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11 there's a subsequent question to get a more  
12 precise estimate of what your actual score is.  
13 But there are also single items, it's, you  
14 know, really flexible. There are adult and  
15 pediatric versions. It does extremely well in  
16 all of your question one categories. It's  
17 being used in two CAR T trials currently. It's  
18 been used in many studies in the 65 and older  
19 population as you can see above. Its measuring  
20 properties really have been pristinely tested.  
21 It also does extremely well in your question  
22 two items really across the board. Again, you  
23 know, I raise that question about age and net  
24 benefit. You know, again, it does have overall  
25 quality of life items in it so I guess, you

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1 know, I would probably say yes, depending on  
2 how you interpret that.  
3 You know, the real limitation here is  
4 that there are only a small number of domains  
5 that you can measure with PROMIS, and so if you  
6 want, you know, a wider number of things to be  
7 measured in a trial, you're going to need

8 PROMIS plus something else, but for what it  
9 measures, it really is excellent, in my  
10 opinion.

11 The ESRA, I was asked to comment on as  
12 well. This really is not well known. As  
13 alluded to in Katherine's presentation, this is  
14 really not a well-known tool. I'm sorry, this  
15 is not a PRO measure, it's an electronic  
16 questionnaire system, so it's not really a PRO.  
17 It happens to include three PRO measures in it,  
18 the QLQ-C30 which you've heard about, the PHQ-9  
19 which we haven't talked about, which is  
20 actually an excellent measure of psychosocial  
21 distress, anxiety, depression, which is  
22 commonly used to assess depression, and the  
23 Symptom Distress Scale, with is really kind of  
24 a lesser used symptom scale. It's not really  
25 been well tested, it's been very few trials

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1 and, you know, because it's been used so  
2 seldom, because it's not a PRO, I didn't even  
3 go into evaluating it for questions one and  
4 two, it wouldn't do well because it just hasn't  
5 been tested in that way. To me it's not

6 applicable to these questions.

7       The FLIC, this is a PRO tool but also  
8 not really well known, it's an old measure. It  
9 had 22 items, it has physical, emotional,  
10 social function, well-being, pain and nausea.  
11 We could actually only find one cancer trial  
12 using this tool, so really not well traveled in  
13 the oncology space. And so again, we really  
14 didn't really go through the 1.A -- I'm sorry,  
15 the questions for one and two for this, because  
16 there's just no data to evaluate, it really  
17 wouldn't perform well, again, in our opinion.

18       This graphic unfortunately, didn't  
19 come over well when conveyed to CMS. It may  
20 have come over better in the size it was  
21 printed, or maybe it was censored.

22       (Laughter.)

23       The double question marks from me were  
24 smiley faces and the other ones were sad faces,  
25 but maybe CMS felt they should be a little

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1 milder. But in our opinion, the ones with  
2 these double question marks are tools that are  
3 well established, well tested and perform well,



4 and if I were designing a trial, with the  
5 caveats that Paul mentioned in his FDA  
6 presentation, we want to make sure that the  
7 tools are appropriate to the domains of  
8 interest. These are tools that I would be  
9 comfortable considering, but the frowning  
10 faces, not so much.

11 All right. So just in the last  
12 four-and-a-half minutes before I finish up,  
13 there are some additional questions to the  
14 panel. Are there other PRO assessments to  
15 consider? I would say yes. One in particular  
16 that I'd like to highlight called the FACT  
17 GP-5, and this is a single item that asks  
18 people if they are bothered by the side effects  
19 of their treatment. This is a global  
20 assessment of side effect burden. This is a  
21 very helpful companion to the PRO-CTCAE, right?  
22 Just to remind you, the PRO-CTCAE is the tool  
23 where patients answer individual items about  
24 their individual symptom side effects, right?  
25 Do you have sleep disturbance? Do you have

1 taste disturbance? Do you have myalgia? This

2 is a global to go along with it. This is a  
3 five-point response scale, it's well developed,  
4 there's broad interest in using this, it's been  
5 alluded to in numerous past FDA and EMA  
6 presentations.

7 Are there additional desired  
8 characteristics besides those in question two?  
9 Yes, I think so. First the general, what we  
10 call measurement properties, all these things  
11 that Dr. Atkinson and I actually commented on  
12 in our responses to you, content validity,  
13 construct validity, reliability, sensitivity or  
14 responsiveness, these are really key measuring  
15 properties of an assessment tool, and really  
16 both need to have been tested and demonstrated  
17 to perform well for a good tool.

18 Prior testing in populations with  
19 cancer. The availability of language  
20 translations, this is essential not just in the  
21 U.S., but particularly outside the U.S. for  
22 international trials. And then, you know, I'd  
23 say really importantly, does this include items  
24 that are salient to the CAR T population?  
25 There really needs to be evaluation in this

1 population, probably qualitative with  
2 interviews, asking patients about what's going  
3 on with them very broadly so that we can  
4 understand what are the outcomes that are  
5 salient to this population, so we can then say  
6 is this the right PRO instrument to use?

7       And this is really on the sponsors,  
8 right? The sponsors spend a lot of money  
9 developing their measurement tools, conducting  
10 these trials. This is an essential part of  
11 understanding the patients' experience. The  
12 sponsors should be going out to patients in  
13 their trials asking what they're experiencing  
14 so they can substantiate the PRO metrics in  
15 their trials and particularly in their  
16 registries. I think in the real world, not  
17 just in the registration trials, this  
18 information needs to be collected.

19       All right. In conclusion,  
20 patient-reported outcomes provide valuable  
21 information about the patient experience and  
22 about the characteristics of products that  
23 cannot be well captured in any other way.  
24 There are well developed available  
25 patient-reported outcome tools that can be used

1 readily in CAR T trials that could be used  
2 tomorrow. Yes, we can do more work to hone it  
3 down, to get more specific to figure out what  
4 exactly would be best to measure, but these  
5 tools are shelf ready in many cases, but we  
6 should do further work to really hone down and  
7 understand what are the outcomes of interest.

8       Assessment of physical function,  
9 symptomatic adverse events and disease-related  
10 symptoms should be considered in any given  
11 trial of oncology, including in this  
12 population. Thank you very much.

13       DR. ROSS: Great, thank you,  
14 Dr. Basch, right on time, and to Dr. Atkinson  
15 for his support of this presentation.

16       So now we are turning from our, to the  
17 scheduled public comments portion of our  
18 meeting. Each speaker will be given six  
19 minutes to speak and we have one, two, three,  
20 four, five, six speakers, because one was  
21 unable to attend. And we are, as each speaker  
22 comes to the podium, I ask that the next  
23 speaker comes to the chair to keep us moving  
24 efficiently, and just as a reminder, to

1 conflicts of interests. And our first speaker

2 is Dr. Kathryn Flynn.

3 DR. FLYNN: Hi. So, just a note that

4 we submitted slides before we knew how long we

5 would have to talk, so I will be skipping over

6 some slides, but they are all available of

7 course online. So yes, I am Kathryn Flynn, I'm

8 an associate professor of medicine at the

9 Medical College of Wisconsin, and I am also as

10 of November last year, now senior scientific

11 director for patient-reported outcomes at the

12 Center for International Blood and Marrow

13 Transplant Research, the CIBMTR. So I am here

14 representing the CIBMTR, CIBMTR paid for my

15 travel to attend the meeting. I don't have any

16 personal financial disclosures related to

17 CAR T, but CIBMTR as an organization receives

18 federal funding from NIH, HRSA and the Navy,

19 and as you heard earlier today, has a cell

20 therapy registry contract with Kite.

21 So CIBMTR, for those of you who aren't

22 aware, collects and maintains clinical outcomes

23 data on all allogeneic transplants as required  
24 by U.S. law. The centers also voluntarily  
25 submit data on auto transplants, and worldwide

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1 centers additionally submit data voluntarily.  
2 So related to blood and marrow transplant  
3 research, we, the registry has information on  
4 nearly a half million, 475,000 patients that  
5 are included in the database.

6 And we are now in the process of  
7 implementing an e-PRO system that will be  
8 available for use by the registry and the  
9 affiliated trials network, the BMT CTN. So, I  
10 will skip this one if I can. No. There we go.

11 So we looked last year at the BMT CTN  
12 studies that have collected PROs, and in 18  
13 trials performed since 2004, half of those had  
14 included as a primary or secondary outcome a  
15 patient-reported outcome measure. Many  
16 different measures have been used in these  
17 studies, most commonly the SF-36 and FACT-BMT.  
18 But we were looking to make some  
19 recommendations going forward and thinking  
20 about the implementation of this e-PRO system,

21 of what to recommend and so -- I'm having  
22 trouble with this. I have to press it really  
23 hard, I guess. Okay.

24 So we had a couple of recommendations,  
25 first to use the same core measures in all

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1 research studies of HCT patients, use a system  
2 that's free and easy to access, try to ensure a  
3 low burden for the patient who's of course  
4 undergoing a difficult treatment, using a  
5 single versatile measurement system for core  
6 concepts supplemented with additional measures  
7 as necessary. And so thinking about the  
8 registry context, the core system that was  
9 recommended in this article by Brown and Shaw  
10 was PROMIS. Even pressing really hard, I'm  
11 having some difficulty there. Okay. I don't  
12 know if it needs new batteries potentially.

13 DR. ROSS: Don't worry, you can have  
14 another minute.

15 DR. FLYNN: Okay, thank you.

16 So we've already hear about PROMIS,  
17 I'm not going to go into detail there, but it  
18 met those recommendations that we were hoping

19 for. Okay.

20       So just to reiterate a point just made  
21 in the last talk, really the most appropriate  
22 PROs to collect in cell therapy are unknown, so  
23 there really is some foundational qualitative  
24 work that needs to be done. We can probably  
25 make some good guesses about some of the

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1 domains that will be, that will need to be  
2 measured, but to get into more specifics, there  
3 does need to be some additional work done, I  
4 think. However, once relevant constructs are  
5 identified, there are absolutely multiple  
6 available high quality measures that can be  
7 used, and can choose the appropriate measures  
8 and time points at that time.

9       Centers need a structure and process  
10 to systematically collect PROs, and so what I'm  
11 going to do with my remaining couple minutes  
12 here is just describe the components of our  
13 CIBMTR e-PRO system. So as you can see here,  
14 the e-PRO system is the integration of  
15 electronic patient-reported outcome collection  
16 with our existing systems for collecting other



17 information, clinical information. So in the  
18 bottom right we use Salesforce to track our  
19 studies, participants, time points, activities.  
20 At the bottom left is our integrated data  
21 warehouse where the clinical outcomes data from  
22 multiple sources are stored for research  
23 retrieval. Top left as I mentioned, we did  
24 identify PROMIS measures as that core system,  
25 but certainly other measures can be added as

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1 necessary, and so certainly for some of the  
2 trials within the BMT CTN already we're adding  
3 items from the PRO-CTCAE for those specific  
4 studies.

5 And then to the right, note that we're  
6 using Qualtrics as the patient interface for  
7 administering patient-reported outcomes, so a  
8 very flexible user friendly system for patients  
9 to complete those PROs.

10 So, this system was developed with  
11 funding from the Navy grant, our partner, the  
12 National Marrow Donor Program, and our pilot  
13 e-PRO study just started this summer. It is a  
14 six-site pilot trial where we're examining

15 quality of life and PROMIS measures in patients  
16 as part of the CMS MDS study. This is just  
17 cross-sectional to explore the use of our  
18 system, but certainly longitudinal studies will  
19 be feasible as well.

20       There is, just a note here, this is  
21 just a brief overview of kind of the study  
22 procedures, but to note that significant  
23 planning and effort is required to manage this  
24 central coordination of multisite PRO data  
25 collection in terms of following patients at

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1 multiple sites and getting their, you know,  
2 being able to contact them directly, when  
3 previously through the registry they are only  
4 contacted by their local center, and so for the  
5 CIBMTR directly to contact them is new.

6       And then the last thing I wanted to  
7 mention is related to this. We've recently  
8 organized a multidisciplinary working group of  
9 about 30 or so people with expertise in many  
10 different fields as part of a late effects task  
11 force. And again, this is in the context of  
12 BMT, but our goal is to develop a strategy for

13 the collection of late effects in patients that  
14 are reported to the CIBMTR. So of course it's  
15 a very heterogeneous population who's receiving  
16 transplants, and so focusing on which  
17 populations we should focus on to get kind of  
18 routine PRO collection, what domains we need to  
19 focus on, what measures to use, what time  
20 points, these are all questions that we're  
21 answering within the context of this task  
22 force, and we have a nine-month time frame, we  
23 started this summer and we're going to present  
24 our recommendations at the Transplant and  
25 Cellular Therapy conference which, in February

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1 of 2019. That's it.

2 DR. ROSS: Thank you. Right on time.

3 Our next speaker is Karen Chung, the senior

4 director of health economics and outcomes

5 research for Juno Therapeutics.

6 DR. CHUNG: Good morning, everyone.

7 Again, my name is Karen Chung, senior director

8 of health economics and outcomes research at

9 Juno Celgene. I have been involved in

10 patient-reported outcome strategy analysis,

11 communication, for over 15 years in the  
12 pharmaceutical industry, and I'm currently  
13 employed by Juno Celgene and do have stock  
14 options with them as well as other companies.

15 Celgene is developing investigational  
16 CAR T-cell products which are not FDA approved,  
17 and any data we discuss today is subject to  
18 change. CAR T-cell agents are novel agents  
19 which fulfill an unmet need in patients who  
20 have not responded to front line therapy,  
21 including Medicare patients. They have limited  
22 effective treatment options as well as limited  
23 survival. CAR T-cell therapies have been  
24 administered across sites of care and as novel  
25 therapies have a long-term follow-up to

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1 continually assess efficacy as well as safety.  
2 And while AEs are specific to each CAR T-cell  
3 therapy, AEs are being increasingly identified  
4 very quickly and managed very efficiently. And  
5 while PRO measurement is important as it  
6 represents the patient voids, it is very  
7 complex from the clinical trial perspective and  
8 even more so from the clinical practice

9 perspective.

10 Celgene is developing two CAR T  
11 therapies which have the potential to  
12 significantly transform patient outcomes.  
13 JCAR017 is a CD19-directed CAR T-cell therapy  
14 for non-Hodgkin's lymphoma. bb2121 is a B-cell  
15 maturation antigen-directed CAR T-cell which is  
16 currently in clinical trials for multiple  
17 myeloma, and the other was for non-Hodgkin's  
18 lymphoma. Each CAR T-cell therapy has a unique  
19 targeted patient population, safety profile and  
20 manufacturing process. As the science of CAR T  
21 is rapidly evolving, we urge CMS to provide  
22 flexibility to consistently ensure patient  
23 access across all these disease states.

24 While we strongly support the  
25 incorporation of the patient voice into

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1 clinical trials, we firmly believe PROs should  
2 not be a condition of coverage due to the  
3 significant barriers in the clinical practice.

4 And again, while we don't think PROs  
5 are appropriate for coverage, we did want to  
6 take a look at the question that CMS had asked

7 the panel to consider, and of the seven  
8 instruments that were delineated, we feel that  
9 four of the seven instruments could be  
10 appropriate for clinical trials involving the  
11 Medicare population.

12 The first is the PRO-CTCAE which  
13 Dr. Basch has mentioned. It does cover a wide  
14 range of symptoms and so for symptom  
15 assessment, it is a very useful tool.

16 The MDASI, or M.D. Anderson Symptom  
17 Inventory, covers a wide range of symptoms.

18 The EORTC-QLQ-C30, which we  
19 implemented in the JCAR017 and bb2121 trials,  
20 is a comprehensive instrument that assesses  
21 symptoms, functioning, as well as  
22 health-related quality of life.

23 The last instrument is PROMIS, which  
24 is basically an item bank, which also covers  
25 various symptoms as well as functioning.

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1 This next question is really  
2 considering all these instruments together, and  
3 together, we feel that they have to have the  
4 breadth of measurement specifically in

5 emotional, physical as well as social  
6 well-being. They can be applied and have been  
7 applied to clinical studies and can be used in  
8 the clinical practice setting as well.

9 We didn't, we felt that they were  
10 sensitive to differences in age, lines of  
11 therapy, as well as comorbidities, and felt  
12 that they were also generalizable and can be  
13 used in combination therapy trials.

14 From end to end, PRO implementation in  
15 clinical trials involves significant resources  
16 in terms of both budget as well as head count.

17 We need to support instrument selection,  
18 licensing, site training, data collection,  
19 analysis, as well as interpretation. PRO  
20 assessment in clinical practice is typically  
21 even more challenging due to the lack of  
22 infrastructure. Institutional barriers could  
23 include the healthcare provider burden, the  
24 additional FTEs that are necessary to  
25 coordinate administration and data collection,

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1 and the lack of consensus on which is the most  
2 appropriate patient-reported outcome tool to

3 use. And then there's the, following the  
4 scoring, the expertise needed in scoring and  
5 analysis as well as interpretation.  
6 Perhaps even more notably are the  
7 patient barriers, and so we're asking these  
8 Medicare patients who are typically very sick,  
9 third line and beyond, to respond to these  
10 questionnaires. They may have poor performance  
11 status and they may also face technology  
12 barriers as we move to more electronic  
13 platforms to collect this data, so it's  
14 something that they might not have the  
15 experience to really manage to do well.

16 So while patient-reported outcomes are  
17 key measures in hematology and oncology trials,  
18 including the CAR T-cell therapies, there are  
19 important considerations, which includes the  
20 wide range of tumor types and stages, also the  
21 broad areas of concepts. You know, are we  
22 interested in physical functioning,  
23 disease-related symptoms, adverse events, or  
24 health-related quality of life, you know, which  
25 do we focus on. And due to the diverse nature



1 and range of symptoms across and within tumor  
2 types, as well as the administrative burden,  
3 assessing patient-reported outcomes with  
4 validated instruments is complex.

5 Celgene has incorporated relevant PRO  
6 assessments in CAR T-cell clinical trials to  
7 complement clinical safety and efficacy data,  
8 which we feel is very important. However,  
9 while we feel it's very important in the  
10 clinical trial setting, we don't feel they  
11 should be a condition of coverage.

12 DR. ROSS: Great, thank you very much.

13 DR. CHUNG: Thank you.

14 DR. ROSS: Our next speaker is  
15 Dr. Surbhi Sidana, from the Mayo Clinic.

16 DR. SIDANA: Good morning and thank  
17 you for this opportunity. I am a  
18 hematologist/oncologist and I am not a PRO  
19 expert, but I'm leading two studies of PROs,  
20 including one of CAR T, and I just want to  
21 speak to the panel of the challenges we have  
22 faced in trying to design and lead the study.  
23 So, here are my disclosures, and ASBMT is  
24 paying for my travel to this meeting.

25 This data has already been shown so I

1 will not belabor this data anymore. However,  
2 CAR T-cell therapy is a novel therapy which has  
3 shown exceeding promise in patients who did not  
4 have other treatment options before. It has  
5 unique side effects, and some of the side  
6 effects we are not even aware about in the long  
7 term.

8       There is, the process for assessing  
9 PROs has already been discussed in detail and  
10 so I want to focus on the approaches of  
11 assessing PRO in patients with CAR T-cell  
12 therapy. We have conducted several studies in  
13 the last couple of years in hematology which  
14 have used various methods of assessing PROs.  
15 So let's focus on the challenges of conducting  
16 the study, and this is from my personal  
17 experience in conducting the study.

18       So what is an optimal outcome that we  
19 should use and what instruments should we be  
20 using? Seven instruments are being asked, you  
21 know, you're rating seven instruments today.  
22 In my study I'm using a completely different  
23 instrument because on my clinical judgment I  
24 thought that was a better instrument, along  
25 with some of the instruments we're reviewing

1 today. So even though we have validated  
2 instruments, not everybody agrees that those  
3 instruments should be the same in different  
4 studies.

5       Second, how do we account for missing  
6 data? A lot of patients who are undergoing  
7 CAR T-cell therapy will have side effects, get  
8 in to the ICU, and these patients potentially  
9 will have significant missing data leading to  
10 bias. A lot of times patients come to referral  
11 centers like Mayo Clinic for their treatment,  
12 and then they go back to their local doctor.  
13 So if we are going to use long-term data, we  
14 might miss patients who are now gone from the  
15 referral center.

16       And then the third thing, do we just  
17 collect this data or do we do something about  
18 it? As a doctor it's challenging. You're  
19 asking patients to give their symptoms and then  
20 you feel you're ethically obliged to do that,  
21 this also keeps the patients engaged. However,  
22 there are problems with that. It requires a  
23 huge infrastructure. It also requires

24 consensus to say when are we going to  
25 intervene. For example, if you ask a patient

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1 for pain, do we intervene for a pain at seven  
2 out of ten, eight out of ten or nine out of  
3 ten? Is seven different than eight? And  
4 similarly for other symptoms as well. That  
5 will also require a lot of resources that  
6 centers and the community will not have  
7 present.

8       The other thing that is challenging,  
9 we want to assess how is the patient's quality  
10 of life in respect to the side effects they  
11 experienced initially, and that's problematic  
12 because right now all the different CAR T  
13 trials are assessing toxicity differently,  
14 Grade 3 CRS in one trial is not the same as  
15 Grade 3 CRS in another trial. The management  
16 of toxicities at my institution is very  
17 different from management of toxicities at  
18 another institution, so this is going to impact  
19 how we interpret this data and what this data  
20 means.

