. Grade 4 is immediately life-threatening, and then, Grade 5 is death.

So, this is just to go through the process in terms of how we are going to go about with coming out with Version 5. And so, we had monitored the comments. There was a help desk email since Version 4 was released, and we have taken all the comments and went through them. We have a contractor to assist us in terms of managing all these comments that came in; personal communications from our investigators as well as investigators within CTEP, as they are looking at these adverse events coming in, if there are ones that really are difficult or the grading, there is any problems with them.

The core group has met as needed for these comments, and we have reviewed the impact. So, one of the things we did in April of last year was we released the draft version for public comments. I'm sorry. Actually, we have let everybody know that we were going to revise CTCAE Version 4 and asked for public comments.

And we got a lot of comments, which delayed the Version 5 release, because we had to process all those comments. How we went about these comments is that we looked at, especially if there are new AEs that they want to add, we wanted to know how frequently it was actually reported. Usually, those will be reported as "other".

So, under CTCAE, each of the categories or the SOC, there is an "other". So, if there is not an appropriate term for a certain adverse event, they can report it under "other," and we have pulled all those up to see if any of them occur frequently enough for us to add as a new event. There has been some confusion in terms of grading, and we try to clarify that. One of the ones is that, for creatine, actually, Grade 1 is anything above baseline. As you know, if you measure your creatinine today and tomorrow, probably half of you will be above what you were yesterday. Unfortunately, nobody actually picked it up until this year, but we will be changing that.

Clinical significance. As to how we manage adverse events and new drugs come out to manage some of our adverse events, the grading sometimes has to be modified because we manage our adverse events better.

The last thing is that any new term has to be a MedDRA term. We have consulted with our Working Group members from Version 4. We actually had a Working Group for each of the SOCs, including experts within that area, to help us in terms of managing and making sure the terms are appropriate in terms of the grading and management of the adverse events, NIH members and academic experts.
So, what is not going to change for Version 5 is that the SOC and the term placement within the SOC stays the same. That is still driven by MedDRA. They are all going to be MedDRA terms. We are still going to stick with five gradings. The guideline for each of the grades does not change. There is no deletion of any AE term. So, one of the concerns is that, if we delete a term and a study takes longer than nine years to do, then that adverse event does not have anywhere to go when the study is reported. So, we are not planning to delete any of the AE terms that are currently in 4.

In the past when we have changed our AE terms between 2 and 3 and 3 and 4, we have produced a mapping document to lead people from one adverse event to another, or if we change any grades, but we are not planning to provide a mapping document this time because they are all MedDRA terms. So, we are planning to delete any terms.

We have a lot of comments for the use of upper limit of normal or lower limit of normal for these lag values. We are planning to keep that because of, I think, some of the things that were discussed this morning.

There is no uniformity in terms of you know, for a white count or WBC or ANC, there are set values that everybody uses in terms of managing toxicity. For AST/ALT there is really no set values right now. It is set by the labs. And so, we are going to keep the ULN and LLN.
What may change in CTCAE Version 5 or what will change is that we have new AE terms added at the recommendations of the public, clarification of certain definitions, add or clarify and change in grading, some editorial changes that were never picked up, despite multiple layers of review.

We are also going to add navigational notes. That was taken out in 4. In 3, those of you that used it, there were things that said, "also consideration" to help in terms of managing different similar AEs, and we are to report them. So, we are, for like ALT, which I will show a little later, we are planning to have a navigational note in terms of considering hepatic failure. We are also going to provide an index so people know where to find these terms.