21       And then as many people have already

22 alluded, CAR T-cell studies are currently being  
23 conducted in various hematologic and oncologic  
24 malignancies and currently are approved for two  
25 diseases, ALL as well as non-Hodgkin's

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1 lymphoma. We expect that soon they will be  
2 approved for other diseases like multiple  
3 myeloma, and the short-term toxicity has really  
4 varied across different trials based on what  
5 instrument, what construct and what disease.  
6 For example, a lot more CRS was seen in  
7 non-Hodgkin's lymphoma than was seen in  
8 multiple myeloma, so how can we put all of  
9 these patients together with different diseases  
10 which have different symptoms, different  
11 constructs, and say we're going to measure all  
12 of these the same?

13       And then, what is our benchmark? As  
14 has been shown before, these patients with  
15 non-Hodgkin's lymphoma previously did not have  
16 many treatment options, their median survival  
17 was six months, and now it's not being reached.  
18 So how do we decide what's reasonable quality  
19 of life or what's reasonable physical function

20 in these patients? How do we compare them to  
21 historical controls or even how do we compare  
22 them to their baseline what is reasonable?

23       So I think there's a lot of room for  
24 study at this point. We are conducting pilot  
25 studies at my institution and several other

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1 institutions to address what's the feasibility,  
2 where is the missing data, how can we do this  
3 better, and do we need specific measures  
4 specific to CAR T-cell therapy? And then in  
5 the context of a working group, we need to come  
6 up with a consensus before we design a  
7 larger-scale study. I think at present we need  
8 at least 12 months to come up with a consensus  
9 based on preliminary data from our study and  
10 the studies being done at other institutions.

11 Thank you.

12       DR. ROSS: Thank you, Dr. Sidana. Our  
13 next speaker is Dr. Cori Abikoff, the medical  
14 director for CAR T at Novartis.

15       DR. ABIKOFF: Thank you very much for  
16 allowing me to speak today. I'm Cori Abikoff,  
17 I'm a medical director for the CAR T program at

18 Novartis Pharmaceuticals Institution. My  
19 expertise is in pediatric stem cell transplant  
20 as well as adult and pediatric apheresis. I am  
21 a paid employee of Novartis.

22 Kymriah, the Novartis CAR T product,  
23 is the first FDA-approved gene therapy product  
24 on the market. It is currently approved in two  
25 indications, both pediatric and young adult

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1 relapsed or refractory ALL, as well as adult  
2 relapsed or refractory large B-cell lymphoma.  
3 It's been extensively studied in clinical  
4 trials, both for validated clinical outcomes as  
5 well as PRO data, as was previously presented  
6 by my colleague, Dr. Ilia Ferrusi. It also  
7 continues to be studied in the outpatient, in  
8 the commercial setting under a risk evaluation  
9 and mitigation strategy.

10 As was previously discussed, chimeric  
11 antigen receptor therapies essentially are a  
12 living drug, which allows the patient's tumor  
13 to be targeted by the patient's own immune  
14 system through a process of gene modification.  
15 This is a complex process that requires that

16 the patient's own immune cells be removed, gene  
17 modified, and returned to the patient in a  
18 setting which has a degree of complexity that  
19 means that the timeline must be observed due to  
20 the significant burden of illness in these  
21 patients.

22       Novartis has chosen to study a  
23 population of patients who have significant  
24 burden of illness. Although pediatric ALL is  
25 not a common condition, it is the most common

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1 cancer of childhood, and relapsed and  
2 refractory ALL represents the most common cause  
3 of childhood cancer death, falling only behind  
4 accidental injuries and inflicted injury,  
5 whereas diffuse large B-cell lymphoma is a more  
6 common illness and one that is more likely to  
7 affect the Medicare population.

8       In both cases when the disease is  
9 relapsed and refractory, there are incredibly  
10 limited treatment options, and these usually  
11 require incredibly toxic therapies that in  
12 order to reach standard of care with even  
13 acceptable outcomes requires the use of a stem



14 cell transplant.

15 In the JULIET trial where we treated  
16 patients with diffuse large B-cell lymphoma,  
17 you can see that approximately a quarter of our  
18 patients were over the age of 65 and these  
19 patients were heavily pretreated, with more  
20 than half of them having received three or more  
21 prior chemotherapies and having been refractory  
22 or relapsed to those therapies, and almost half  
23 of these patients having already received a  
24 standard of care therapy of autologous stem  
25 cell transplant.

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1 Unlike the data that's previously been  
2 shown regarding complete responses as low as  
3 seven percent, the JULIET trial had a best  
4 overall response of 52 percent, complete  
5 response rate of 40 percent. This is really  
6 unheard of in this population. And when we  
7 look across the groups again, you can see that  
8 the patients aged 65 or older had a 59 percent  
9 overall response rate, consistent across all  
10 subgroups with the overall response in our  
11 trial.

12 But more importantly is not just the  
13 response, but the ability of these responses to  
14 be sustained, and you can see that in patients  
15 who were complete responders, there was a 95  
16 percent overall survival at one year and 78.5  
17 percent of patients were relapse-free during  
18 this time point.

19 In addition because of the living  
20 nature of this drug, patient response is not  
21 determined by their initial response, but in  
22 fact 54 percent of patients will progress from  
23 a partial response to a complete response over  
24 time frames as long as nine to 12 months.

25 These are not benign therapies, and

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1 certainly we acknowledge the adverse events  
2 that need to be followed. Here in the JULIET  
3 trial you can see that adverse events greater  
4 than, at Grade 3 or higher, included 23 percent  
5 of patients with CRS, and 18 percent of  
6 patients with neurological toxicity. We also  
7 evaluated toxicity such as infection, and  
8 longer-term toxicities such as  
9 hypogammaglobulinemia.

10 It is important to understand that  
11 Novartis too has begun collaboration with the  
12 CIBMTR in order to provide a registry which  
13 will follow 2,500 patients, including at least  
14 1,500 patients with diffuse large B-cell  
15 lymphoma, for 15 years after their therapy.  
16 This is in accordance with the FDA guidelines  
17 and includes an incredibly robust amount of  
18 information, including patient-level  
19 characteristics as well as disease  
20 characteristics, and the efficacy and short-  
21 and long-term safety information that can be  
22 followed for these patients. By partnering  
23 with the CIBMTR, we choose a leader in registry  
24 data for cell therapy, and one that all of our  
25 sites are familiar with. By doing so, we

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1 believe this will encourage early and robust  
2 use of this registry data, and encourage and  
3 ensure that the real world data that's  
4 collected really reflects the patient  
5 population who is being treated with Kymriah.  
6 In addition to this by partnering with the  
7 CIBMTR, the data is not only owned by Novartis

8 but it actually belongs, in fact belongs in the  
9 purview of CIBMTR, allowing access to that data  
10 and the analysis sets that can be considered to  
11 be done by CIBMTR and their research networks,  
12 as well as Novartis and health authorities.

13 As a clinician not far out from being  
14 part of the care provided to patients who would  
15 be receiving Kymriah, I am not, the importance  
16 of treating patients and including them in  
17 decisions about their care is not lost on me,  
18 but Novartis does urge CMS to leverage the  
19 existing data as well as the robust mechanisms  
20 for further data collection in order to make  
21 decisions about how best to approach payment  
22 decisions. Thank you.

23 DR. ROSS: Thank you, Dr. Abikoff.  
24 The next speaker is Dr. Merav Bar, assistant  
25 member of the Fred Hutchinson Cancer Research

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1 Center.

2 DR. BAR: I am Merav Bar, I'm an  
3 assistant member at the Fred Hutch in Seattle  
4 and I'm a transplanter, and I also take care of  
5 patients after CAR T-cell therapy, and I'm also

6 part of the long-term follow-up team for  
7 patients after transplant, and we are now  
8 building also our long-term follow-up for  
9 patients after receiving CAR T-cell therapy.  
10 And today I'm mainly focused on question number  
11 four regarding timing of evaluations of PROs in  
12 patients after CAR T-cell therapy and mainly  
13 for the long-term follow-up of those patients.

14 My disclosure, I have no personal  
15 financial or intellectual conflicts of  
16 interest. However, I just learned after I  
17 submitted this slide that a member of my family  
18 has shares in Bluebird.

19 For long-term follow-up of patients  
20 after CAR T-cell, most patients participating  
21 in CAR T-cell studies have been followed only  
22 for a short period of time, most studies for  
23 one or two years after they receive treatment.  
24 And the two commercial CAR T-cell products have  
25 only been approved in the last year by the FDA.

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1 Therefore, the data regarding those patients is  
2 also limited in time. So, currently there is  
3 only limited data regarding the long-term

4 effects of those treatments.  
5 Main concerns regarding long-term  
6 effects of CAR T-cells are prolonged B-cell  
7 aplasia with a hypogammaglobulinemia, acquired  
8 infections secondary to that, subsequent  
9 malignancies, and also new incidence or  
10 exacerbation of neurologic or autoimmune  
11 disorders.

12 There are objectives of a long-term  
13 follow-up after CART T-cells, which are to  
14 identify and mitigate the long-term risks of  
15 patients receiving treatment, and capture  
16 delayed adverse events.

17 There are several challenges in  
18 long-term follow-up of patients after CAR T-cell  
19 therapy. Most of them are the heterogeneous  
20 patient populations, the variety of the  
21 constructs of the CAR T-cells product.

22 Although currently the two approved products  
23 and also for most of the products that are  
24 under investigation target the CD19, in the  
25 future we will see more products with different

1 targets, that they will affect the toxicity and

2 the safety profiles of those products.

3       There is a transition of care of the  
4 patients; most of the patients come to big  
5 centers in order to get the CAR T-cell therapy.  
6 However, after a short period of time of a  
7 month or two they return back to their  
8 referring physician, so it is a challenge to  
9 follow them for the long term.

10       Although there is very good responses  
11 that have been reported with the CAR T-cell  
12 products, there is still a relatively high rate  
13 of relapse of those patients and therefore, the  
14 patients are subsequently exposed to other  
15 treatment which will affect how the patients  
16 are feeling, their quality of life and side  
17 effects that you would see in the long term.  
18 And additionally, patients have multiple  
19 comorbidities that will affect the PROs.

20       And there are also specific challenges  
21 when you are talking long-term quality of life  
22 after CAR T-cell therapy. So for example,  
23 there is no validated instrument for quality of  
24 life and we see that there are different  
25 options that can be used, there is lack of

1 uniformity between centers. So although there  
2 is a number of centers that incorporate PROs  
3 into evaluation of patients after CAR T-cell  
4 therapy, there is no uniformity, and also, we  
5 don't know what optimal study design is.

6 In addition, other people here also  
7 reported about the significant resources that  
8 are indicated, so we need the resources in  
9 order to build the questionnaires into  
10 electronic forms, to follow-up with the  
11 patients after leaving the treatment center  
12 back to their referring physician, and we need  
13 a lot of resources in order to collect the data  
14 and then to analyze the data.

15 In our institution we right now are  
16 studying a pilot study to evaluate a patient  
17 after CAR T-cells and the objective is mainly  
18 feasibility, and we are using mainly the PROMIS  
19 Global Health and PROMIS-29, which have been  
20 validated in the transplant setting. And  
21 currently as I said, there is a variability  
22 between centers and there are only a small  
23 number of studies that are currently ongoing,  
24 and we support a collaborative work group in  
25 order to provide recommendations for the



1 instrument to be used, unify the study design,  
2 harmonization of the data, and potentially  
3 define a multicenter study between  
4 institutions. So currently, we think that  
5 efforts should be made in order to incorporate  
6 the PROs in CAR T-cell studies. However, we  
7 don't feel that PRO should be mandated for  
8 payer reimbursement for CAR T-cell therapies.

9 DR. ROSS: Great, thank you, Dr. Bar.  
10 Just before, I want to confirm that Dr. Heather  
11 Jim is not in the audience because she wasn't  
12 able to get here today. Good.

13 So our last speaker will be Dr. Gunjan  
14 Shah, hematologic oncologist at Sloan  
15 Kettering, who's representing the American  
16 Society for Blood and Marrow Transplantation.

17 DR. SHAH: Hi everyone, thank you for  
18 allowing me to speak with the committee. I am  
19 a bone marrow transplant physician and also  
20 work on cellular therapies, as well as part of  
21 the health-reported outcomes program at MSK,  
22 and I am receiving travel funds today and am  
23 speaking on behalf of our program as well as  
24 the ASBMT.

1 last several hours about what patient-reported  
2 outcomes are and the differences with the  
3 different scales, and we agree with a lot of  
4 the comments already presented.

5 What I'd like to do with my time today  
6 is present to you how we have used several  
7 different scales and changed over time and  
8 incorporated them into different trials, as  
9 well as how we are converting these into a  
10 standard of care approach across our entire  
11 service, as well as for the CAR T-cell  
12 patients, in terms of how to capture these by  
13 paper surveys and our conversion to an  
14 electronic process, and whether we're going to  
15 use them for research and clinical care, and  
16 how that works.

17 So, I present this today just as a  
18 review article that was done in Transplant  
19 looking at 114 studies, and you've learned  
20 today along the way of how many different  
21 patient-reported outcome measures there are,  
22 and why they can be used in different ways, and

- 23 how they do tend to cluster around certain
- 24 symptoms and certain assessments that can be
- 25 used at different times.

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1       On the upper right you can see a  
2 picture of sort of the different subscales of  
3 the MDASI that are disease-based, and what  
4 we've used over the last five to ten years in  
5 many of the transplant trials, specifically the  
6 autologous transplant trials, has been the  
7 MDASI myeloma scale. And what we've been able  
8 to do in that and the reason we use it is it's  
9 been able to be done at several time points  
10 through the first 30 days, and you've seen  
11 today that there are differences in kind of the  
12 scale of early toxicities and sort of later  
13 recovery. And what we've done is been able to  
14 look at changes over time using an area under  
15 the curve method, and so being able to condense  
16 a lot of that information into one data point  
17 that can be compared, especially in  
18 intervention studies where you're really trying  
19 to affect the system burden as opposed to just  
20 collecting some of this information.

21 On the bottom right, you've seen this  
22 already today, is the PRO-CTCAE, and we've  
23 incorporated this into more recent trials and  
24 used the symptom bank in a way to actually  
25 incorporate similar questions to the MDASI to

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1 see if patients really answered the questions  
2 the same way. We also in our long-term  
3 maintenance trials and microbiota trials have  
4 specifically taken out the questions that are  
5 related to diarrhea and constipation and other  
6 GI symptoms, and have been able to correlate  
7 those with the collected stool samples.

8 On the upper left you see the PROMIS  
9 score that's also been described many times  
10 today, and the reason I present this here is  
11 that we are in the process of converting from  
12 the MDASI over to the PROMIS scale to better be  
13 generalizable across centers and as you've  
14 seen, you know, the plans from the CIBMTR and  
15 several other centers that have presented  
16 today, and so in an effort to be able to  
17 combine data, we are switching over to this  
18 scale.

19 The bottom left, you can see sort of  
20 what the paper version of a survey looks like,  
21 and sort of a scale system of this as being a  
22 five-point scale versus some others being  
23 ten-point scales.

24 Our informatics colleagues and  
25 surgical colleagues, using a grant from PCORI,

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1 have converted the MSK system from a paper  
2 format to what they call MSK Engage, or an  
3 online system for collecting some of this  
4 information, and we're going to adopt this over  
5 to the transplant service and cellular  
6 therapies.

7 On the left side you can sort of see a  
8 particular patient's symptoms over time, and  
9 this is going to be available in the clinic,  
10 that you can look at a particular patient,  
11 convert it into their electronic record, and  
12 sort of follow them over time for a particular  
13 patient. Partly this is important because we  
14 are, and our institution has determined that it  
15 is important to act in some way on this  
16 information in real time, and so you can set

17 criteria of if you are above a particular  
18 score, that they will send a message both to  
19 the patient to call the office, but also to the  
20 office practice nurse to call the patient and  
21 determine if further things need to be done  
22 about it.

23 On the right side you can kind of see  
24 information sort of that was presented by other  
25 colleagues today of how do we present that

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1 information and what do we do with it in terms  
2 of both a research and clinical following over  
3 time. And so we have software where you can  
4 aggregate this data across trials, across  
5 patients, and present data in a very  
6 interesting way to be able to look at both  
7 intervention trials, as well as just following  
8 over time.

9 And so we're going to be incorporating  
10 all of this into our proposed new plan going  
11 forward.

12 And so, we know in the CAR T-cell  
13 space that patient-reported outcomes are still  
14 in development and too early to mandate in

15 terms of coverage. However, we do agree that  
16 these are important to capture and study in  
17 both the clinical trial and commercial setting,  
18 which is what we are embarking on as well now,  
19 that we are going to use the PROMIS scale,  
20 PROMIS-29, and do weekly assessments, and  
21 follow that with monthly assessments for the  
22 first year using our electronic system, and be  
23 able to capture whether this is partly feasible  
24 and partly their scale over time.

25 One of the interesting things in this

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1 and part of the discussion in our switching  
2 from MDASI to PROMIS was the time frame of all  
3 of this, that the MDASI scale was in a 24-hour  
4 recall period versus the one-week recall period  
5 of the PROMIS scale. There are sort of pluses  
6 and minuses obviously on both sides of this,  
7 but one of the things that, we think that some  
8 of the missing data can probably be accounted  
9 for by having this every seven day scale, that  
10 there are those days where you were in the ICU  
11 or you weren't able to answer some of the  
12 questionnaires on any sort of every 24-hour

13 scale, but over the last week be able to  
14 aggregate some of that data, and potentially  
15 account for less missing data with that.  
16 The other sort of further along  
17 questions that have been asked by the committee  
18 in terms of timing and feasibility, we do agree  
19 that the three- to six-month window seems to be  
20 the most reasonable option because of the  
21 patients going back as has been described by  
22 other people, and we do think that the use of  
23 technology can allow for more collections over  
24 time, and we look forward to working with CMS  
25 and the rest of the people who have discussed

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1 today about doing this over time. Thank you.  
2 DR. ROSS: Thank you, Dr. Shah. That  
3 concludes our scheduled public comment period.  
4 We have had one individual sign up for  
5 the open public comment period and they have  
6 been told that they will have one minute at  
7 this front mic to make comments, and that is  
8 Mallory O'Connor. Please introduce yourself,  
9 and make sure to disclose your conflicts of  
10 interest.



11 MS. O'CONNOR: Thank you. My name is  
12 Mallory O'Connor, with the Biotechnology  
13 Innovation Organization. BIO is an industry  
14 trade association, so we do represent  
15 manufacturers of CAR T-cell therapies.

16 And I will be very brief here today,  
17 but thank you for your time. The Biotechnology  
18 Innovation Organization appreciates the  
19 opportunity to provide comments to the MEDCAC  
20 during this meeting on the state of evidence  
21 for CAR T-cell therapies.

22 BIO is the world's largest trade  
23 association representing biotechnology  
24 companies, academic institutions, and state  
25 biotechnology centers and related

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1 organizations. We appreciate the committee's  
2 focus on developing better understanding of the  
3 patient experience and PROs in cancer clinical  
4 studies and care. BIO believes that patients  
5 must be involved in decision-making regarding  
6 their care and that patients and patient  
7 advocacy organizations play a vital role  
8 throughout the drug development process as they

9 know what desired outcomes, risks, and other  
10 considerations are most appropriate for their  
11 disease states and the diseased states that  
12 they serve.

13 We believe an open stakeholder  
14 dialogue on PROs is an important and useful  
15 exercise across many therapy areas, but we have  
16 significant concerns around the use of PROs in  
17 governing coverage decisions, particularly for  
18 this new therapy area serving vulnerable  
19 Medicare beneficiaries. It is critical to  
20 ensure that Medicare patients are able to  
21 receive timely access to the highest standard  
22 of treatment for their health condition.

23 We therefore urge MEDCAC and the  
24 Agency to move forward cautiously in the NCA  
25 process and not to incorporate PROs into

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1 coverage determinations for CAR T. BIO's  
2 position is detailed further in written  
3 comments submitted to MEDCAC in advance of this  
4 meeting, and in response to the NCA. Thank you  
5 very much.

6 DR. ROSS: Thank you very much.

7 So, that concludes the morning session  
8 of the formal presentations and both the  
9 scheduled public comments and open public  
10 comment period. We are running a half an hour  
11 ahead of schedule, which I was told is a good  
12 thing, that will allow people to get into the  
13 cafeteria before the CMS lunch rush.

14 People are asked to return to this  
15 room in 60 minutes, by 12:30, so you actually  
16 have 63 minutes to eat lunch.

17 MS. ELLIS: Excuse me. When we come  
18 back from lunch, if all of the presenters could  
19 please sit in the very first row where it says  
20 reserved, for the second half? Thank you.

21 (Luncheon recess.)

22 DR. ROSS: If people could start  
23 coming in and taking their seat, I just want to  
24 remind all presenters to take an assigned seat  
25 in the front row.

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1 MS. JENSEN: All right, we're going to  
2 get started because I want to make sure that  
3 everybody is able to get out on time to make  
4 their flights.

5           So for the panel and for the speakers,  
6 this is the time for the panelists if they have  
7 any questions, that they can ask any of the  
8 speakers those questions. We have an hour, so  
9 hopefully we can keep our answers succinct as  
10 best as possible, so that we can get through  
11 everybody's answers and all the panelists'  
12 questions, so that they will be able to answer  
13 our 23 questions at the end of the meeting.  
14 All right.

15           DR. ROSS: Great, so at this point  
16 I'll just open it up to the committee to see if  
17 anyone has questions for the presenters.

18           DR. GOSS: I have a couple of  
19 questions, one is for the panel members or for  
20 the speakers. Do either of the existing CAR T  
21 therapies that were approved by the FDA have a  
22 labeled claim for PRO outcomes? We heard that  
23 the FDA has a very clear set of standards for  
24 PRO outcomes. Have either of those products  
25 had a labeled claim that reports PRO data, or

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1 do they have PRO data reported as part of their  
2 clinical trial endpoints on the label?

3 DR. GO: Hi again, Will Go from Kite.

4 We do not have any labeled claim to my

5 knowledge in our USPI for PROs.

6 DR. GOSS: Okay, thank you.

7 DR. ABIKOFF: Novartis also does not

8 have any labeled claim with regard to PROs

9 within our U.S. label.

10 DR. GOSS: Do you have it in other

11 labels?

12 DR. ABIKOFF: Within our European

13 labels.

14 MS. ELLIS: Excuse me. Could you

15 please state your name for the record?

16 DR. ABIKOFF: Sorry. Cori Abikoff,

17 from Novartis.

18 MS. ELLIS: Thank you.

19 DR. ABIKOFF: Within our European

20 labels we do.

21 DR. GOSS: Can you --

22 DR. ABIKOFF: I can't speak to the

23 specifics.

24 DR. GOSS: Can you suggest why it's

25 not in the U.S. label, versus an EU label?

1 DR. ABIKOFF: I don't have access to  
2 that specific information.

3 DR. GOSS: I have another question.  
4 In terms of the CAR T trials. What percent of  
5 the patients, where both sponsors mentioned  
6 that in the pivotal trials PROs were used, what  
7 percent of the patients failed to complete  
8 scheduled assessments at scheduled time points  
9 when PROs were used, and how did you address  
10 that in terms of responder bias?

11 DR. ABIKOFF: I'm going to actually  
12 ask Dr. Ferrusi to respond to that question.

13 DR. ROSS: I want to just remind  
14 speakers at the mic, because I've been told the  
15 same, please speak up so everybody can hear and  
16 the mic picks it up. Thanks.

17 DR. FERRUSI: Thank you. Ilia  
18 Ferrusi, with Novartis. I don't have the exact  
19 percentage and what I can tell you is that in  
20 the JULIET study analyses of the PRO data, we  
21 focused on patients who did have a complete  
22 response or a partial response there because  
23 that's where we had data to analyze.

24 DR. GO: Will Go from Kite. In our  
25 pivotal ZUMA-1 study it's a single-armed design

1 so we did not do any prospective PROs in  
2 cohorts one and two of the pivotal study, which  
3 was the data that was used for the labeling of  
4 the USPI. We then incorporated PROs as  
5 exploratory endpoints in additional cohorts of  
6 ZUMA-1, such as in cohort three. This has not  
7 been reported out yet, so we don't have that  
8 data on hand, but this is obviously one of the  
9 challenges that we, as other speakers have  
10 said, in terms of collecting missing data.

11 As I said on the podium, ZUMA-7, our  
12 randomized controlled phase three global  
13 trial we are collecting PROs prospectively  
14 and it is a secondary endpoint.

15 DR. ROSS: Thank you.

16 DR. CUYJET: Aloysius Cuyjet. This  
17 question is for Dr. Basch, am I pronouncing  
18 that correctly? First I'd like to thank you  
19 for a very cogent presentation of the different  
20 PRO tools. Anytime I see seven of anything, I  
21 know one of them is not an ideal tool to  
22 provide the information. So what I'd like to  
23 ask you, what suggestions might you have in  
24 terms of improving the patient-reported  
25 outcomes process, since we have seven different

1 instruments to look at? What would you to do  
2 to come up with one or two ideal instruments?

3 DR. BASCH: All right. Ethan Basch  
4 for the University of North Carolina, so do you  
5 mean in this particular population or in  
6 general?

7 DR. CUYJET: Well, I haven't seen  
8 any -- it's a whole area for discussion, so I'm  
9 assuming, and I'm taking to -- I'm going back  
10 to my experience at Rutgers Medical School  
11 where we had robust end of life care, so  
12 patients would make decisions based on how much  
13 pain they were having, how much sleep they got,  
14 who in their family they spoke to, so I'm sure  
15 there's diversity in genders, there's diversity  
16 driven by cultural backgrounds, ethnicity,  
17 socioeconomic status, education status, there's  
18 a whole list of variables that we consider in  
19 how patients report outcomes, and I'm clearly  
20 not an expert in that field. So if you had to  
21 come up with an instant, what additional  
22 questions or parameters would you want to look  
23 at?



24 DR. BASCH: Yeah, I think it's a  
25 nuanced question, I'll do my best, and

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1 Dr. Kluetz from the FDA may also have some  
2 insights on this.

3 So in terms of putting together a tool  
4 that would give us insights about how people  
5 feel with this therapy, you know, I go back to  
6 something that I mentioned and Dr. Kluetz did  
7 as well, that physical functioning is very  
8 important. Now physical -- you know, a lot of  
9 people talked about oh, we don't know what  
10 tools we can use yet, we have to go back and,  
11 you know, start at first principles. That's  
12 not the case for physical function, physical  
13 function is physical function, right? I mean,  
14 I see patients getting all kinds of therapy  
15 with all different diseases, and physical  
16 function is pretty uniform, there are excellent  
17 tools which are already available, some of  
18 which are on your list.

19 You know, the EORTC QLQ-C30 has very  
20 good physical function, PROMIS has very good  
21 physical functioning. I think those are ready

22 now and in an assessment I would absolutely  
23 include them, number one.  
24 Number two, I would measure, I would  
25 let patients self-report their own side

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1 effects. We know that this is, you know, it's  
2 not that it's underreported, it's just that we  
3 miss a lot of stuff and we misattribute.  
4 Patients know better than we do as  
5 investigators, so I'd absolutely include  
6 symptomatic adverse events. And to figure out  
7 what adverse events are important in a given  
8 trial, that's really dependent on the products  
9 that are being tested and what's known about  
10 those products, and hypothesizing over time as  
11 we accumulate experience, you know, we start to  
12 know, okay, which ones should we ask, and those  
13 gets loaded into a form. So now you've got a  
14 form that's got physical function and a bunch  
15 of side effects, right?

16 And then the third, I think, which is  
17 more challenging, and Paul Kluetz can comment  
18 on this, is disease-related symptoms. I think  
19 that's a little more challenging in this

20 context but that could be considered, I'm going  
21 to put that aside for a moment.  
22       And then the final piece is overall  
23 quality of life, and that includes some of the  
24 domains we talked about, you know, emotional or  
25 social functioning, and we already know that

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1 and that stuff is generic too, that crosscuts  
2 diseases. And so I think you could put  
3 together a tool, you and I could do it on the  
4 back of a piece of paper like after the  
5 meeting, we could just, you know, put down  
6 those domains and those actually would probably  
7 be pretty reasonable as a start from where we  
8 are today, okay?

9       Now that said, I think it would be  
10 useful to take a step back and go to the  
11 population and really talk to people to see  
12 what symptoms and things are really an issue to  
13 them, and then we could go to Version 2.0. But  
14 you know, I think we are ready now to measure  
15 things that are meaningful to people and most  
16 likely will detect signal.

17       DR. ROSS: Dr. Shah? Oh, I'm sorry.

18 DR. SIDANA: Surbhi Sidana from Mayo  
19 Clinic. Just as a comment to that, you know,  
20 we are also using PRO-CTCAE, but the  
21 challenges, there are 78 questions, and I had  
22 to, based on my clinical judgment, pick which  
23 20 of them. Now my colleagues who are using  
24 PRO-CTCAE may pick another 20. And right now  
25 my patients are filling out a questionnaire

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1 which is taking them 45 minutes for 20  
2 questions.  
3 Are they all of the right questions?  
4 I think that is where the prelim data comes in,  
5 like which questions exactly, and we'll know  
6 which questions are changing over time, talk to  
7 patients who had CAR T, okay, what was  
8 important to you, what symptoms did they have,  
9 what is important, so I think we need that  
10 data.

11 And I think one thing which none of us  
12 talked about is a lot of these people get  
13 neurotoxicity, like about up to a third can get  
14 that, we are testing questions for cognitive  
15 function, did they recover cognitive function?

16 If they had neurotoxicity, did they still have  
17 cognitive impairment at six months, 12 months,  
18 I think that's important to address because it  
19 may be subtle and we need to pick it up. Thank  
20 you.

21 DR. CUYJET: Let me ask one other  
22 question before you go. I haven't heard  
23 anything -- you mentioned that people have to  
24 come to certain centers because not everybody's  
25 providing CAR T therapy. So if you're talking

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1 a Medicare population on a fixed income, what  
2 about ancillary considerations? How do people  
3 factor in financial burdens, ancillary costs in  
4 terms of their decision and how they're making  
5 decisions to commit to a new therapy where the  
6 outcomes may or may not be desirable? There  
7 are considerable side effects to take into  
8 consideration, and there's some economic  
9 considerations that may impact the family  
10 members or the members themselves. Is that  
11 part of the assessment?

12 DR. SIDANA: That's not part of our  
13 assessment for this study. We are doing

14 another study where we are looking at people  
15 enrolling in trials or not, and a lot of people  
16 don't enroll in trials because coming back and  
17 forth to a center is more money, it takes time,  
18 somebody has to take time off from work. But I  
19 think it's an important question to ask. We  
20 are not collecting that information right now  
21 but it is important, especially if you're going  
22 to mandate someone collect questionnaires or  
23 come back for follow-up to a referral center,  
24 but who is paying for that, you know, who's  
25 paying for the caregiver to take time off. I

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1 think those are challenges and I think they  
2 need to be addressed.

3 DR. ROSS: Dr. Kluetz, were you going  
4 to stand up?

5 DR. KLUETZ: Hi, this is Paul Kluetz  
6 from the FDA, and I just wanted to address a  
7 couple things. The first was a little bit  
8 about labels, you know, FDA labels versus  
9 European labels and what's the threshold for  
10 data regarding those two different ways of  
11 communicating. Europe definitely has a

12 different threshold for what to put in their  
13 labels and how to put it in, they have  
14 different regulations, et cetera.  
15 For our labels, especially if you're  
16 making a claim of treatment benefit saying our  
17 drug reduces pain, our drug improves  
18 health-related quality of life, it needs to be  
19 statistically tested, substantial evidence, and  
20 that's not frequently done, they're typically  
21 not incorporated in the statistical hierarchy  
22 and tested in that fashion. But we have many  
23 examples of using descriptive PRO data in  
24 labels to further describe a therapy, and so I  
25 was just jotting down some of the more recent

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1 examples.

2 For safety, which I think kind of is  
3 interesting in this context, crizotinib, which  
4 is a really important lung cancer therapy, was  
5 known to cause ocular toxicities through normal  
6 clinician report, and ocular toxicity is  
7 somewhat unusual, so they wanted to get a  
8 little more information about how that was  
9 actually affecting patients so they did

10 incorporate a patient-reported outcome specific  
11 to that and in the label it notes that yes,  
12 there was a lot of ocular toxicity, but  
13 patients did not feel that they were bothered  
14 by it, and there were several other facets of  
15 it that were from the patient that really gave,  
16 I think, a lot more information about that  
17 toxicity.

18       There's several efficacy examples and  
19 one where we added, did actually have a lot of  
20 flexibility in what we would normally accept,  
21 would be the Hemlibra label as far as  
22 improvements in function and joint pain, and  
23 that was, it was statistically tested but the  
24 instrument had some flaws, so we do put this  
25 data in labels.

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1       I would say on the other question,  
2 which is what should we do if we could tailor  
3 something right now, I agree with Dr. Basch, I  
4 think physical function is a very, as I  
5 mentioned, disease-agnostic type of measure  
6 that's going to be pretty applicable. There is  
7 some finesse in there because you do want to



8 make sure you have, you're where you need to be  
9 in your scale because if your baseline function  
10 is very high, like in the female adjuvant  
11 breast cancer trial where you have young women  
12 that are actually functioning very well, you  
13 might want to add a couple higher functioning  
14 items on there to capture that level. So  
15 there's some finessing, but I think physical  
16 function is important.

17 I do think wearable devices in  
18 addition to PRO in that physical function  
19 domain is going to probably be something that's  
20 going to be very valuable in the future as  
21 well.

22 Then finally for the value of  
23 symptomatic adverse event reporting by  
24 patients, one of the things that we're looking  
25 at that I think is going to help, especially in

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1 single-armed clinical trials, is we have a very  
2 hard time understanding what's actually disease  
3 and what's actually treatment-related side  
4 effects. And the way FDA does it currently is  
5 we don't look at the attribution that the

6 physician gives to the AE, we just assume it's  
7 due to the drug because we don't really know  
8 how else to do it. So you'll see in phase one  
9 trials and early accelerated approvals like 80  
10 percent fatigue, very high levels of fatigue  
11 which, you know, is probably, some was there at  
12 baseline. What you will do with these PROs is  
13 that you will get a baseline measure, and then  
14 it will be systematically assessed, and so you  
15 can take baseline into consideration. We're  
16 looking at ways to say we're not going to call  
17 it a drug-related adverse event unless it goes  
18 above what it was at baseline, and I think Amy  
19 Ludek from Mayo has done some work in that, so  
20 we're exploring that, we think that could be  
21 valuable to sort of cut through some of the fog  
22 that we see in these single-arm trials where  
23 you really want to talk to your patient about  
24 what they might experience. You know, it looks  
25 relatively significant if there's high levels

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1 of symptomatic side effects that may or may not  
2 be attributed to the drug.

3 MR. FRANKEL: Can I just follow-up on

4 that point? One of the things you mentioned on  
5 a slide, you categorized besides the  
6 patient-reported outcomes, you had, I think you  
7 called it observational reported outcomes, and  
8 you noted that that may be both from the  
9 caregiver, for example?

10 DR. KLUETZ: Yeah.

11 MR. FRANKEL: Do you really view that  
12 as being two separate measurements? Because I  
13 imagine, certainly with a pediatric population,  
14 and we're discussing an elderly population that  
15 is very ill and is undergoing this therapy.  
16 They're typically going to be accompanied by a  
17 caregiver, loved one, their spouse perhaps, who  
18 will be able to provide insight for a PRO that  
19 they may not be able to do on their own, so it  
20 would seem to be inherently part of a  
21 patient-reported outcome rather than a separate  
22 category. Am I correct with that?

23 DR. KLUETZ: Yes. It's a subtle  
24 point. I think what you might be referring to  
25 is what we call proxy reporting, where it's

1 someone other than the patient filling in the

2 same questionnaire that the patient was  
3 supposed to fill in. We don't actually, FDA is  
4 not a fan of that, our outcomes assessment  
5 staff doesn't like that. Rather, for infants  
6 or those who are faced with a brain tumor or  
7 major dementia that is unlikely that they're  
8 going to be able to fill out the form  
9 themselves, they would look for observable  
10 signs that the care provider can record. And  
11 that's a little different because you don't get  
12 that non-observable nausea type of pain thing  
13 that you can actually observe. So in those  
14 cases you get diarrhea, you get activity levels  
15 for kids, and so that's kind of the way we look  
16 at it, observational-reported outcomes need to  
17 be observable signs.

18 MR. FRANKEL: And how do you tease out  
19 things like financial toxicity as it's phrased,  
20 or general anxiety because they're grappling  
21 with a serious illness, versus that being  
22 specific to the therapy involved?

23 DR. KLUETZ: Yeah. I tried to make it  
24 clear that there's no perfect way to tease that  
25 out completely. Symptoms are probably the

1 closest to the drug effect, as I said, and even  
2 within symptoms, teasing out whether it's a  
3 drug-related symptom or a disease symptom, or  
4 even a symptom of a comorbidity is unclear.  
5 Now that one thing that we tend to do is to  
6 hold PRO to a higher standard than we do any  
7 other clinical trial measure. We know that  
8 CTCAE also suffers from the same challenge, so  
9 yes, I think teasing that out is a challenge.

10 MR. FRANKEL: How much do you think  
11 that biases the actual measurement?

12 DR. KLUETZ: Which part of the bias?

13 MR. FRANKEL: Well, in the sense that  
14 there can be an increased, let's say whatever  
15 they're specifically measuring, let's say  
16 anxiety, and you can say whether it's related  
17 to the drug. Do you use a baseline comparative  
18 to other patient populations to be able to say  
19 well, this is something that we see  
20 consistently with other therapies in patients  
21 who are undergoing therapies for serious  
22 illness, and we can actually deduct that from  
23 our overall evaluation, this is actually set  
24 aside from that benchmark?

25 DR. KLUETZ: It's one of the reasons

1 why we don't typically label things like  
2 anxiety in a cancer trial. It may be obviously  
3 where, you know, anxiety is the actual disease,  
4 but there's so many non-drug influences to  
5 anxiety, sleep, for instance, because there are  
6 so many nondrug influences. Financial toxicity  
7 we don't look at at all, because drugs aren't  
8 even being paid for in the clinical trial. So  
9 some of those concepts that you're referring to  
10 are used a lot in NIH trials or in  
11 postmarketing trials to understand the patient  
12 experience once the drugs are marketed, but for  
13 our premarket, those we look at a little bit  
14 less, and focus more on the disease  
15 treatment-related symptoms.

16 DR. ROSS: Dr. Gottschalk?

17 DR. GOTTSCHALK: I have one question.  
18 Right now we're looking in the CD-19 space,  
19 we're probably going to measure a lot of  
20 outcomes which are confounded by the treatments  
21 where the patients have already been treated,  
22 so what is the value of getting PROs in the  
23 setting right now when we will hopefully move  
24 these therapies more in the outcome setting,

25 more than an autologous transplant or lymphoma,

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1 or instead of an allotransplant for children.

2 And so I was wondering, you know, Dr. Basch or

3 Dr. Kluetz, how do you adjust for that?

4 DR. BASCH: Well, I would just say in

5 response to your question, and also your prior

6 question, that --

7 MS. JENSEN: Can you identify

8 yourself?

9 DR. BASCH: I'm sorry, Ethan Basch,

10 sorry. You know, many of these PRO tools have

11 been evaluated in populations with advanced

12 disease who are highly symptomatic, heavily

13 pretreated, with multiple comorbidities, and

14 have been able to delineate very clearly

15 between arms when there's, you know, when

16 there's no real effect there. And so there are

17 many examples of, despite the challenges that

18 you allude to, where these tools perform

19 extremely well, and that's because some

20 therapies really improve the way people feel

21 and some therapies really worsen the way that

22 people feel and you know, many therapies do a

23 little bit of both in different ways, and these  
24 tools are able to detect that. So I would  
25 argue that in an advanced population or in a

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1 heavily pretreated population, it's perfectly  
2 appropriate to use these tools. In fact, those  
3 are the settings in which these tools are most  
4 commonly used.

5 Now that said, I think yes, you might  
6 get a crisper signal in an adjuvant setting or  
7 in a healthy population as you move therapies,  
8 you know, more up front, but I don't think that  
9 that's a reason not to use it later on. In  
10 addition, you know, you can collect a lot of  
11 information that's hypothesis generating for  
12 earlier.

13 DR. GOTTSCHALK: I think that was not  
14 my question. The question was, you know, side  
15 effect profile will be probably different. You  
16 know, for example, giving therapy in a patient  
17 who has a history, there is probably more  
18 expansion, more neurotoxicity, et cetera. So  
19 then if you have a very validated PRO set of  
20 data but you haven't measured every



21 pretreatment therapy with CAR T, and so then  
22 the question is how does this data look like  
23 when the patients are not so heavily  
24 pretreated?  
25 DR. BASCH: Do you want to take that?

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1 All right.  
2 DR. GO: Will Go from Kite. So, I  
3 totally agree with you. I mean, this is where  
4 the, I think a challenge that we're all facing  
5 across industry as well as our academic  
6 partners and patient standpoint, you're exactly  
7 right. Let's just take CD-19 as an example,  
8 right? In our trial, in the pivotal trial and  
9 effectively third, fourth, fifth-line patients,  
10 two-thirds of them already had B-cell aplasia  
11 because they had so much prior rituximab. And  
12 as we are, you know, continuing to look at the  
13 B-cell aplasia, which is one of the long-term  
14 questionable side effects, about what that  
15 means for patients, how is that going to go  
16 over time? You're exactly right.  
17 As we get to earlier lines of therapy,  
18 potentially we might see fitter T-cells, fitter

19 patients, and that's why, again, I defer to  
20 ZUMA-7, because why? That's a second line  
21 therapy with a randomized controlled trial  
22 where we are going to be looking at that with  
23 some classic PRO measurements.

24 DR. ROSS: Can I -- I wanted to ask a  
25 question, and I think Dr. Shah is one of the

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1 people who actually raised their hands. So,  
2 we've heard a bit about how, you know, this  
3 therapy is so effective, kind of like why do we  
4 need PROs. We also heard among the comments  
5 from the panel that the PRO should only be used  
6 as part of randomized controlled trials. I was  
7 hoping that some of the clinicians who've used  
8 PROs in practice, not research, could talk to  
9 some of the, not just the challenges which we  
10 heard more about, but the successes of how  
11 they've been used and how they've informed  
12 clinical decision-making.