Though currently CTCAE is online and it is an Excel spreadsheet, so that you could actually use a Find function to search any AEs.
So, just examples of new AEs: disease progression was done; it is not an adverse event, but it is added so that it is helpful in terms of tracking. Some of the hepatitis B reactivation will be added as an adverse event because of some of the immunotherapy agents that are out there. Budd-Chiari syndrome will also be added as a new term.
Examples of changed or revised definitions

• Spleen Disorder
  – An disorder abnormality of the spleen

• Diarrhea
  – A disorder characterized by an increase in frequency and/or loose or watery bowel movements

• Peripheral sensory/motor neuropathy
  – A disorder characterized by damage or dysfunction of the peripheral sensory/motor nerves

What will be changed in terms of definition? None of these really are in terms of the DILI, but if there is any in terms of the definitions that you felt needs to be changed, please let me know.
Examples of added and changed grades

• Grade 4 myositis
• Grade 1 Capillary Leak Syndrome
• Death Neonatal
  – Change grade 5 to grade 4 so patient could continue on study

Added or changed grades, the biggest one is actually the last one. So, neonatal death, because it was a death, it was listed as Grade 5. The problem is the patient is still alive, and the computer system does not allow patients to go forth in terms of further treatment. So, we are going to change neonatal death into a Grade 4, so that patients can continue on treatment, if needed.
Grade clarifications. We added various things to clarify some of the adverse events.

Examples of grade clarifications

- Allergic reaction added bronchospasm to grade 3
- Proteinuria add 3+ proteinuria to grade 2 and 4+ proteinuria to grade 3
- Sleep Apnea clarify associated with “pulmonary” hypertension
- Diarrhea added limiting instrumental ADL to grade 2
- Seizure added “new onset seizures (partial or generalized)” to grade 3
And then, navigational notes. If you will look at the yellow part, the AST, ALT, and bilirubin, we are going to add a navigational note to those because those are lab values and only use specific numbers.

**Examples of Navigational Notes**

- **Direct to a more definitive AE term**
  - Under Enterocolitis directed to consider Colitis if site of abnormality known

- **Direct to a different AE**

- **Direct to include another AE**
  - AST, ALT, Bilirubin: Consider also reporting Hepatic failure if appropriate

- **Death NOS, Sudden Death or Disease Progression**
  - If death is due to a specific AE, report as grade 5 under that AE
We are asking that you also consider hepatic failure, if appropriate, for reporting. So, these are the adverse events in CTCAE Version 4, and the yellow ones will be added to 5.
I just wanted to talk about the investigational SOCs. So, a lot of the first sign in terms of any adverse event is laboratory values. Unfortunately, it doesn’t always reflect what is going on in the patient if you use an absolute value. However, that is a way that is common and easy for us to assess for these.
CTCAE v4: Hepatic Toxicities
Investigational SOC

- Activated PTT, INR increased,
- ALT, AST, Alk Phos, GGT increased
- Blood bilirubin
- Fibrinogen decreased
- Haptoglobin decreased

So, everything that is an investigational SOC is predominantly driven by numbers. Usually, we use upper limit of normal because of lack of a standard value, but we selected for the ALT is greater than three times upper limit of normal.
After discussion today, actually, one of the considerations is if we should consider a change from baseline as well. If you note, there is no Grade 5 in that we don't think anybody can die from a laboratory value. They die from a medical condition. So, we want them actually to report the Grade 5 under the actual condition in which the patient's death had occurred.
So, just areas of consideration for our discussion for today, alkaline phosphatase, though there is a Grade 3 and Grade 4, because Grade 3 and Grade 4 is very important in terms of some of the oncology trials for stopping patients' drugs, we actually would like to change those to just Grade 2, because anything above that that leads to hospitalization or immediately life-threatening should really be reported under the actual medical condition. GGT is the same thing. We are proposing to convert the pure values, everything down to Grade 2. And then, for everything above that, to actually be reported under the medical condition.

And the question is if we should consider that for both AST/ALT, and I guess for bilirubin. I would certainly love to hear your thoughts in terms of that. Any other AEs that we need to include. With recent use of immunotherapy as well as some of the targeted agents, there have been new adverse events, and we want to make sure we include those new AEs as they come up. And then, any other CTCAE changes that would assist in better assessment of DILI.
The CTCAE, the link is to Version 4. And then, I guess the last actually also has the email address in terms of if there are any comments. Thank you.