13 DR. SHAH: Gunjan Shah from Memorial  
14 Sloan Kettering. So, I think that while I can  
15 fully understand your questions of sort of  
16 timing and duration of looking at these PROs,

17 that specifically to what we can do with them  
18 even now is, we expect even if we continue to  
19 use them in these later line settings with  
20 several lines of therapy, that there will be  
21 several iterations of these CAR T-cells, and we  
22 expect that future ones will be better than the  
23 ones now.

24 And one of the things that we've been  
25 doing with the autologous transplant as part of

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1 looking at all of this is, essentially you have  
2 a therapy that's safe enough that what you're  
3 really researching is how to decrease the  
4 symptom burden and how are you actually making  
5 a difference, that these are your primary  
6 outcomes, you know, it's safe to give, it's  
7 effective, we know that this works, but how do  
8 you make it better for the patients, how do you  
9 make them not need to be in the hospital or not  
10 be in the ICU, that kind of thing.

11 So some of these measures are really  
12 for that, and so I think that partly to answer  
13 your question, having these at the baseline of  
14 sort of the first generations of these drugs

15 being used commercially and, you know, on  
16 trials, it's helpful to then sort of inform the  
17 studies of the future.

18 In the autologous transplant setting,  
19 you know, one of the studies and one of the  
20 only studies that's really shown to make a  
21 difference has been an acupuncture study that  
22 we did with our integrated medicine colleagues  
23 at MSK, and were able to show a difference in  
24 their patient-reported outcomes as a primary,  
25 of decreasing fatigue and changing their

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1 symptom burden, and so I think that having this  
2 information is valuable over time.

3 DR. KLUETZ: May I?

4 DR. ROSS: Yes.

5 DR. KLUETZ: Paul Kluetz. Just one  
6 comment about late stage versus early stage.  
7 You know, most of our single-armed trials are  
8 multiply refractory, our dose finding trials  
9 particularly, and there's actually been some  
10 interest in using sort of side effect bother  
11 and side effect PRO to help better find dose,  
12 so that's one possible, actually a pretty good

13 utility for that.

14 And I'd also argue that it's still

15 important to measure safety and it's very

16 important to measure safety in that setting.

17 For instance, we know that in second and third

18 line multiply chemo-treated patients, we're

19 going to see a lot more neutropenia with

20 another cytotoxic agent. And so I think we'll

21 see, it's important to understand that toxicity

22 profile and I think, I look at it as

23 complementary to how we're looking at safety as

24 well.

25 With things like health-related

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1 quality of life and physical function, I may

2 have to agree with you that maybe that's not

3 the right spot for those more broad net benefit

4 kinds of questions, but for safety, I think

5 it's actually a pretty important use.

6 DR. BASCH: Ethan Basch. I'll just

7 comment briefly on the real world use of PROs.

8 So, our group and others have done many

9 registries. We currently have a large national

10 U.S. trial, or study I should say, real world

11 study supported by PCORI, in which patients  
12 receiving systemic cancer treatment for  
13 advanced disease at 50 community practices  
14 around the U.S. are self-reporting their own  
15 patient-reported outcomes on a weekly basis  
16 throughout their entire treatment trajectory.  
17 The compliance rate is 96 percent, meaning that  
18 if you look at the average proportion of  
19 patients who self-report every, at any given  
20 week, it's 96 percent. 80 percent of those are  
21 self-reporting on their own, and the additional  
22 15 or 16 percent, they actually get recovered  
23 by somebody calling them if they don't  
24 self-report, so it's augmented by having a  
25 central person in addition to collect the

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1 information.

2 I would also mention, there's been  
3 some questions about informative missingness  
4 when patients are hospitalized or have severe  
5 toxicities, and in those settings we do use  
6 proxy reporting, so we will use a caregiver or  
7 clinician who will provide the information and  
8 that's generally used in sensitivity analyses,

9 so that we understand the reason for the  
10 missingness, but again the missingness is  
11 extremely low, and these are patients with  
12 advanced disease, often close to death.

13 DR. ROSS: Dr. Perissinotto, and then  
14 Dr. Goss.

15 DR. PERISSINOTTO: So, one, I  
16 appreciate Dr. Sidana for mentioning the  
17 potential cognitive side effects that happen to  
18 be particularly important to our Medicare  
19 beneficiaries. So my question is for Dr. Go  
20 and any of the panel members in terms of the  
21 trials with the reported neurotoxicities if we  
22 know the extent of the variability of the  
23 toxicities, if there is any cognitive  
24 assessments that were done at baseline or the  
25 follow-up, and what the long-term sequelae are.

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1 DR. GO: Will Go from Kite. I'll  
2 comment first and then I'm going to ask our FDA  
3 colleague to comment as well. I think it's  
4 very challenging in terms of neurocognitive  
5 behavioral testing. What we did in ZUMA-1, the  
6 pivotal trial, we incorporated a mini-mental

7 status exam, which is not obviously a great  
8 office tool. We chose that because in previous  
9 FDA-approved products like blinatumomab from  
10 Amgen, they also used it as well, so that is  
11 what I would say is a very blunt tool to look  
12 at that. Obviously, we are exploring  
13 possibilities of other more complex  
14 neurocognitive testing, but this, I agree with  
15 everyone here that as CAR T's go to other  
16 disease states, different lines of therapies,  
17 that this will be something that I think we  
18 would want to as a community to continue to  
19 support, and we at Kite Gilead will definitely  
20 keep supporting it.

21 DR. KLUETZ: Paul Kluetz with the FDA,  
22 and I think it's an excellent question because  
23 I think it's, I like these targeted questions  
24 that are getting at things that we know that  
25 are happening, can we further describe and

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1 characterize the effect. Cognitive testing  
2 using a, is a clinical outcome.  
3 Patient-reported outcomes are obviously  
4 challenged. If you're cognitively impaired,



5 filling things out can be challenging, although  
6 there are some cognitive scales.

7       There is interest in, again, looking  
8 at technology, so are there different types of  
9 gaming types of situations where you have  
10 certain kinds of, almost a performance outcome  
11 where you're filling in certain things on an  
12 iPad, and there are some interesting things  
13 that are coming out with that, but they're, we  
14 haven't seen that arrive at the Agency.

15       DR. PERISSINOTTO: Thank you.

16       (Pause.)

17       DR. ROSS: Dr. Goss, and then  
18 Dr. Lamon.

19       DR. GOSS: I had a couple of  
20 questions. Dr. Basch, I appreciated your  
21 presentation because it was really very  
22 helpful. There were a couple of other -- there  
23 was a question that I just wanted to clarify.  
24 The way our question is asked, it's not asked  
25 specifically about CAR T at this point, it's

1 just PRO, and in one of your conclusions you  
2 made comment about the utility for CAR T, and I

3 just wanted to make sure that I'm understanding  
4 the question correctly, number one, and number  
5 two, to know if that would change how you're  
6 thinking about the issue of PROs if it were  
7 specific to CAR T.

8       And I also had a question about, kind  
9 of pragmatic, so our question two has to do  
10 with, you know, transferable to community  
11 practice and, you know, quick throughput to a  
12 trial setting, and I was trying to go through  
13 the data that I had available. With the  
14 exception of the presentation on the FACT,  
15 which wasn't one of the measures we're looking  
16 at, in none of them did anyone report what was  
17 a minimally important clinical difference. And  
18 so I would be interested in our general  
19 assessment of the experts out there about in  
20 which of these measures do we have kind of a  
21 defined clinically important difference that we  
22 could use as a benchmark.

23       And also, there was some lack of  
24 information about the cost of licensing, for  
25 example. So, EORTC I think has a licensing

1 arrangement, you know, and as mentioned, it's a  
2 strongly validated measure, I would agree, but  
3 I'm just curious if anybody has any details on  
4 those types of practical implementation  
5 limitations, because I think that may be  
6 relevant to how we think about this.

7 DR. BASCH: We did --

8 DR. ROSS: Dr. Basch, please --

9 DR. BASCH: I'm sorry, my apologies.  
10 Ethan Basch from University of North Carolina.  
11 Yeah, so we did report on which tools were used  
12 in CAR T trials really just as a matter of  
13 information, but the basis for particular use  
14 in community practice or how widely we use the  
15 tools for generalizability came from use in the  
16 Medicare-aged population, and I did show that  
17 as a separate item for each individual tool,  
18 and that was the basis of that, not the use in  
19 CAR T.

20 DR. GOSS: Okay. Any thoughts on the  
21 minimally important clinical differences, and  
22 whether or not there are any of them that have  
23 really well-established guidelines or some that  
24 you feel that may be missing as well?

25 DR. BASCH: Well, I and some others

1 can comment on this as well. So, you know, in  
2 FDA lingo, this has been sort of changed to  
3 view a score that represents a meaningful  
4 change, so for all of the tools that we gave a  
5 smiley face to, there have been evaluations of  
6 what is a clinically meaningful score change,  
7 with the caveat that the PRO-CTCAE is, you  
8 know, about adverse event reporting that's  
9 generally descriptive rather than, you know,  
10 comparison of proportions, hitting a certain  
11 score threshold.

12 DR. ROSS: All right, so I know there  
13 are a number of questions here. Dr. Lamon was  
14 next, and let's just try to keep the questions  
15 as short as we can so we have enough time.

16 DR. LAMON: I have a question for  
17 Dr. Snyder and anyone else who wants to answer.  
18 I really liked the graphic presentations you  
19 did on the issues of getting clinician  
20 engagement, but I'm thinking about all the  
21 technological issues, and my impression is that  
22 the ability to do the PRO measurements is  
23 technology and that we have more information  
24 systems. How are you getting the information  
25 on those graphs, are they in real time, and

1 what's the interface with the electronic record  
2 that you're using at Hopkins, or any other  
3 records if anyone else wants to comment? I  
4 think that's limiting clinician involvement and  
5 putting a wedge between collecting data and  
6 using it, and do we have it in real time to use  
7 it in real time?

8 DR. SNYDER: Claire Snyder from Johns  
9 Hopkins, thank you for the question. For the  
10 purposes of our research we made up the data so  
11 it was really easy to get.

12 (Laughter.)

13 However, the rationale behind the  
14 research was work that our group had done at  
15 Johns Hopkins and my colleague Michael Brundage  
16 had done in terms of clinical trial data where  
17 we wanted to show the data to patients and  
18 clinicians and we didn't know the best way to  
19 convey all the information we wanted to, how is  
20 the patient doing over time, what's an  
21 important difference, what is statistically  
22 significant, what does the doctor need to pay  
23 attention to? They're not going to learn all

24 about these questionnaires, we need to make  
25 them immediately interpretable and intuitive.

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1       So, the reason that we had to do the  
2 research that we did is that there is a huge  
3 increase in the collection and use of these  
4 data in clinical practice, so our team at  
5 Hopkins started doing this in 2005. I would  
6 say we were some of the pioneers in the U.S., I  
7 feel like we are now almost obsolete, but the  
8 work done by Ethan Basch and others has moved  
9 this so far forward where he is, for example,  
10 doing this study in 50 community practices.

11       A colleague of ours, Roxanne Jensen,  
12 who's now at the National Cancer Institute, did  
13 a review of e-PRO systems in 2014 and even then  
14 in cancer care alone, there were 33 unique  
15 systems meant for clinical practice. The big  
16 challenge now is getting the data in the  
17 electronic health record. With funding from  
18 PCORI, a group of us, including some folks  
19 here, developed a users guide for how to  
20 integrate patient-reported outcomes into  
21 electronic health records. It is freely

22 available on the PCORI website and it walks  
23 step by step through all the considerations  
24 involved. It does not provide one right answer  
25 but a range of options and their relative

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1 advantages and disadvantages. So I think  
2 increasingly, there are tools that are going to  
3 get us there. Thank you for the question.

4 DR. ROSS: Dr. Shah, do you have a  
5 quick response?

6 DR. SHAH: Yes, just very quickly,  
7 Gunjan Shah from Memorial Sloan Kettering. So,  
8 I briefly was able to show you some of the  
9 figures from our MSK Engage platform that's  
10 being created and sort of in use on the surgery  
11 side and being transferred into a more  
12 long-term use for the transplant and cell  
13 therapy side. And you know what, the way it's  
14 working right now and what we're hoping to  
15 continue is that you can actually pull it up in  
16 the office, that you can pull up an individual  
17 patient and show that patient, here's what  
18 you've reported over time, and with one click  
19 you can actually decide to include that in

20 their electronic record, and so that it can be,  
21 you know, part of their record over time, but  
22 also pulled up in sort of a dynamic fashion to  
23 intervene on if you so choose to, but also see,  
24 you know, which things are higher at which  
25 visit, which ones are worse today, which are

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1 better today, and look over time.

2 We on the clinician side can then also  
3 say here's your entire panel of patients with  
4 the same disease, or answered the same survey,  
5 and then have more aggregate data also built in  
6 to be able to look at.

7 And so I think it's kind of important  
8 to be both ways, sort of aggregated across the  
9 population, but also to include the patient in  
10 showing them what they reported along the way  
11 also.

12 DR. ROSS: Thank you. Dr. James,  
13 you've had your hand up the longest.

14 DR. JAMES: All my questions have been  
15 answered by the last two.

16 DR. ROSS: Great. Dr. Feinglass?

17 DR. FEINGLASS: For our FDA colleague,



18 Dr. Kluetz, how often does the result from a  
19 PRO assessment tool become a deciding factor  
20 for a binding FDA decision?

21 DR. KLUETZ: Thank you for that  
22 softball, this is Paul Kluetz.

23 DR. FEINGLASS: You're welcome.

24 DR. KLUETZ: Paul Kluetz from the FDA.

25 So, I think it's a really important question,

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1 it's something I talked about over lunch and  
2 that is, are we using patient-reported outcomes  
3 to further characterize how a therapy affects  
4 the patient in the totality of data, and then  
5 we organize that in a qualitative or a  
6 quantitative risk-benefit determination, which  
7 is what we do at FDA, mostly qualitative right  
8 now, yes, we do that all the time.

9 We wrote a recent New England Journal  
10 of Medicine article on the use of  
11 metastasis-free survival, which is a new  
12 endpoint for nonmetastatic castration resistant  
13 prostate cancer so it was a novel endpoint, and  
14 in this particular case patients normally don't  
15 get a therapy and they're usually asymptomatic,

16 and so it was like sort of a maintenance  
17 therapy question so we were really quite  
18 concerned about the tolerability, this was an  
19 important part of our decision, because we knew  
20 that the benefit was there, that it was pushing  
21 back metastatic disease, but how tolerable was  
22 it? And so in that case we did use, looked  
23 very carefully at this overall side effect  
24 bother question and different side effects, and  
25 made sure there was no significant signal there

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1 in addition to the normal CTCAE data, and so  
2 that weighed in.  
3 I think the bigger question is, have  
4 we ever used it for a negative nonbinding  
5 decision, and I think that's obviously what  
6 everyone is really concerned about, and that's  
7 not to my knowledge. We've used it for  
8 positive, important positive decisions. For  
9 instance, Jakafi, as I said, it was a key  
10 secondary endpoint that moved the regulatory  
11 decision from an accelerated approval because  
12 it was a surrogate endpoint as a primary  
13 endpoint, to a regular approval because the

14 secondary endpoint was a symptom improvement, a  
15 clinical benefit that was meaningful to  
16 patients.

17 DR. ROSS: Dr. Civic, I think you were  
18 next.

19 DR. CIVIC: Yeah. One of the  
20 questions we're asked is how long to measure,  
21 sorry, a PRO, to be able to identify a valid  
22 treatment effect and, you know, we're looking  
23 at late toxicity but also, I think it was  
24 Dr. Abikoff talked about late benefits, that  
25 there wasn't a response until, in some patients

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1 until nine to 12 months, which makes it seem  
2 like we should be measuring PROs for at least  
3 12 months. Does anyone want to comment?

4 DR. GO: Will Go from Kite. So yeah,  
5 similar to other trials and in our pivotal  
6 trials, number one, we've actually seen that  
7 with a single dose of CAR T, as well as at the  
8 NCI, and we'll hear Dr. Yang comment as well,  
9 that we've seen conversions from stable disease  
10 to PR to complete remission as late as over 12  
11 months, and this is why -- and without any

12 other intervening therapy. And so this is why,  
13 and again, I am not a PRO expert, I'm a  
14 hematology oncologist, but if I were to design  
15 the PROs, again, that's where the challenge  
16 lies, because you're going to start seeing  
17 potentially late converters as far as 12 to 15  
18 months.

19 DR. ABIKOFF: Cori Abikoff from  
20 Novartis. I agree, it was my point that we do  
21 see these patients progress over time and that  
22 is one of the things that differentiates CAR T  
23 therapy from other therapies, and I also am not  
24 an expert in PROs, but I think that this along  
25 with the questions that have been raised about

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1 things like neurologic toxicity, these are  
2 still fairly young technologies and they've  
3 been studied for a fairly short period of time,  
4 so understanding what those late effects are  
5 and how that impacts PRO measurement as well as  
6 understanding the immediate effects and how  
7 that affects PRO regimen, are still things that  
8 we're trying to understand, and why we are  
9 actively utilizing them in our current and

10 future clinical trials, because they will help  
11 us to answer those questions.

12 DR. BAR: Merav Bar from the Fred  
13 Hutch. Regarding the long-term follow-up for  
14 PROs, I think there is two sides of it. One is  
15 the one that patients might respond later but  
16 on the other hand, there is still relapsed  
17 disease or progression of disease after and a  
18 lot of patients that we are looking at receive  
19 subsequent therapies that may also affect how  
20 they feel, their quality of life, and symptoms.  
21 So there are two groups of patients that, one  
22 may respond later, but on the other hand there  
23 still are patients who will have progressive  
24 disease and relapse after, either because of  
25 interim therapy, they have symptoms of disease

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1 progression or because of subsequent therapies,  
2 so these two things need to be taken into  
3 consideration as well.

4 DR. ROSS: Okay. Dr. Garrido, I think  
5 you had your hand up next.

6 DR. GARRIDO: So, from Dr. Snyder's  
7 presentation, we saw that individuals,

8 including clinicians and researchers with quite  
9 substantial education aren't so great at  
10 reading graphs and interpreting changes in  
11 PROs. So I'm wondering, either in your own  
12 personal experience in working with patients  
13 with limited literacy or education, are people  
14 able to understand just the questions  
15 themselves, not even the changes, or have these  
16 been evaluated in people of limited literacy or  
17 education?

18 DR. SIDANA: Surbhi Sidana, Mayo  
19 Clinic. While I don't have the exact answer  
20 you are asking, you know, I had a patient who  
21 was filling out a similar questionnaire in our  
22 study. He did not have neurotoxicity but his  
23 heart rate was fast, but he had not slept  
24 because of all the alarms going off in the ICU,  
25 and that patient had to read a question three

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1 times on that questionnaire to understand. Now  
2 I don't know what to do with that answer, do I  
3 even trust the answers the patient gave? So  
4 yes, I mean, those are challenges, not only of  
5 patients understanding questions, but even

6 well-educated patients who are having side  
7 effects of treatment, you know, being able to  
8 answer them in the state that they're in.

9       The one more point I would like to  
10 make from before is, I think it's important to  
11 study late effects because as you know, for  
12 allogeneic transplant, we found out, you know,  
13 there are late effects like chronic graft  
14 versus host disease that impact quality of  
15 life. Now we don't know any about CAR T yet,  
16 but who knows what's going to happen when these  
17 people are like three years out, four years  
18 out? So I think it's important to study them,  
19 we just don't know what they are right now.

20       DR. PERISSINOTTO: Can I just add to  
21 the question about low literacy also? Because  
22 I think you'll be able to answer this if some  
23 of the PRO measures have looked at multilingual  
24 and multiethnic populations.

25       DR. BASCH: Yeah, absolutely, so --

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1 thank you, Dr. Snyder. I'm Dr. Basch, Ethan  
2 Basch, and yeah, I need to get like a sticker  
3 on me or something to me as a reminder, which

4 speaks well to your question, right, I need to  
5 be prompted.

6       So, a couple things. First, you know,  
7 in looking at Claire's evidence, which I think  
8 is, you know, terrific studies about  
9 interpretation of the graphic, you know, we  
10 haven't applied that level of scrutiny to  
11 clinicians, for example, in interpreting  
12 waterfall plots or Kaplan-Meier curves, or all  
13 the different graphics that we are expected to  
14 interpret in journal articles or in drug  
15 labels, right? So I mean, people have trouble  
16 digesting data. You know, I told Claire that  
17 personally I like the USA Today, I like a  
18 simple graphic, like I can get that, so I think  
19 there's something to simplicity in  
20 understanding graphical displays. But I think  
21 that, you know, as Paul alluded to, we  
22 sometimes apply a greater level of scrutiny to  
23 these patient measures than we do to the  
24 metrics that we all take for granted every day,  
25 and I just want to caution us not to be, not to

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1 apply a higher level of scrutiny.



2        Regarding your question, so there have  
3 been many many PRO studies done in patients  
4 with low education levels, low health literacy  
5 levels. In a study that my group conducted  
6 that was reported last year at ASCO and in  
7 JAMA, we had a very large arm of patients who  
8 had never used a computer before and they were  
9 using a computer and they, that population had  
10 low literacy and almost universally had less  
11 than high school education, and they were  
12 universally almost able to self-report, and  
13 actually that group saw greater benefits from  
14 reporting PROs and having information conveyed  
15 to the clinicians for management of  
16 symptomatology.

17        So I mean, as far as language, there  
18 have also been many studies done in groups  
19 speaking other languages. I'd say all of the  
20 tools with the smiley faces have been  
21 linguistically adapted into other languages  
22 using a pretty, I'd say a pretty rigorous  
23 translation process that often involves both  
24 cognitive interviews of people and if done  
25 well, includes people with different levels of

1 literacy and education as well, so I think for  
2 the good tools, it's generally pretty good.  
3 MR. FRANKEL: A quick follow-up to  
4 that. Do you regularly, I assume this may have  
5 come up when you evaluate these tools, to ask  
6 the patient how burdensome they find the tool  
7 that they're answering? So, is that every  
8 single tool you have that question and you have  
9 the data from there to be able to say well,  
10 this tool, we have a very negative response and  
11 this one -- and I assume that would be true  
12 for, as the patient progresses through  
13 treatment they may have different responses to  
14 that as time goes on, and what do you see with  
15 those terms?

16 DR. BASCH: So, I'm sorry, maybe you  
17 can restate that; what is the thing you're  
18 interested in knowing?

19 MR. FRANKEL: The patients' feedback  
20 of how burdensome they find the tool that  
21 you're actually using to measure their  
22 feedback.

23 DR. BASCH: Yeah. So we've done a lot  
24 of that, others have, I think Claire has too,  
25 so we've done a lot of work with how burdensome

1 people find questionnaires. You know, there  
2 are a few people who find these questionnaires  
3 to be burdensome, but just like they find going  
4 to get their CAT scan burdensome, and their  
5 liver biopsy burdensome, you know, not that a  
6 PRO instrument is similar to a liver biopsy,  
7 but part of the things people do as a part of  
8 trials or care is burdensome, but may have  
9 value.

10       The vast majority of patients are very  
11 enthusiastic. In multiple surveys that we've  
12 done, on average, about 94 percent of people  
13 say they'd recommend doing this to others,  
14 they'd do it again, they find it highly  
15 valuable, it improves communication with the  
16 care team, they feel that they're an active  
17 participant in care, an active participant in  
18 the clinical trial enterprise, and people feel  
19 engaged, people like doing this. I'd say that  
20 in some of the settings where we do studies  
21 where we ask people the same questions week  
22 after week after week, you know, there are  
23 people who push back, like couldn't you come up  
24 with a few new questions or like, you know, I

25 already told you I don't have fatigue, why do

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1 you keep asking me about fatigue? And this is  
2 where we're starting to use technologies to try  
3 to make things a little more user friendly, but  
4 in general people don't find these things  
5 burdensome at all, in fact quite the opposite.  
6 You know, most people are delighted to be, you  
7 know, a part of what we're doing.

8 DR. ROSS: Dr. Flynn.

9 DR. FLYNN: Yes, Kathryn Flynn from  
10 Medical College of Wisconsin and CIBMTR chair.  
11 Just one additional point. I can't speak for  
12 all of the measures, all seven measures, but  
13 certainly for the PROMIS measures, one of the  
14 stated goals in developing those was to  
15 evaluate every single item in people with low  
16 literacy, so every item at a minimum had at  
17 least two people with less than a ninth-grade  
18 reading level evaluate the item through a  
19 cognitive interview, I think the PRO-CTCAE also  
20 had cognitive interviews specifically targeted  
21 to people with low literacy, so for those  
22 meticulously developed measures, I think you

23 can have confidence that most people will  
24 understand them.  
25 With those modular approaches, of

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1 course, that's where, you know, taking into  
2 consideration how many different domains, how  
3 many different questions you're choosing, and  
4 testing that again to make sure in that  
5 particular patient population, you're not  
6 asking something that people can't complete.  
7 But then another question you had  
8 asked earlier about licensing fees, also, both  
9 PROMIS and PRO-CTCAE do not have licensing fees  
10 associated with them, so that's not a burden.

11 DR. CHUNG: Hi, Karen Chung from Juno  
12 Celgene. Just addressing, again, the literacy  
13 levels in most of these instruments, the four  
14 of the seven that would, you know, move  
15 forward, they are built to be at a fifth grade,  
16 you know, kind of education level, so  
17 hopefully, you know, we're trying to take care  
18 of the literacy by making sure that the  
19 language is really understandable.  
20 With regard to understanding the

21 outcomes, you know, some of the analyses we  
22 really try to do so it's understandable to  
23 clinicians as well as patients include  
24 responder analyses so they know, well, this is  
25 the proportion of the patients in the clinical

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1 trial who had a clinically meaningful  
2 improvement or, you know, worsening, or  
3 stabilized. So those are the kind of metrics  
4 we feel, you know, help them really understand  
5 the outcomes more than kind of what is the mean  
6 change from baseline, you know, and the other  
7 kind of, you know, modeling that we do on the  
8 PRO data.

9       So it's all trying to be, you know,  
10 very concrete in the level of change and  
11 filling out the difference between responder or  
12 minimally important difference, and a lot of  
13 people have done different analyses around  
14 that. You know, there's anchor-based,  
15 distribution-based, and for the EORTC-QLQ-C30  
16 we felt very comfortable using that because  
17 there have been solid MID research done out  
18 there by (inaudible) and so that's what we're

19 using to identify our responders.

20 DR. ROSS: Dr. Cheng, you had a

21 question earlier?

22 DR. CHENG: Yes. Go ahead.

23 DR. FERRUSI: Sorry for the delay. I

24 saw a nice lineup of people and I thought I

25 would wait to see what they had to say.

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1 DR. ROSS: Just introduce yourself.

2 DR. FERRUSI: My name is Ilia Ferrusi

3 and I'm from Novartis.

4 A lot of good points have been covered

5 here. Standard practice when developing

6 instruments is to develop them at no more than

7 eighth-grade reading level, and I did want to

8 address one component, whether all of the items

9 are relevant, I can't remember who asked the

10 question, but for instruments that are

11 developed as standalone instruments, so I'm not

12 talking about something like an item bank where

13 you pick and choose, but something like the

14 FACT-G for example has been developed, and has

15 domains within it.

16 When cognitive debrief is done, so a

17 first draft of the instrument has been  
18 developed and the cognitive debrief is taking  
19 and sitting down with a patient in that  
20 population, that's a really important part.  
21 You're talking to real patients who have the  
22 disease condition of interest, and you ask them  
23 to work through the items and tell them how  
24 they're interpreting this, how they understand  
25 the response options. You also would go

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1 through a practice of asking is this relevant  
2 to you, do you feel that any of these items are  
3 repetitive, and that's a very purpose-driven  
4 process that we go through to ensure that we're  
5 not asking too many questions and the fit is  
6 just right.

7       So some instruments like, the  
8 instruments that, Dr. Basch has actually  
9 summarized their development, and he talked  
10 about content validity, if you saw a smiley  
11 face or checkmark next to content validity,  
12 that's some of what he was talking about.

13       DR. ROSS: Thank you. Dr. Cheng.

14       DR. CHENG: Joe Cheng. I just, I



15 still need some clarification as far as what  
16 the concerns are about collecting  
17 patient-reported outcomes, and I guess my  
18 question really is, there seems to be a lot of  
19 concern about using PROs in following how  
20 patients do. Do you have another suggestion,  
21 then, for collecting quality added life years,  
22 or how do you really assess things like  
23 minimally clinically important difference, and  
24 then really, how do you risk adjust without  
25 collecting this data, the results of your

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1 patients? And then how do you then coordinate  
2 whether this is related to an episode of care  
3 versus fixed time points?

4 And I guess that's what I'm saying,  
5 because all the concerns about PROs seem  
6 applicable through all of medicine, whether  
7 it's a stroke, or spine, or any tertiary center  
8 would seem to have the same concerns that you  
9 have about follow-up patient care. I'm just  
10 still trying to figure out how does this apply  
11 directly to CAR T, and are you saying that we  
12 shouldn't be collecting any of these PROs for

13 anything we do, or quality added life years are  
14 not as important? I guess I just want some  
15 clarification on that.

16 DR. SIDANA: Surbhi Sidana, Mayo  
17 Clinic. I think it's very important to collect  
18 these data, that's why we are doing them. I  
19 think what's not clear is exactly which ones.  
20 Again, we don't want to burden our patients too  
21 much but we also want to get the answers right,  
22 what is important to collect and then how  
23 frequently do we need to collect it? Do we  
24 collect it every week for one year, do we  
25 collect it every month for two years, like when

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1 are we seeing the changes? I think that's the  
2 finesse we need to get right, but it's very  
3 important to collect.

4 And I think the third part no one  
5 really talks about is who's going to pay for  
6 it, because right now I'm doing a study that  
7 has only 30 patients we need to collect. It  
8 takes one patient one hour per questionnaire,  
9 each patient will fill out seven or eight  
10 questionnaires, so that's a lot of time for the

11 coordinator. And once that patient goes home,  
12 someone has to call that patient up, or if  
13 they're filling it electronically and they  
14 don't answer, someone will be asking that  
15 question over the phone to ensure completeness.  
16 And if they've gone away from my practice and  
17 now they're seeing a local clinician and if  
18 there's a symptom, even if I see it, what do I  
19 do? Say they say they're having severe pain on  
20 that question. Now I'm not following them on  
21 an everyday basis, so that creates an ethical  
22 dilemma as a clinician, I don't know what the  
23 right answer is, but I think it's very very  
24 important to collect them, but in some way as a  
25 community, and we're already talking about

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1 forming a working group. How do we answer  
2 these questions, like what do we do about the  
3 data we get, and who pays for it, and how do we  
4 collect it in a standardized manner so that we  
5 are collecting things that are important.

6 DR. ROSS: Just in interests of time,  
7 try to keep your answers moving along. There's  
8 a long line.

9 DR. CHUNG: Karen Chung, Juno Celgene.  
10 I completely agree that patient-reported  
11 outcomes are important and I think it's  
12 important to assess them in kind of a  
13 systematic way, and so that's why in clinical  
14 trials, you know, we have very good kind of  
15 follow-up to all these rigorous schedule of  
16 assessments. If they go off study, we have one  
17 last assessment. I think the concern is really  
18 if we had it in the real world that would be  
19 great, but I don't think the infrastructure is  
20 there. I don't think there's, you know, a way  
21 of getting the data systematically and cleanly.  
22 I mean, we have learned from a lot of trial and  
23 error in clinical trials a lot of issues with  
24 data, you know, getting the data collection  
25 right. And so I think to, you know, have the

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1 general practices pulling this data together in  
2 meaningful ways so that we can use it is still,  
3 we're a little bit far away, you know, with  
4 regard to that and all the other issues with  
5 regard to instrument selection and analysis,  
6 and all the logistics around it.

7 DR. GO: I just want to give a  
8 clinical perspective as a former transplanter,  
9 as a former allogenic stem cell transplanter.  
10 CIBMTR has been obviously the biggest group  
11 that has been for all, mandated by law. That  
12 took them almost 20 to 30 years before we could  
13 understand GVHD scoring, and so I think if it  
14 takes 20 or 30 years to even get GVHD scoring  
15 right, our opinion is it's going to take a long  
16 time to really get PROs right, and this is why  
17 from Kite Gilead, we don't believe that right  
18 now it's warranted in terms of coverage  
19 analysis.

20 DR. BASCH: Ethan Basch, University of  
21 North Carolina. Thank you.

22 I really, I have to say I came here  
23 today, I was very very surprised, as you might  
24 be, to hear the reticence on behalf of some  
25 stakeholders to collect this information that

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1 cannot be gathered in any other way in a  
2 population that we are bringing back to the  
3 clinic all the time, harvesting from,  
4 reinfusing, scanning, et cetera, et cetera. We

5 are spending a lot of resources on this patient  
6 population and to not collect patient-reported  
7 outcomes, which is essentially handing somebody  
8 a questionnaire, to me frankly seems rather  
9 absurd.

10       There's a many-decade experience  
11 administering questionnaires to people in  
12 trials and in the real world with very high  
13 rates of compliance. There are all different  
14 kinds of ways to do it, it can be done on  
15 paper, it can be done with a telephone survey  
16 system, it can be done with an i-Phone or  
17 Android system. This is done all the time.  
18 There are hundreds and hundreds and hundreds of  
19 registries in oncology patient populations with  
20 90-plus percent compliance rates using  
21 electronic devices all over the world now, and  
22 to say that feasibility is a barrier to me is  
23 simply refuting an enormous amount of  
24 accumulated knowledge and ability.

25       To the 45-minute or hour-long

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1 questionnaire, I mean, that seems very unusual  
2 to me. Our questionnaires that we use

3 repeatedly take between five and ten minutes  
4 long, and we often ask people, to your  
5 question, did you find the questionnaire  
6 burdensome or too long, I mean, it's really  
7 never an issue. There's some trials that have  
8 longer questionnaires that are spaced out maybe  
9 every three months, but again, I mean to me,  
10 compared to what we are asking patients to do  
11 in order to receive these therapies, this is  
12 minuscule, so I don't really see the barriers.

13 DR. CHENG: Can I ask a follow-up to  
14 that question?

15 DR. ROSS: No. Well, I just wanted to  
16 allow her to speak, and Dr. Yang has been  
17 waiting for a long time. I want to make sure  
18 everyone gets a chance to ask.

19 DR. FERRUSI: Thank you, Ilia Ferrusi  
20 from Novartis. You know, I think many valuable  
21 viewpoints have been expressed here. What I  
22 would like to add is that PROs generally, yes,  
23 are a great thing to measure to understand  
24 ultimately how the patient's experience is  
25 going. But what, I want to bring us back to

1 principles and make sure we're focusing on why  
2 we're asking for PROs, what is the research  
3 question, what is the context in which, because  
4 the answer to that question, which measure to  
5 use, is going to vary depending on what you  
6 want to measure and what the context is.

7       So in broad strokes, it is hard to  
8 answer that question and our position, I would  
9 like to clarify, is simply that we are not  
10 comfortable with PROs being required as a  
11 requirement for coverage or access to a  
12 medication.

13       DR. ROSS: Great. Dr. Yang, do you  
14 still want to ask your question?

15       DR. YANG: This is a question  
16 addressing the fact that almost everything  
17 we've talked about here today is about  
18 capturing acute or on-therapy toxicities, or  
19 under-appreciating them. The main difference  
20 in my experience with CAR T, especially with  
21 CD-19, is it's a one-time treatment, and at the  
22 back end patients who are responding or doing  
23 well, which is almost half of those patients or  
24 more, have a paucity of any interventions or  
25 requirements at that point, and are we



1 capturing that? So do any of the people who  
2 have PROs associated with their studies have  
3 questions such as how many people have gone  
4 back to gainful employment, how much more care  
5 have they required in the last year or two, and  
6 how often do they think about their disease,  
7 how often do they have concern or anxiety about  
8 their disease, because this can be a one-time  
9 treatment and then a walk away.

10 DR. GO: Will Go from Kite. So, we  
11 are looking exactly into that, Dr. Yang, in  
12 terms of the work productivity and activity  
13 impairments in Version 2.0 in our randomized  
14 Phase III trial. I think that's the biggest  
15 thing we're doing, so we are actually looking  
16 at that in all of our trials since this was  
17 mandated by the FDA for 15-year follow-up, so we  
18 are going to get adverse events, look at the  
19 B-cell aplasia, the use of IVIG, as well as  
20 some of these other PRO and back to work  
21 products.

22 DR. FERRUSI: Ilia Ferrusi from  
23 Novartis. To answer your question, no, we are  
24 not collecting return to work, but the work  
25 productivity, activity impairment questionnaire

1 is a very good tool for that. I would say that  
2 we are using, again, the FACT-Lym, which has  
3 physical, social, emotional and role  
4 functioning, so as a component of role  
5 functioning, we can certainly look at a return  
6 to normal activity, and we are continuing to  
7 collect that data 12, 18, 24 months after their  
8 administration of CAR T in JULIET.

9 DR. ROSS: Mr. Frankel, you get the  
10 last question.

11 DR. BAR: Sorry. To answer this  
12 question about the long-term follow-up, so yes,  
13 an effort has been made and is continuing to be  
14 made to learn about those long-term effects.  
15 Currently we don't have the data, CAR T-cell  
16 clinical trials started maybe about five, six  
17 years ago so the data we have right now is  
18 limited, and I think in the first few years the  
19 most excitement was about whether the treatment  
20 works or not, what was the response rate, and  
21 people paid less attention to more long-term  
22 effects and quality of life. However, now when  
23 we know that maybe there is approximately a

24 50-percent response rate and long-term  
25 response, so people are paying more attention

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1 to those quality of life questions, and we are  
2 planning to follow-up patients at least yearly  
3 for 15 years from now according to the FDA  
4 requirements, so we are making an effort to  
5 learn that, but we still don't have data.

6 And the thing that I would like to say  
7 here is that effort has been done, and we will  
8 make even more effort to learn those questions.  
9 The question is if we need to make this a  
10 mandatory thing when we make the decision  
11 whether or not to reimburse patients for such  
12 treatment.

13 MR. FRANKEL: This question is for  
14 Dr. Basch and Dr. Kluetz. You advocate for  
15 PROs to also be given to patients who were  
16 receiving the standard of care until now. So  
17 in other words, as a patient, I think that many  
18 would be interested to know how are patients  
19 faring in terms of their observation of their  
20 own outcome when they receive CAR T therapy in  
21 a specific instance, and how are the patients

22 who did not undergo the therapy and have a,  
23 let's say three-to-six-month survival on  
24 average, how did their feedback look? And that  
25 way you could actually compare those two groups

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1 of patients, and I think that that would  
2 probably influence many patients much more than  
3 if they only saw receiving the therapy and they  
4 saw the drawbacks there, let's say, if they  
5 were looking at the advantages and  
6 disadvantages, and they could actually compare  
7 that to the alternative. Because I think  
8 without that, the patients are really at a very  
9 weak position to really have a fully informed  
10 decision.

11 DR. KLUETZ: Paul Kluetz from the FDA.

12 So I think one of the problems, one of the  
13 issues is context which I was talking about a  
14 little bit earlier, and that is, is this a  
15 single-armed trial or is this a randomized  
16 trial. I mean, you won't have that --  
17 comparing to a historic control is obviously  
18 going to be very challenging in this field  
19 right now given the heterogeneity of the tools

20 that are used, and assessment frequency and  
21 things like that, and so really when you  
22 compare it to the standard of care you're  
23 talking about a randomized trial much like the  
24 one that was actually presented as, I guess,  
25 the second-line trial that was presented.

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1 Now you could do that, and in fact  
2 that's the majority of what we get at the FDA  
3 in oncology, is randomized trials, and they do  
4 ask the same questions of both arms, and that  
5 does help to give you a comparison of how well  
6 they may feel or function on one arm versus the  
7 other.

8 MR. FRANKEL: And how about moving  
9 forward? So in other words, does that, for  
10 whatever reason they're not eligible, or they  
11 opt not to go through CAR T therapy? Maybe  
12 they're concerned about certain toxicities  
13 involved, but capturing the data from those  
14 patients so that the patients in the future who  
15 have to decide between the two could have that  
16 at their disposal.

17 DR. KLUETZ: Yeah, that may be outside

18 of more of a regulatory question but it is an  
19 interesting question, and I don't know how you  
20 would design that, but it doesn't seem like  
21 something you would normally see in the  
22 regulatory setting.

23 I did want to actually add one more  
24 point to the point of, have people ever used at  
25 the FDA patient-reported outcomes to make a

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1 negative decision? Let's remember that in  
2 oncology we have objective tumor-based  
3 measures, and survival is our primary efficacy  
4 measure, and we always have. In many other  
5 therapeutic areas that's not the case, so I  
6 don't want to speak for the entire FDA by  
7 saying we don't use patient-reported outcomes  
8 in a very important way to make key efficacy  
9 decisions, because that's actually not true.  
10 There are many therapeutic areas where the  
11 disease manifestation is only a symptom and  
12 that's the only thing to measure, an analgesia  
13 being an obvious example, and in those you need  
14 to show that patient-reported outcome is  
15 improving, or that therapy is not going to show

16 any efficacy.

17 DR. ROSS: So at this time --

18 DR. BASCH: I just want to respond to  
19 the question briefly.

20 DR. ROSS: Please introduce yourself  
21 first.

22 DR. BASCH: Ethan Basch from the  
23 University of North Carolina.

24 So, the most valuable comparative data  
25 will be from a prospective randomized

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1 controlled trial, that's one of the reasons why  
2 it's really important for, you know, sponsors  
3 in their discussions with regulatory  
4 authorities, to really think about these  
5 outcomes and pick them right at the very  
6 beginning, so we can really understand in that  
7 context because, you know, we have a little bit  
8 more equipoise in that setting.

9 I think your question really alludes  
10 to real settings, to registries and postmarket  
11 surveillance, I would guess. You know, I do  
12 think there's value in having comparative data  
13 after a drug is on the market in order to do

14 comparisons, especially if that information was  
15 not really fully characterized pre-approval, or  
16 if there are not long-term outcomes prior to  
17 marketing. That said, there are limitations.  
18 Obviously there are many dimensions of  
19 selectivity, patient and provider selectivity,  
20 and so these populations will inherently  
21 differ, those who did and didn't get the  
22 therapy of interest, in this case CAR T. And  
23 so if that was done, then there are methods of  
24 balancing those differences in observational  
25 data, they just have to be done very well.

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1 DR. ROSS: So, thank you to the  
2 presenters again, and speakers, for continuing  
3 to answer our questions. So I let us go about  
4 ten minutes over, this was obviously a very  
5 rich discussion, and many of the panel members  
6 had questions.

7 We're now supposed to transition to  
8 the period where we have an open panel  
9 discussion. I will just note that we are not  
10 precluded from asking the speakers or  
11 presenters additional questions, but if you are



12 asked, I would request that you keep your  
13 answers very short. But this is really an  
14 opportunity now for the panel to further  
15 discuss the area, to think about in  
16 anticipation of the voting which is going to be  
17 in an hour from now, what further information  
18 we need or that we still feel uncertain on.  
19 Dr. Goss. Oh, and then -- go ahead.

20 DR. GOTTSCHALK: I would like to  
21 circle back to two things. One of these is  
22 duration of follow-up. You know, some have  
23 mentioned the FDA mandate of 15 years, but that  
24 really comes out of the gene therapy arena to  
25 look at the risk of insertional mutagenesis

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1 after the transplantation of genetically  
2 modified T-cells, so the question is really,  
3 how long should we really follow-up these  
4 patients?

5 And the other question is, or kind of  
6 comment is, right now there's no clear proof  
7 test to track the commercial products, and I  
8 would encourage the companies to develop those  
9 because in the PRO assessment if something

10 comes up, of course we want to know, what is  
11 the precursor, are there some measurable  
12 CAR T-cells, and that is not right now  
13 available outside the research setting, so I  
14 think that probably is another key thing you  
15 really need to assess the safety involved in  
16 the long-term outcome of these cells.

17 DR. ROSS: Can I just ask,  
18 Dr. Gottschalk, are you asking that question to  
19 the panel to say clinically, what's the  
20 appropriate time?

21 DR. GOTTSCHALK: What is the  
22 appropriate time, how long should we really  
23 follow these patients?

24 DR. CHENG: So basically from what I  
25 understand and from what I heard, like

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1 Dr. Abikoff mentioned, that 54 percent of  
2 patients went from partial to complete. I  
3 assume the symptomatology would also follow the  
4 difference between a partial versus complete  
5 remission in nine to 12 months, which means it  
6 would seem to me you would have to follow at  
7 least 12 months in order to get -- and that was

8 a question that was asked before, so if it's a  
9 question about the three choices that are  
10 listed there, it would have to be at least 12  
11 months or up to 24, in order to see whether or  
12 not the patient symptoms would follow the  
13 response rate.

14 DR. GOSS: Actually I have a  
15 contextual question because I mentioned it  
16 before, but I was wondering if Tamara could  
17 clarify it for us. The way these questions are  
18 asked, they're not asked specifically about CAR  
19 T, I just want to be sure that's correct. So  
20 we're asking about PROs in the Medicare  
21 population, and we're asking about some  
22 specific measures, and then we're asking about,  
23 you know, ability to implement. But nowhere  
24 does it say specific conditions and nowhere  
25 does it say, you know, specific treatments, so

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1 we might have to think more broadly if we're  
2 putting a time frame. I understand for CAR T,  
3 you know, six, 12 or 24 months might be  
4 appropriate, but for other situations it may be  
5 longer, and so it may affect how we answer

6 these questions. I just want to make sure I  
7 understand the questions.

8 MS. JENSEN: Do you want to add to  
9 this, Joe? So, I do think it's broader than --  
10 yes, we didn't specifically say CAR T, so is it  
11 generalizable, but I'll also look to the team  
12 to see if they want to add to anything. Okay,  
13 I'm good. Yes, you are absolutely right.

14 DR. CHENG: If that's the case, then  
15 it makes some of these questions challenging,  
16 like the length of duration of follow-up,  
17 because if it's not disease-specific, the  
18 duration will then obviously change.

19 DR. GOSS: And again, most of these  
20 measures are PRO oriented, or I should say  
21 oncology oriented, so there's an implication  
22 there, but it's not, it certainly wouldn't be  
23 relevant for cardiovascular disease, but the  
24 way we're answering some of these questions in  
25 that general sense, CMS could apply these

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1 recommendations, I guess, more broadly. I just  
2 want to make sure we know what we're voting on.

3 MS. JENSEN: Correct. So, you know,

4 the national coverage determination that's open  
5 is CAR T, but yes, some of these answers could,  
6 depending on what happened, could be used, we  
7 might be able to use these more generally as we  
8 move forward in other types of technologies.

9 DR. JAMES: And I'd just like to put  
10 forth a question I have for CMS. The selection  
11 of the PROs is one that you have judged based  
12 on oncology. There's a whole host of others  
13 out there. AHRQ has developed a whole series  
14 of CAHPS measures that are used for making  
15 judgment on the quality of care that is being  
16 done to patients from their perspective. And  
17 the National Quality Forum also contracts with  
18 CMS in looking at PROMIS for the development of  
19 quality-based measurements. Are any of those  
20 in play or are those future developments?

21 MS. JENSEN: Those are not in play for  
22 this MEDCAC.

23 DR. CHENG: I would actually, then,  
24 just kind of think that we are looking at this  
25 specifically for CAR T, because for example if

1 you look at PROMIS, PROMIS goes from everything

2 from, you know, the PROMIS-10 which you can  
3 crosswalk to EQ-5D-3L for example, as a  
4 historical control to these other  
5 disease-specific measures, so I think when  
6 we're looking at this, unless we put it in the  
7 context of oncology and specifically CAR T, it  
8 would be very challenging to make heads or  
9 tails of how to answer it, because you can't  
10 compare PROMIS, for example, to MDASI outside  
11 of a specific context.

12 DR. ROSS: Yes, I think we should be  
13 encouraged on oncology for sure, including  
14 CAR T. I would keep us, we should not be  
15 thinking outside of the oncology space.

16 DR. GOSS: Just a comment, or really  
17 thought that I had that I want to share with  
18 the other panel members is particularly when  
19 you think of a situation like CAR T, I was an  
20 observer at a MEDCAC a month ago on a  
21 completely different therapeutic area, and one  
22 of the presenters got up and said, you know,  
23 one of the most important things for a patient  
24 that they want to know is what can I do to stay  
25 independent.

1           So on one level, PROs, everything that  
2 is local and specific to an individual patient  
3 is important to them, and you know, being  
4 functional and not being a burden on their  
5 families or their caregivers is very important,  
6 and it seems to me that the patients who got  
7 into the CAR T trials didn't get there by  
8 chance, there is significant selection bias  
9 where patients sought out treatments, they had  
10 nothing, you know, they felt they had nothing  
11 else to lose, but not every patient with a  
12 cancer actually feels that way, so some  
13 patients are willing to forgo treatment and  
14 toxicity in order to be able to have peace, you  
15 know, for whatever time they have left.

16           And so I think there's a -- and the  
17 industry team I think did a very nice job of  
18 presenting your studies, except I don't think  
19 your findings from your trials are  
20 generalizable to Medicare per se because of  
21 that, number one. And so I think your notion  
22 that well, we believe in PROs but we're going  
23 to measure them in trials, I think is great and  
24 is important, helps the regulators make  
25 decisions, but it doesn't generalize to what

1 Medicare has to deal with in terms of whether  
2 or not these should be more broadly available.  
3 And so I think it's important if you're not  
4 going to support this type of notion for going  
5 forward in some really systematic way, I think  
6 you'd be well advised to Phase IV studies to  
7 include additional PROs to help inform these  
8 questions that will inevitably come up again,  
9 because I think, you know, the population  
10 you've studied is a very slim narrow part of  
11 the population that could eventually be trying  
12 to seek out this treatment, and I think that's  
13 a concern.

14 DR. CUYJET: I just have a comment to  
15 make and I think one of, part of this  
16 conversation in order to be used as a  
17 brainstorming operation on how to do things  
18 better, it was mentioned that physical activity  
19 is a very important monitor for improvement.  
20 In my past experience we used telemedicine in  
21 experiences with heart failure in Medicare  
22 patients, and usually you don't just have heart  
23 failure, you have diabetes or hypertension, or  
24 an abnormal lipid profile, and if you can get



25 patients to invest -- it doesn't make any sense

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1 to invest in the heart failure and not take  
2 care of your diabetes and not take care of your  
3 other comorbid conditions. So I think we ought  
4 to start thinking about the mobile technology  
5 that's emerging as an opportunity to track  
6 patient improvement independent of pure  
7 patient-reported outcomes which can be very  
8 subjective depending on time of day and how I'm  
9 feeling and how much pain I'm having. But  
10 there may be a more, a better tool to improve  
11 outcomes over a period of time, and it's stuff  
12 that can be transmitted electronically, it  
13 doesn't require -- you can decide whether you  
14 want to monitor on a weekly or monthly, or  
15 bimonthly basis, it's entirely -- I think we  
16 ought to start thinking about how going forward  
17 we can track better patient outcomes and  
18 responses more easily with better information.

19 DR. PERISSINOTTO: I just want to add  
20 to what you said because, or to both of you  
21 actually, because my biggest challenge now as a  
22 clinician in geriatric and palliative medicine

23 is exactly this question. When my patients go  
24 to see their oncologists or their surgeons, and  
25 they're trying to understand the risks and

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1 benefits of consenting to these procedures, and  
2 most of the time the data that's presented is  
3 around survival, it's around dying in the OR  
4 and very narrow-based things. Yet what my  
5 patients want from me is to know what is my  
6 quality of life going to be like afterwards and  
7 am I going to walk, what is my cognition going  
8 to be like? So these tools, whether we use  
9 them to approve drugs, or we use them in what  
10 part, it is important to know how is this going  
11 to inform them, and help me as a clinician in  
12 assisting them in their decisions.

13 DR. GOSS: Yeah, I think a shared  
14 decision-making model would be really important  
15 here.

16 DR. PERISSINOTTO: A novel idea.

17 DR. GOSS: And you know, honestly, and  
18 I don't know how this would play to the PRO  
19 experts, but if you look at the PRO and getting  
20 some kind of time trade-off, and giving the

21 vignette of what, you know, if you think about  
22 what cytokine release syndrome looks like and  
23 explain that to a patient, you know, here's  
24 your chance of survival but here's what you're  
25 going to have to go through before you're

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1 feeling better that might be even more  
2 relevant because that has to do with the  
3 decision to treat or not to treat, which is  
4 different than what do I look like nine months  
5 from now. So just a thought, because it's a  
6 different set of concerns, but it could be very  
7 important to patients and to providers.

8 MR. FRANKEL: I don't want to harp on  
9 it, but when you treat those patients in a  
10 geriatric population, when it's presented to  
11 them, do you think that it's crucial for them  
12 to see the alternate paths? So in other words,  
13 if you hone in on one potential therapy and you  
14 discuss the risks versus benefits, and they say  
15 well, they don't want to have these types of  
16 potential adverse events, and then I think a  
17 key part of that discussion has to be well, if  
18 you don't do this therapy, these are the

19 quote-unquote adverse effects of not doing  
20 anything and it's not exactly a pretty list  
21 either. So I think if you don't give that list  
22 in a very clear and transparent way, then the  
23 patients are not really making an informed  
24 decision, they're making a very biased decision  
25 because they're only seeing the drawbacks,

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1 they're not seeing the optimal potential  
2 outcomes and the risks, in this case death, and  
3 a death that could potentially have a very  
4 challenging period of time until that point in  
5 the next few months.

6 DR. PERISSINOTTO: Yeah. I think if  
7 you really look at a shared decision-making  
8 model, you're not really starting with the  
9 risks and benefits, you're starting with what  
10 are your goals and what are you hoping for, and  
11 if you start from that point, then you back in  
12 to the risks and benefits of treatment versus  
13 not treatment. So I think that absolutely you  
14 have to, you know, weigh the cases of, for  
15 example, you have metastatic GI cancer and you  
16 can go through a surgery and chemotherapy and

17 have significant toxicity and end up with, you  
18 know, a pouch after the surgery, and without  
19 that treatment you will have a bowel  
20 obstruction, so it is looking at how you will  
21 die. It is also looking at limited life  
22 expectancies, and as we heard with these  
23 trials, you're looking at people already with  
24 limited life expectancies, and you do have to  
25 weigh those, but it is starting from the start.

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1 What we don't often do as clinicians is saying  
2 what are you hoping for, because if someone  
3 tells me I don't want to prolong my life and I  
4 want to focus on the quality, then that's a  
5 different thing than saying I want to prolong  
6 my life at all costs regardless of side  
7 effects.

8 MR. FRANKEL: Do you think that that  
9 answer can change depending on the data that's  
10 provided to them, so if a person says --

11 DR. PERISSINOTTO: Yes, absolutely.

12 MR. FRANKEL: Right, so that's what  
13 I'm saying that may be critical here, because  
14 we're dealing with a patient population where

15 education is key and that's what the PROs are  
16 all about, it's to be able to educate the  
17 clinician and the patient alike. And if you're  
18 only collecting and emphasizing the data of the  
19 risks versus benefits of the new therapy and  
20 not very clearly articulating the alternative  
21 course, then I just think that patients are, I  
22 mean in the context of patient advocacy, most  
23 patients in my experience want to live and they  
24 want to live with good quality of life, that's  
25 ideal.

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1 Then the question comes, well, if you  
2 can't have that, then what's the best  
3 alternative? And many times if the best  
4 alternative is survival, it's well, how's that  
5 survival going to look, is it going to be  
6 painful next few months and death in one, let's  
7 say for example. Is it going to be a painful  
8 next six weeks and then survival with a  
9 restoration of quality of life, perhaps with  
10 CAR T therapy.

11 DR. JAMES: We're addressing the whole  
12 area of patient preference, which is really not

13 addressed in PROs, but is the next step up from  
14 that, because you can get informed information  
15 and share that with the patient, but without  
16 understanding what the patient's goals and what  
17 the family goals are, you don't have that  
18 preference.

19 DR. ROSS: Yeah, and I'll just note  
20 that in shared decision-making, it's not  
21 treatment yes-no, it's treatment path A versus  
22 treatment path B, and PROs are aspects of  
23 information that help inform those goals of  
24 care, they're not actually the shared  
25 decision-making themselves. So we're talking

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1 about information that can inform the patient  
2 care plan in terms of what their goals are,  
3 what their objectives are, if quality of life  
4 is more important than mortality, or whatever  
5 the tradeoffs may be.

6 DR. CHENG: I think that's the  
7 disconnect that I'm seeing here, is that we're  
8 talking about the quote-unquote real world  
9 application and real world assessment versus  
10 the clinical trials and the inclusion-exclusion

11 criteria, because we know that when we treat  
12 patients in a clinic we don't follow  
13 exclusion-inclusion criteria the way we do in  
14 these clinical trials.

15       And so maybe getting back to one of  
16 the discussion points was are there other PRO  
17 assessments, I guess the question I would pose  
18 to the group is, are these too specific for  
19 cancer per se, and should we be looking at this  
20 as a simple EQ-5D to say look, all we want to  
21 care about is what's the quality of life here  
22 of a treatment, something that's easy to do.  
23 EQ-5D, I think it's hard to argue that that's  
24 an onerous add, but yet would give us a general  
25 health assessment whether or not going for a

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1 treatment, or any type of treatment, whether  
2 it's CAR T or lifelong IVIG, et cetera, how  
3 much effect it would really help. Because  
4 that's something that we could then talk to our  
5 patients about, the whole idea of the quality  
6 of life here.

7       So I guess that's a question. I know  
8 we're being asked to talk about these PROs, but



9 one of the concerns from everything we heard is  
10 that these are just too onerous to get on a  
11 regular basis for the data that we're getting  
12 out of it, and should we take a step back and  
13 just say for example for PROMIS, let's start  
14 off with a PROMIS-10, let's start off with  
15 something modular that we can build up, but  
16 still gives us the idea that, is this treatment  
17 really helping somebody, or are we looking at  
18 administrative or other variables that the  
19 patients may or may not care about?

20 DR. GARRIDO: I think there's a  
21 tension between finding a scale that provides  
22 useful enough information but that is still  
23 going to be sensitive to changes after  
24 receiving a treatment. We don't want measures  
25 that are too specific related to very specific

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1 adverse events that are only going to occur in  
2 a subset of patients or a subset of therapies,  
3 but if we go to too global of a measure, will  
4 we see any meaningful change in that after  
5 receiving some type of therapy, whether it's  
6 CAR T or something else. I don't know the

7 answer.

8 DR. PERISSINOTTO: And also I think  
9 that it was mentioned a couple times before,  
10 you know, in surveys you have patients that say  
11 oh, I remember three words from last time, I  
12 don't have problems with cognition if I  
13 remember them from last time, but certainly  
14 that's part of it. But I do like one of the  
15 things that I think Dr. Basch said in terms of  
16 the additional characteristics of maybe having  
17 some general health assessments and part of  
18 that would be dealing with function and  
19 physical health, because I think I mentioned  
20 earlier, it is clearly a struggle for all of us  
21 in how we measure cognition in a more reliable  
22 way, both in terms of adequate measures and  
23 then being self-reported.

24 DR. CIVIC: I have kind of a related  
25 thing, a little bit of a committee process

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1 that, you know, we're looking at these  
2 instruments and we may or may not want to add  
3 more to our list at this point, but we've also  
4 talked about how this is a developing field and

5 that there aren't necessarily, you know, there  
6 might be better instruments developed in the  
7 future or CAR T specific instruments. So it's  
8 like choosing some, you know, one, two, three,  
9 four, or seven of them now, probably that's not  
10 going to preclude the addition of other  
11 instruments as they get developed, but it's not  
12 entirely clear.

13 DR. ROSS: Well, I can let CMS answer  
14 that. I think because it's part of the  
15 discussion questions that they are looking for  
16 our advice on things that they should be  
17 considering in the future as well. Is that  
18 correct, or not exactly?

19 MS. JENSEN: No, I think -- I mean,  
20 that's -- I don't think this is the end of this  
21 conversation, and so this is what we have for  
22 today.

23 DR. ROSS: Dr. Yang.

24 DR. YANG: You know, I think we can  
25 either make these PROs too specific or too

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1 general. If you make them specific, you have  
2 the advantage of them being applied to the

3 treatment you're talking about. If they're too  
4 general, you put the burden on patients to  
5 decide their global assessment. And if they're  
6 nauseated at the time they're filling out the  
7 questionnaire, they're not thinking about the  
8 surgery they need next week or the IV they  
9 might need next week, they're thinking about  
10 this problem right now, so I see that as the  
11 problem in both directions.

12       And so -- and the other problem I have  
13 is when you're talking about metastatic cancer,  
14 for instance, the outcomes for solid tumors are  
15 all the same, so you're just discussing how  
16 much intervention, quality of life and other  
17 issues, but if you're talking about a  
18 potentially curative treatment, who fills out  
19 the questionnaire for the patient who dies, and  
20 what do they put down? So I don't really know  
21 how you can globally assess, then, the impact  
22 of the treatment if the other alternatives, if  
23 one of the possibilities is you could get over  
24 this cancer.

25       DR. GARRIDO: Related to that, we have

1 our question about the optimal duration, or how  
2 confident we are about whether we can get  
3 meaningful results if we look at a six-month  
4 trajectory, or a 12- or 24-month trajectory of  
5 PROs. I'm concerned about long-term monitoring  
6 of PROs and survival drop off, especially if we  
7 end up doing some kind of long-term follow-up of  
8 a therapy versus standard of care using a  
9 registry. So if we have patients who aren't  
10 able to answer questions either because of an  
11 adverse event or due to differential mortality  
12 in the two groups, it's going to make it very  
13 difficult to isolate these after the treatment,  
14 even with the best practices in observational  
15 data analyses.

16 I run into this all of the time in  
17 palliative care research where one of the main  
18 goals is improving quality of life, we're not  
19 trying to improve survival, but it's, the  
20 people who are getting palliative care versus  
21 not, no matter what we do to try and make  
22 comparable treatment groups, they're so  
23 different that it's really hard to isolate the  
24 effects of palliative care.

25 Just something to take into account as

1 we're thinking about meaningful durations for  
2 looking at these measures.

3 DR. CHENG: And I guess I would just  
4 answer, you know, if someone passes away,  
5 certainly functional outcomes are pretty  
6 irrelevant, so I don't think that's really a  
7 good point. But I think one of the things  
8 we're really talking about is just the  
9 challenge of postmarket surveillance of any  
10 treatment, and I don't think that's something  
11 that we can say isn't needed or is too hard to  
12 do, because the durability of any treatment is  
13 going to be pretty important irrespective of  
14 the field. And so I think from a larger  
15 standpoint, we do need to look at ways of  
16 assessing what is the durability and the  
17 long-term outcomes for our patients, and  
18 whether or not it's a short-term gain or  
19 long-term gain does depend on whether or not we  
20 want to put our patients through this overall.

21 So as a surgeon, if I do a surgery  
22 for, you know, for a metastatic tumor, then  
23 sure, I can get them through it and they'll do  
24 fine for six months and still pass away, but  
25 boy, is that worth it if they have

1 postanesthesia issues like postoperative  
2 cognitive issues, et cetera. And I think that  
3 is the question that needs to be answered here,  
4 which is, is there a surveillance tool, you  
5 know, that we can use to assess whether CAR T  
6 or other treatments have the durability of  
7 effect, or is it something that we follow for  
8 three to six months, it seems okay, and then in  
9 two years durability starts waning, and whether  
10 or not that's worthwhile, or is it the IVIG  
11 that helps keep it from getting there?

12 DR. ROSS: And I also want to  
13 emphasize, particularly in the realm of  
14 postmarket surveillance, we're not necessarily  
15 just thinking about these PROs for patients who  
16 lived versus died and how to then assess the  
17 missingness, but you know, quite often this  
18 type of information as new therapies come to  
19 market and other therapies gets tweaked, this  
20 happens quite commonly in the medical device  
21 space, you know, that the devices themselves  
22 improve over time, you use this type of  
23 information to better understand symptom burden

24 with those sort of, you know, iterative product  
25 over time, and comparatively across products.

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1 MR. FRANKEL: In terms of the  
2 neurologic toxicities, which really goes hand  
3 in hand again with the question of how long to  
4 capture the data, I think that it was mentioned  
5 by Dr. Go and Dr. Ferrusi about 14 months or  
6 so, that Dr. Go mentioned 14 months in terms of  
7 seeing a complete response when there wasn't  
8 until that point. But what about, in terms of  
9 neurotoxicity, how long did you see that at  
10 that point at 14 months, what percentage of the  
11 patients that had neurotoxic effects did you  
12 still see at that point along the line?

13 DR. ROSS: If you get a question  
14 directed to you, you may stand.

15 DR. GO: Will Go from Kite. So yeah,  
16 we're still exploring that in all of our  
17 studies, so we don't really have all the data  
18 right now, but in general we only had at that  
19 point in time when we get a cutoff that we will  
20 then file with the FDA as well as will be  
21 publishing in a journal, we had one patient



22 with grade one memory impairments. So that's  
23 sort of the work that we're doing, but again,  
24 these are sort of crude measures as well, and  
25 so as I said before, we're trying to figure out

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1 how to do this because we are very interested  
2 in PROs, as well as neurocognitive testing, so  
3 we're exploring those opportunities right now.

4 MR. FRANKEL: And how do you, did you  
5 adjudicate which neurotoxicities observed were  
6 related specifically to therapy versus just  
7 because of hospitalization that you see in an  
8 older population?

9 DR. GO: Right, where's my FDA  
10 colleague? Oh, he's gone, all right. I'm  
11 going to tap him in in a second here. So  
12 that's exactly right, and so obviously we do  
13 have attributions in our clinical study to, is  
14 it related to the CAR T therapy, is it related  
15 to disease, is it related to the cytotoxic  
16 conditioning chemotherapy.

17 MR. FRANKEL: Or is it delirium  
18 because of an in-hospital experience?

19 DR. GO: Correct, so we don't have it

20 specifically, so all we ask is, is it related  
21 to CAR T, yes-no, and then in our new trials is  
22 it related to disease, yes-no, and that's the  
23 only thing that we really have, it's very crude  
24 and rudimentary, but this is exactly the  
25 question to clinically, and as I used to

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1 practice, I mean, I get delirium in the ICU  
2 with all the beeping, you know, when I was an  
3 ICU resident, so that's --  
4 DR. GOSS: Was the neurotoxicity  
5 measured with a PRO measure or was it usually  
6 Barthel or something else?

7 DR. GO: So, this is why -- sorry to  
8 interrupt, but this is why the second time we  
9 did a mini-mental status exam, because one,  
10 that had already been tested in blinatumomab  
11 prospectively, but obviously you can't even do  
12 a mini-mental status exam because you're in  
13 Grade 3 neurotox that means a mini-mental  
14 status exam's a zero. And that's why, you  
15 know, rudimentary we went from a 27 to 30,  
16 which is roughly normal, the patients who had  
17 Grade 3 neurotox went to zero and then came

18 back to roughly 27 or 30.

19 This is the challenge. We didn't do  
20 any proxies, because obviously that's another  
21 challenge to collect that. And then to your  
22 point, though, this is why I think it's  
23 challenging, especially in the neurotox  
24 setting. What we try to do for consistency,  
25 number one, we use a CTCAE 4.03, we do not

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1 have, we collected all of it, we provided all  
2 of it. And this is a challenge because some of  
3 the neurotoxicities were at the time of death  
4 and clearly with patients who had progressive  
5 disease, so this is why this is a challenge,  
6 because as a lot of people know, how do people  
7 die of leukemia and lymphoma and fascial  
8 diseases and progressive diseases, and a lot of  
9 times the patients are in an impaired  
10 neurologic state.

11 And I'll tap in my FDA colleague.

12 DR. KLUETZ: Paul Kluetz from the FDA.

13 The issue of attribution, I can't stress, is  
14 one of the most challenging factors in  
15 evaluating clinical trial data because of all

16 of the situations that you've just mentioned.  
17 Disease can cause it, treatment can cause it,  
18 comorbid disease can cause it, and many times  
19 it's very complicated and challenging. In  
20 fact, this is why we don't like disease-free  
21 survival as an endpoint. Even though it would  
22 be nice and clean, when patients die, it's very  
23 hard to determine whether or not it was due to  
24 disease or due to something else.  
25 And so what, the way we look at

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1 attributions in a randomized trial, if it was a  
2 randomized placebo-controlled trial, even  
3 better, but we hardly see those much anymore,  
4 so in single-armed trials we just assume that  
5 for now, until we get more data, that it is at  
6 least possibly related to the drug.

7 DR. BAR: Specifically regarding the  
8 neurotoxicity, so there is some data from our  
9 institution, and definitely patients that are  
10 undergoing the CAR T-cell CD-19, they do have  
11 neurotoxicity, patients who develop CRS are at  
12 high risk for developing neurotoxicity, and  
13 there has been a trial that was published a few

14 months ago from our institution trying to  
15 understand the mechanism that caused the  
16 neurotoxicity.

17       There is no clear answer but there is  
18 some direction showing probably that there is  
19 some permeability of the blood-brain barrier  
20 that caused increased toxicity. However, what  
21 we found was that the neurotoxicity is usually  
22 short term, and even patients that develop  
23 neurotoxicities, patients with CRS  
24 neurotoxicity, it is usually short term and  
25 patients do recover within a number of weeks.

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1       So when we started to look at  
2 longer-term data on those patients, we did not  
3 see the patients that had short-term  
4 neurotoxicity have some cognitive defects  
5 later, its early data, and we didn't study  
6 that very systematically, but from the data  
7 that we have, even though they had high risk of  
8 neurotoxicity if they developed CRS, it was  
9 short term and with no long-term cognitive  
10 effects.

11       DR. ROSS: Dr. Yang.

12 DR. YANG: You know, when I think  
13 about the issue of mandating a PRO, I think of  
14 you have a purpose for that, you know how to  
15 use that information if you're going to mandate  
16 its acquisition, and I wonder how I would use  
17 that information if I were a clinician and had  
18 an infinite database on PRO information, I  
19 could present 13 percent nausea incidence to a  
20 patient, five percent severe, or I could say,  
21 you know, 87 percent of patients don't have  
22 nausea, and I could say the same thing about  
23 almost every complication. And then I would  
24 also have to integrate that with, you know, you  
25 have a 30 to 35 percent chance of having a

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1 durable complete response. So I find this, the  
2 information is definitely helpful, definitely  
3 useful, but I don't know how I would  
4 specifically apply it in a uniform consistent  
5 fashion, if I had it all.

6 DR. OLSON: I can respond to that to a  
7 certain extent as a patient, specifically as a  
8 patient who reported outcomes with one of the  
9 CAR T clinical trials since I was in one

10 unfortunately about, almost eight years ago.  
11 There was one patient, actually two patients  
12 treated before me. We had no idea what was  
13 going to happen, but fortunately I had two  
14 patients just ahead of me, and I was warned  
15 that I was going to get sick and what the  
16 symptoms were going to be and what to expect,  
17 and that really helped because when I started  
18 getting sick I went yay, it's working. But it  
19 takes a little of the scary out of it to know,  
20 okay, somebody else got treated this way, I'm  
21 reacting the same way, it makes me feel better.

22       And again, you know, whether it's  
23 percentages or just general information of  
24 here's what to expect, especially in clinical  
25 trials where, you know, the trial I was in, the

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1 only animals that had been treated were mice  
2 before the three of us, so there's not much  
3 data, but as that data grows, they will feed it  
4 back to the patient who is considering a  
5 clinical trial, and I think that is really  
6 important.

7       And another piece of that is that I'm

8 part of the LLS First Connections program, so I  
9 provide to a certain extent the  
10 patient-reported outcomes, a lot of CAR T  
11 patients that we have now, to approved drugs,  
12 I'm getting probably a connection one or two  
13 times a month, and what the patients want to  
14 hear is what do I expect, what's going to  
15 happen, I've read this. And of course you have  
16 to be careful, you're not their doctor, but at  
17 the same time it's so comforting to them to  
18 hear somebody else that's been through this and  
19 they survived, and to know what they're going  
20 to expect, you know, when they go into those  
21 things, okay, you know, Doug told me that's  
22 going to happen.

23 I literally just yesterday got an  
24 email from one of my First Connections patients  
25 that I had talked to probably three months ago,

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1 and she sent me a note. She said I want you to  
2 know I went through my CAR T therapy and it was  
3 really a battle, and she had a lot of  
4 neurological effects, she said they knew how to  
5 treat them, she was rough, but on the other



6 side she's in complete remission, and it was  
7 really worth the fight, but she knew all the  
8 stuff going in. So really, it takes the fear  
9 away.

10 And then I have one more comment since  
11 I have the microphone. We were talking about  
12 duration of follow-up. CAR T-19 is creating a  
13 whole new group of patients that haven't  
14 existed before. A lot of us don't have  
15 B-cells. I get my IVIG once every, right now  
16 I'm getting it every other month, I was getting  
17 it every three months, and we're feeling our  
18 way along, but to be able to continue, I'm  
19 almost eight years out as I said, but I'm still  
20 without B-cells, and there's a whole bunch of  
21 folks coming behind me, so I think long-term  
22 follow-up is going to be important.

23 And just one more comment about PROs  
24 and clinical trials. I get a little bit  
25 worried when I hear some folks expressing the

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1 fact that it may make it difficult to get some  
2 clinical trial started or that it's going to  
3 slow down enrollment or whatever, and I

4 certainly would caution CMS with regard to how  
5 it gets the requirement for PROs in clinical  
6 trials, how it gets applied, such that it  
7 doesn't get in the way of patients getting  
8 enrolled and being able to participate in the  
9 clinical trials, because right now it offers so  
10 much help and hope to patients.

11 DR. ROSS: That was very helpful,  
12 thank you. Other questions from the committee,  
13 or discussion points that they want further  
14 considered?

15 DR. CHENG: I think, you know, when we  
16 talk about PROs and clinical trials, I think,  
17 you know, there's a number of what I would call  
18 disconnects because we're seeing a number of  
19 societies and national organizations develop  
20 their own registry effort to collect patient  
21 outcomes, whether it's Neurosurgery with QOD,  
22 or the Society of Thoracic Surgeons, et cetera,  
23 and so it seems that some of the concerns that  
24 were brought up before, with for example data  
25 acquisition I think Red Cap is a fairly cheap

1 or free tool. And so I think as we move

2 forward, I think PROs are going to be something  
3 that is going to be captured, like in  
4 Washington State where we capture scope over in  
5 Seattle on a regular basis, irrespective of  
6 whether it's a trial or not, and I think the  
7 idea of understanding what is the quality of  
8 the care we provide patients is going to be  
9 important, not just for oncology but just for  
10 medicine in general, and I'm saying that the  
11 tide is going in that direction where we have  
12 to be able to show the benefits of anything  
13 that we do in medicine, and whether we like it  
14 or not, the PROs are probably going to be the  
15 best way to do that, because you can't do a  
16 randomized controlled trial for every single  
17 question we have in medicine, not  
18 realistically.

19 DR. ROSS: Dr. James.

20 DR. JAMES: One point that Dr. Basch  
21 raised that I think we need to consider, and  
22 that is as we sit and talk in terms of what is  
23 being recorded by physicians on adverse effects  
24 versus what comes out from a PRO, there's a  
25 gap, and how do we explain to our patients that

1 gap between what's being reported to the FDA  
2 and what patients are reporting.

3 DR. ROSS: Dr. Feinglass.

4 DR. FEINGLASS: I think everybody on  
5 this panel, industry included, would be the  
6 first to say that the patient's view is  
7 important, and at the end of the day the  
8 patient comes first. None of us are here for  
9 any other reason than that, or I hope we're  
10 not. But I think the other piece surrounding  
11 PROs in general is the heterogeneity of the  
12 field, which in some cases the PRO is  
13 constructed to be different from another PRO on  
14 purpose, so I think what the panel has to make  
15 a decision on at the end of the day in answer  
16 to the questions from CMS are not specific to  
17 CAR T, they are specific to, are PROs useful in  
18 the arena of clinical research, and how do they  
19 inform the decisions that we are going to make  
20 while we see patients, while we conduct trials,  
21 while we design treatments.

22 So one of the things I want to make  
23 sure we all remember at the end of the day is  
24 not only the number one thing, that the patient  
25 is at the end of it, the second part is as

1 we're considering the tools, they're  
2 heterogeneous on purpose in some cases, and how  
3 are we going to use that uniformly, are they  
4 generalizable, are they not generalizable, and  
5 I think what we've heard many of the presenters  
6 say today is they are meant to be used in very  
7 specific cases, they are meant to be used with  
8 care, they are not applicable to everything,  
9 and I think as we consider the questions, we  
10 need to keep that in the back of our minds.

11 DR. GOSS: I was just going to say a  
12 couple last thoughts, and I agree. I mean, the  
13 patient effectively is critical, and I think  
14 it's valuable that CMS is actually asking these  
15 questions and addressing this issue. I  
16 remember a number of years back, so some of the  
17 data we can get from clinical trials that is  
18 very useful, and obviously it's almost a  
19 standard, and probably is a standard for FDA to  
20 require PRO endpoints in, or PRO data in  
21 clinical trials. And there's still, even with  
22 that, there's still some gaps, so there's  
23 opportunities to fill gaps.

24 My recommendation to CMS is to keep

25 asking these questions, and to be adaptable and

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1 flexible because the field is in motion, it's  
2 evolving, and I think there's valuable  
3 information here that will guide decisions made  
4 by patients, decisions made by payers on, you  
5 know, what's valuable and important in  
6 treatment and technology. And you know, I  
7 think overall, we would be well served to  
8 remember that. When we don't have complete  
9 clinical information, PRO data can at least  
10 provide good color and give guidance.

11 So, I remember 15 or 20 years ago, CMS  
12 issued a coverage determination or an NCD for  
13 treatment refractory seizures. The important  
14 question was, well, it doesn't cure the  
15 disease, why would we pay for this, and the  
16 answer is because it showed a significant  
17 reduction in the events, and there was a strong  
18 correlation between the reduction in events and  
19 patients' quality of lives. So there is a way  
20 to bring it back to patients, and that's really  
21 important for us to remember.

22 So even if we don't have a perfect

23 solution, it's worth trying to improve the  
24 field and make incremental gains as we go,  
25 rather than throw our hands up and say there is

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1 nothing to do.

2 DR. ROSS: Okay. Do any of the  
3 committee members want to make any final  
4 comments during this discussion period?

5 MR. FRANKEL: I echo a point that was  
6 made a little bit earlier, that I would be  
7 hopeful that CMS would, when evaluating PROs in  
8 general, are not necessarily specific to CAR T  
9 therapy because I think it's broader than that.  
10 Dr. Basch had noted that he was skeptical of  
11 the concerns of it being a barrier to implement  
12 PROs. On the other hand, I can't help but  
13 notice that that wasn't the position that was  
14 being suggested by multiple stakeholders, both  
15 in the background materials we have, the  
16 presentations today, and anecdotally. I've  
17 heard such a sentiment before, and I would hope  
18 that there wouldn't be any barrier to access  
19 for patients because ultimately, as was just  
20 said, the patients ultimately are the focus

21 here, and if there was a potential barrier for  
22 a hospital or clinician to providing the CAR T  
23 therapy for a patient, or whatever therapy that  
24 might be due to the lack of resources to  
25 implement the PRO, whether the CMS would have

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1 some kind of pathway in place, that that type  
2 of concern could be processed and addressed so  
3 that those patients wouldn't be detrimentally  
4 affected by a PRO being implemented, and that  
5 you would just get the gains from PRO, not that  
6 kind of unfortunate unintended trickle down  
7 consequence.

8 DR. ROSS: I think it's an important  
9 point to be cautious. I would be very  
10 surprised if there was any hospital or  
11 facility, a place that could perform CAR T and  
12 couldn't collect PROs, it's just --

13 MR. FRANKEL: That's basically what  
14 was presented.

15 DR. ROSS: I understand. And I just  
16 wanted to say, Dr. Goss, to my knowledge, and I  
17 thought about this, I do not think PROs are  
18 required as part of an oncology approval or any



19 other FDA regulatory action. Our FDA colleague  
20 has left us, but I just wanted to make sure  
21 that was correct.

22 So, we've basically chatted for an  
23 hour, we're a little bit ahead of schedule, but  
24 I think now is the time when we're going to get  
25 ready to call a motion to vote. Is there

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1 anything formal that has to happen?

2 MS. JENSEN: So, not necessarily  
3 formal, but I just want to go on record. We  
4 are planning on doing this vote different than  
5 we have done in the past, not in the voting,  
6 but just that they're not going to record it on  
7 their phones or with an electronic device.  
8 We're going to, the panel will be saying their  
9 name and their vote, we will record it, you  
10 will see it behind us just because, we're doing  
11 this because we thought we might run out of  
12 time and there are 23 questions.

13 I also wanted to go on record to say  
14 the official vote is the piece of paper that  
15 the panelists give us, so when we are done with  
16 this meeting we will take those papers, we will

17 compare with what we have here and make sure  
18 that it's accurate before we post it on our  
19 website.

20 So before we continue, I want to make  
21 sure the panel is okay with moving forward and  
22 how we're going to vote, and that you say your  
23 name and give us your vote, we'll record it.  
24 It's supposed to be put on behind us, are  
25 they -- okay, good. So, go ahead.

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1 DR. GOSS: One question on the ballot.

2 MS. JENSEN: Sure.

3 DR. GOSS: So question number -- are  
4 we going to answer each question and go through  
5 the vote on each question, because question  
6 number two really is contingent on the vote on  
7 question one, so is that an average score of  
8 2.5 for my scoring, or the average of 2.5 for  
9 the group scoring is required before we would  
10 vote on number two?

11 DR. ROSS: The group scoring.

12 DR. FEINGLASS: So we will be going  
13 through them one by one.

14 DR. ROSS: I think it will be easier

15 to go one by one. I'm going to just read the  
16 questions from the beginning to make sure we're  
17 all on the same page, give everyone a chance to  
18 just think them through, and --

19 DR. YANG: One other clarification.

20 DR. ROSS: Yes, of course.

21 DR. YANG: With respect to section  
22 five, question B, the how confident are we that  
23 any of those studies in these populations,  
24 you're talking about usual care versus a  
25 protocol-driven intervention. Is that a

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1 randomized trial you're talking about  
2 predominantly?

3 DR. ROSS: Correct, that is my  
4 understanding of the question.

5 DR. YANG: Okay.

6 DR. ROSS: So, on May 16, 2018, CMS  
7 opened a national coverage determination on  
8 CAR T-cell therapy for Medicare beneficiaries  
9 with advanced cancer. As part of this NCD  
10 analysis, MEDCAC will review the evidence  
11 specific to PROs. We are seeking  
12 recommendations from the MEDCAC panel regarding

13 how existing PRO assessment tools should be  
14 incorporated into future clinical studies,  
15 including future clinical studies on CAR T-cell  
16 therapy.

17 I think just as a side note, we've  
18 discussed future clinical studies in the  
19 oncology space and I think we've come to that  
20 as an agreement or expectation that we're  
21 talking about oncology studies specifically,  
22 including CAR T-cell therapy studies.

23 The MEDCAC will focus on specific PRO  
24 assessment tools and important characteristics  
25 of a PRO assessment tool.

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1 Then we are going to assess whether  
2 the scientific evidence supports a specific  
3 number of outcome assessment studies, design  
4 characteristics, study duration, and suitable  
5 controls for applying PROs to health outcomes  
6 research. This meeting will explore these  
7 challenges. And just to note, MEDCAC panels do  
8 not make coverage determinations but CMS  
9 benefits from their advice.

10 So, voting questions. For each voting

11 question, please use the following scale  
12 identifying your level of confidence, with a  
13 score of one being low or no confidence, and  
14 five representing high confidence, so it's a  
15 scale of one to five, and I'll go one by one.

16 Question 1.a. How confident are you  
17 that the PRO-CTCAE, the Patient-Reported  
18 Outcomes Common Terminology Criteria for  
19 Adverse Events, is valid and generalizable to  
20 the Medicare population?

21 DR. CUYJET: Al Cuyjet, I'm going to  
22 vote three.

23 DR. CHENG: Joe Cheng, vote four.

24 DR. CIVIC: Diane Civic, four.

25 MR. FRANKEL: Naftali Frankel, three.

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1 DR. GARRIDO: Melissa Garrido, three.

2 MS. ELLIS: Can you excuse me one  
3 second?

4 DR. ROSS: Can we start from the  
5 beginning?

6 DR. CUYJET: Al Cuyjet, I voted three  
7 on question 1.a.

8 DR. CHENG: Joe Cheng, vote four.

9 DR. CIVIC: Diane Civic, four.  
10 MR. FRANKEL: Naftali Frankel, three.  
11 DR. GARRIDO: Melissa Garrido, three.  
12 DR. GOSS: Tom Goss, three.  
13 DR. JAMES: Tom James, four.  
14 DR. LAMON: Joel Lamon, four.  
15 DR. PERISSINOTTO: Carla Perissinotto,  
16 four.  
17 DR. FEINGLASS: Shami Feinglass,  
18 three.  
19 DR. GOTTSCHALK: Steve Gottschalk,  
20 four.  
21 DR. OLSON: Doug Olson, four.  
22 DR. YANG: Jim Yang, three.  
23 DR. ROSS: Question 1.b, how confident  
24 are you that the M.D. Anderson Symptom  
25 Inventory is valid and generalizable to the

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1 Medicare population?

2 DR. CUYJET: Al Cuyjet, I vote four.  
3 DR. CHENG: Joe Cheng, three.  
4 DR. CIVIC: Diane Civic, three.  
5 MR. FRANKEL: Naftali Frankel, three.  
6 DR. GARRIDO: Melissa Garrido, three.

7 DR. GOSS: Tom Goss, four.  
8 DR. JAMES: Tom James, four.  
9 DR. LAMON: Joel Lamon, four.  
10 DR. PERISSINOTTO: Carla Perissinotto,  
11 three.  
12 DR. FEINGLASS: Shami Feinglass,  
13 three.  
14 DR. GOTTSCHALK: Steve Gottschalk,  
15 three.  
16 DR. OLSON: Doug Olson, four.  
17 DR. YANG: Jim Yang, four.  
18 DR. ROSS: Okay, question 1.c. How  
19 confident are you that the European  
20 Organization for Research and Treatment of  
21 Cancer Quality of Life Questionnaire, the  
22 EORTC-QLC-C30 core questionnaire, is valid and  
23 generalizable to the Medicare population?  
24 DR. CUYJET: Al Cuyjet, three.  
25 DR. CHENG: Joe Cheng, four.

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1 DR. CIVIC: Diane Civic, four.  
2 MR. FRANKEL: Naftali Frankel, three.  
3 DR. GARRIDO: Melissa Garrido, four.  
4 DR. GOSS: Tom Goss, five.

5 DR. JAMES: Tom James, five.  
6 DR. LAMON: Joel Lamon, four.  
7 DR. PERISSINOTTO: Carla Perissinotto,  
8 four.  
9 DR. FEINGLASS: Shami Feinglass, four.  
10 DR. GOTTSCHALK: Steve Gottschalk,  
11 four.  
12 DR. OLSON: Doug Olson, four.  
13 DR. YANG: Jim Yang, four.  
14 DR. ROSS: Question 1.d, how confident  
15 are you that the University of Washington  
16 Quality of Life, UW-QOL, is valid and  
17 generalizable to the Medicare population?  
18 DR. CUYJET: Al Cuyjet, I voted two.  
19 DR. CHENG: Joe Cheng, two.  
20 DR. CIVIC: Diane Civic, two.  
21 MR. FRANKEL: Naftali Frankel, one.  
22 DR. GARRIDO: Melissa Garrido, one.  
23 DR. GOSS: Tom Goss, one.  
24 DR. JAMES: Tom James, two.  
25 DR. LAMON: Joel Lamon, two.

1 DR. PERISSINOTTO: Carla Perissinotto,  
2 one.



3 DR. FEINGLASS: Shami Feinglass, two.

4 DR. GOTTSCHALK: Steve Gottschalk,

5 two.

6 DR. OLSON: Doug Olson, two.

7 DR. YANG: Jim Yang, one.

8 DR. ROSS: Question 1.e. How

9 confident are you that the Patient-Reported

10 Outcome Measurement Information System or

11 PROMIS, is valid and generalizable to the

12 Medicare population?

13 DR. CUYJET: Al Cuyjet, four.

14 DR. CHENG: Joe Cheng, five.

15 DR. CIVIC: Diane Civic, four.

16 MR. FRANKEL: Naftali Frankel, five.

17 DR. GARRIDO: Melissa Garrido, four.

18 DR. GOSS: Tom Goss, three.

19 DR. JAMES: Tom James, five.

20 DR. LAMON: Joel Lamon, four.

21 DR. PERISSINOTTO: Carla Perissinotto,

22 five.

23 DR. FEINGLASS: Shami Feinglass,

24 three.

25 DR. GOTTSCHALK: Steve Gottschalk,

1 four.

2 DR. OLSON: Doug Olson, four.

3 DR. YANG: Jim Yang, four.

4 DR. ROSS: Question 1.f. How

5 confident are you that the Electronic

6 Self-Report-Cancer, ESRA-C, is valid and

7 generalizable to the Medicare population.

8 DR. CUYJET: Al Cuyjet, two.

9 DR. CHENG: Joe Cheng, two.

10 DR. CIVIC: Diane Civic, one.

11 MR. FRANKEL: Naftali Frankel, one.

12 DR. GARRIDO: Melissa Garrido, one.

13 DR. GOSS: Tom Goss, two.

14 DR. JAMES: Tom James, two.

15 DR. LAMON: Joel Lamon, two.

16 DR. PERISSINOTTO: Carla Perissinotto,

17 two.

18 DR. FEINGLASS: Shami Feinglass, one.

19 DR. GOTTSCHALK: Steve Gottschalk,

20 two.

21 DR. OLSON: Doug Olson, one.

22 DR. YANG: Jim Yang, one.

23 DR. ROSS: And the final, question

24 1.g, how confident are you that the Functional

25 Living Index for Cancer, or FLIC, is valid and

1 generalizable to the Medicare population?

2 DR. CUYJET: Al Cuyjet, two.

3 DR. CHENG: Joe Cheng, two.

4 DR. CIVIC: Diane Civic, one.

5 MR. FRANKEL: Naftali Frankel, one.

6 DR. GARRIDO: Melissa Garrido, one.

7 DR. GOSS: Tom Goss, two.

8 DR. JAMES: Tom James, one.

9 DR. LAMON: Joel Lamon, two.

10 DR. PERISSINOTTO: Carla Perissinotto,  
11 one.

12 DR. FEINGLASS: Shami Feinglass, one.

13 DR. GOTTSCHALK: Steve Gottschalk,  
14 one.

15 DR. OLSON: Doug Olson, one.

16 DR. YANG: Jim Yang, two.

17 DR. ROSS: Great. So before we move  
18 on to the next section of questions, each panel  
19 member does have an opportunity to state for  
20 the record why they voted the way they voted,  
21 or if they want to explain any of the intention  
22 behind their vote.

23 MR. FRANKEL: On just PROMIS, the one  
24 trend that stuck out listening to the different  
25 stakeholders was, that was the common thread, I

1 think, from across the board, where it was  
2 either, even those that aren't very  
3 enthusiastic about PROs in general noted that  
4 PROMIS was recommended and it was in that  
5 context. So there was, if I'm not mistaken,  
6 that was, had the broadest consensus among the  
7 speakers and different stakeholders today.

8 DR. ROSS: Do any other panel members  
9 have comments?

10 DR. YANG: I think it's not only to  
11 win, but whether they're adequate in and of  
12 themselves that is deeply important so, you  
13 know, the range of your vote matters too.

14 MS. JENSEN: Can you state your name  
15 for the record for that last comment, please.

16 DR. YANG: Jim Yang.

17 MS. JENSEN: Thank you.

18 DR. GOSS: Just one last quick  
19 comment, Tom Goss. For the PRO-CTCAE, I was  
20 concerned about the respondent burden there for  
21 many items, and I was unclear on how it's  
22 useful. It sounded like people are using bits  
23 and pieces of it, and I think that when you cut

24 something up that was developed as a whole,  
25 that undermines some of the validity

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1 potentially.

2 DR. ROSS: Are we allowed to take  
3 comments at this point in response?

4 MS. JENSEN: One. Go ahead.

5 DR. BASCH: It was actually developed  
6 as a library, so each individual item is  
7 validated individually, so it's not meant to be  
8 used, so actually the purpose is for people to  
9 use little pieces of it, you know, anywhere  
10 between, you know, one and, you know, as many  
11 as you want.

12 MS. JENSEN: What's your name?

13 DR. BASCH: Ethan Basch.

14 DR. ROSS: Thank you, Dr. Basch.

15 Okay. Four of the PRO assessments  
16 were rated as a 2.5 or higher. That's the  
17 PRO-CTCAE, the MDASI -- is that how you say it  
18 -- MDASI, the EORTC-QLQ-C30, and PROMIS.  
19 Whoever invented PROMIS, they had a good  
20 thought in mind, marketing in mind.

21 So we now move on to question number

22 two, which is, considering those four PRO  
23 assessments with greater than or equal to 2.5,  
24 we're going to vote whether or not those  
25 assessments -- it says combined, but are we

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1 considering them independently? I'm looking to  
2 the CMS team to make sure that the wording is  
3 right.

4 (Inaudible discussion.)

5 DR. ROSS: So it will be all four of  
6 those.

7 DR. FEINGLASS: Josh, can I clarify  
8 one thing?

9 DR. ROSS: It's Joe, but yes.

10 DR. FEINGLASS: Joe, sorry.

11 DR. ROSS: That's fine.

12 DR. FEINGLASS: So my clarification is  
13 on age, and one thing we didn't discuss before,  
14 I believe that many of these that we've now  
15 picked were designed for adults, and so when  
16 we're asking this question of not sensitive to  
17 difference of age, can we make an assumption  
18 there that we're not talking about pediatrics?

19 DR. GOSS: Actually I don't think so,

20 because one of the studies showed that even in  
21 the pediatrics, they were Medicare  
22 beneficiaries, some 25 percent of the patients  
23 had Medicare, presumably because they were  
24 disabled because of their illness.

25 DR. FEINGLASS: So the reason I'm

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1 asking is because it potentially changes some  
2 people's votes, because if you're looking at  
3 who is sensitive to age, if they're only  
4 designed for someone over the age of 18, that  
5 impacts it. So can we make, for the purposes  
6 of the panel in voting, can we make an  
7 assumption that we're looking at focus on the  
8 Medicare age?

9 DR. ROSS: Yes, I believe we are  
10 making the assumption that we are considering  
11 the use for Medicare beneficiaries with cancer.

12 DR. YANG: The other wording,  
13 available supporting evidence, do you mean  
14 available or sufficient?

15 UNIDENTIFIED PANELIST: Adequate.

16 DR. ROSS: I think it fits our job to  
17 say whether it's sufficient.

18 DR. YANG: Should that word be  
19 available or adequate? Because available means  
20 any evidence.

21 DR. ROSS: Would the CMS team like to  
22 respond?

23 DR. SZARAMA: Any evidence.

24 DR. ROSS: Any evidence, okay. Thank  
25 you.

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1 DR. CIVIC: And then like for A, are  
2 we adding them all up, or each one has to stand  
3 on its own?

4 MS. JENSEN: So it's a single vote.

5 DR. CIVIC: No, I know that, but is it  
6 additive or, you know what I mean?

7 MS. JENSEN: Well, it is how the panel  
8 wants to interpret it, the questions are the  
9 questions, but you're making a single vote,  
10 realizing you're taking the four that you've  
11 done 2.5 or higher and saying whether, yes or  
12 no collectively on that.

13 DR. ROSS: So conceptually it's a  
14 challenging exercise, to consider all four PRO  
15 assessment tools and whether any, yes-no, will



16 meet these criteria.

17 So, does the panel need me to restate  
18 the four that we're voting on, or is everybody  
19 on board? Okay.

20 So question A, the characteristic is  
21 the breadth of measures in emotional, social  
22 and physical well-being, yes-no.

23 DR. CUYJET: Al Cuyjet, yes.

24 DR. CHENG: Joe Cheng, yes.

25 DR. CIVIC: Diane Civic, yes.

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1 MR. FRANKEL: Naftali Frankel, yes.

2 DR. GARRIDO: Melissa Garrido, yes.

3 DR. GOSS: Tom Goss, yes.

4 DR. JAMES: Tom James, yes.

5 DR. LAMON: Joel Lamon, yes.

6 DR. PERISSINOTTO: Carla Perissinotto,  
7 yes.

8 DR. FEINGLASS: Shami Feinglass, yes.

9 DR. GOTTSCHALK: Steve Gottschalk,  
10 yes.

11 DR. OLSON: Doug Olson, yes.

12 DR. YANG: Jim Yang, yes.

13 DR. ROSS: 2.B, quick throughput to

14 apply to clinical study.

15 DR. CUYJET: Al Cuyjet, yes, again.

16 DR. CHENG: Joe Cheng, yes.

17 DR. CIVIC: Diane Civic, yes.

18 MR. FRANKEL: Naftali Frankel, yes.

19 DR. GARRIDO: Melissa Garrido, yes.

20 DR. GOSS: Tom Goss, yes.

21 DR. JAMES: Tom James, yes.

22 DR. LAMON: Joel Lamon, yes.

23 DR. PERISSINOTTO: Carla Perissinotto,

24 yes.

25 DR. FEINGLASS: Shami Feinglass, yes.

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1 DR. GOTTSCHALK: Steve Gottschalk,

2 yes.

3 DR. OLSON: Doug Olson, yes.

4 DR. YANG: Jim Yang, yes.

5 DR. ROSS: 2.C, transferable to

6 community practice settings.

7 DR. CUYJET: Al Cuyjet, yes.

8 DR. CHENG: Joe Cheng, yes.

9 DR. CIVIC: Diane Civic, yes.

10 MR. FRANKEL: Naftali Frankel, yes.

11 DR. GARRIDO: Melissa Garrido, yes.

12 DR. GOSS: Tom Goss, yes.  
13 DR. JAMES: Tom James, yes.  
14 DR. LAMON: Joel Lamon, yes.  
15 DR. PERISSINOTTO: Carla Perissinotto,  
16 yes.  
17 DR. FEINGLASS: Shami Feinglass, yes.  
18 DR. GOTTSCHALK: Steve Gottschalk,  
19 yes.  
20 DR. OLSON: Doug Olson, yes.  
21 DR. YANG: Jim Yang, yes.  
22 DR. ROSS: 2.D, measures are not  
23 sensitive to differences in age.  
24 DR. CUYJET: Al Cuyjet, with the  
25 clarification, yes.

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1 DR. CHENG: Joe Cheng, no.  
2 DR. CIVIC: Diane Civic, yes.  
3 MR. FRANKEL: Naftali Frankel, yes.  
4 DR. GARRIDO: Melissa Garrido, yes.  
5 DR. GOSS: Tom Goss, yes.  
6 DR. JAMES: Tom James, yes.  
7 DR. LAMON: Joel Lamon, yes.  
8 DR. PERISSINOTTO: Carla Perissinotto,  
9 yes.

10 DR. FEINGLASS: Shami Feinglass, yes.  
11 DR. GOTTSCHALK: Steve Gottschalk, no.  
12 DR. OLSON: Doug Olson, yes.  
13 DR. YANG: Jim Yang, no.  
14 DR. ROSS: Question 2.E, measures are  
15 not sensitive to line of therapy.  
16 DR. CUYJET: Al Cuyjet, yes again.  
17 DR. CHENG: Just a point of  
18 clarification. So this is a double negative,  
19 so we're saying it is sensitive to line of  
20 therapy?  
21 MS. JENSEN: Correct.  
22 DR. CHENG: Then no.  
23 DR. ROSS: No, no, the measures are  
24 not sensitive to line of therapy. It doesn't  
25 matter which line of therapy they're receiving,

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1 but PRO is still a valid assessment.  
2 You're voting no?  
3 DR. CHENG: I'm saying it's a double  
4 negative, so if I'm saying that PROs are  
5 sensitive to a line of therapy, the vote is no.  
6 DR. ROSS: Right.  
7 DR. CHENG: Then Joe Cheng, no.

8 DR. CIVIC: Diane Civic, yes.  
9 MR. FRANKEL: Naftali Frankel, yes.  
10 DR. GARRIDO: Melissa Garrido, yes.  
11 DR. GOSS: Tom Goss, yes.  
12 DR. JAMES: Tom James, yes.  
13 DR. LAMON: Joel Lamon, yes.  
14 DR. PERISSINOTTO: Carla Perissinotto,  
15 yes.  
16 DR. FEINGLASS: Shami Feinglass, yes.  
17 DR. GOTTSCHALK: Steve Gottschalk, no.  
18 DR. OLSON: Doug Olson, no.  
19 DR. YANG: Jim Yang, no.  
20 DR. ROSS: Okay, 2.F, the measures are  
21 not sensitive to comorbidities.  
22 DR. CUYJET: Al Cuyjet, yes.  
23 DR. CHENG: Joe Cheng, no.  
24 DR. CIVIC: Diane Civic, no.  
25 MR. FRANKEL: Naftali Frankel, yes.

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1 DR. GARRIDO: Melissa Garrido, yes.  
2 DR. GOSS: Tom Goss, yes.  
3 DR. JAMES: Tom James, yes.  
4 DR. LAMON: Joel Lamon, yes.  
5 DR. PERISSINOTTO: Carla Perissinotto,

6 yes.

7 DR. FEINGLASS: Feinglass, yes.

8 DR. GOTTSCHALK: Steve Gottschalk, no.

9 DR. OLSON: Doug Olson, yes.

10 DR. YANG: Jim Yang, no.

11 DR. ROSS: Question 2.G, measures are

12 generalizable to studies of combinations of

13 therapies.

14 DR. CUYJET: Al Cuyjet, yes, again.

15 DR. CHENG: Joe Cheng, yes.

16 DR. CIVIC: Diane Civic, yes.

17 MR. FRANKEL: Naftali Frankel, yes.

18 DR. GARRIDO: Melissa Garrido, yes.

19 DR. GOSS: Tom Goss, yes.

20 DR. JAMES: Tom James, yes.

21 DR. LAMON: Joel Lamon, yes.

22 DR. PERISSINOTTO: Carla Perissinotto,

23 yes.

24 DR. FEINGLASS: Feinglass, yes.

25 DR. GOTTSCHALK: Steve Gottschalk,

1 yes.

2 DR. OLSON: Doug Olson, yes.

3 DR. YANG: Jim Yang, yes.

4 DR. ROSS: And the last question, 2.H,  
5 used in net benefit analysis based on symptom  
6 burden and well-being.

7 DR. CUYJET: Al Cuyjet, yes, again.

8 DR. CHENG: Joe Cheng, yes.

9 DR. CIVIC: Diane Civic, no.

10 MR. FRANKEL: Naftali Frankel, yes.

11 DR. GARRIDO: Melissa Garrido, yes.

12 DR. GOSS: Tom Goss, yes.

13 DR. JAMES: Tom James, yes.

14 DR. LAMON: Joel Lamon, no.

15 DR. PERISSINOTTO: Carla Perissinotto,  
16 yes.

17 DR. FEINGLASS: Feinglass, yes.

18 DR. GOTTSCHALK: Steve Gottschalk,  
19 yes.

20 DR. OLSON: Doug Olson, yes.

21 DR. YANG: Jim Yang, yes.

22 DR. ROSS: Again, I'd like to open it  
23 up to give panel members an opportunity to  
24 explain their vote or any of the information  
25 they want to state for the record.

2 DR. GARRIDO: This is Melissa Garrido.  
3 I used a very minimal standard, so if any of  
4 the PROs had any of the evidence, I voted yes.

5 DR. GOSS: Tom Goss. I would say the  
6 same thing. My assumption was that if in the  
7 aggregate either one of them covered it, then  
8 the answer had to be yes.

9 DR. JAMES: I'm Tom James with  
10 B and C. Specifically we've heard from some of  
11 the health systems that there were  
12 difficulties, but we heard from others that  
13 they have been able to achieve those, so that's  
14 why I voted yes, I think it's possible.

15 DR. ROSS: Any other panel members  
16 want to make a comment?

17 DR. FEINGLASS: One thing I neglected  
18 to state at the very opening of this meeting,  
19 which is probably obvious to all industry in  
20 here, but my comments reflect the all-industry  
21 point of view, they do not reflect any  
22 individual company's view.

23 DR. ROSS: Stated for the record.

24 DR. GOTTSCHALK: Steve Gottschalk. I  
25 just want to state for D, since I'm the only



1 pediatrician on the panel, I think they are age  
2 sensitive, and we need PRO measurements  
3 specifically for pediatric patients.

4 DR. ROSS: Okay. We have two  
5 discussion questions to address before we move  
6 on. Just to state to the panel explicitly, are  
7 there PRO assessments other than those listed  
8 in question one that have adequately stated  
9 evidence-based criteria and processes that you  
10 would want to raise, bring to the attention of  
11 CMS for further consideration? Then, are there  
12 additional desired characteristics other than  
13 listed in question two that you believe should  
14 be taken into consideration? They're not voted  
15 on, these are discussion questions for the  
16 panel members, if people have responses.

17 DR. GOSS: So, a couple quick things.  
18 I would say -- this is Tom Goss -- I think that  
19 the FACT has been used, and it has a number of  
20 condition-specific measures that I think have  
21 been validated in a variety of cancer types.

22 And I would also say that the EORTC  
23 has a number of tumor-specific add-on modules  
24 that I would encourage CMS to evaluate them as  
25 far as their utility for specific conditions.

1 DR. CHENG: I would just make a  
2 comment that we need to look at the PROs in a  
3 context of the presenting episode of care. So  
4 for example, someone made allusion to using,  
5 you know, CAR T therapy in the future for  
6 multiple myeloma, but if the patient, for  
7 example, had a pathological spine fracture with  
8 spinal cord compression or injury, they would  
9 certainly need a different type of assessment  
10 based on metastatic spine disease or their  
11 presenting episode of care, compared to using  
12 what we're talking about today as well.

13 DR. CUYJET: Okay, Al Cuyjet, I'll  
14 just make a comment, it might sound like a  
15 broken record, but I'm looking out at the  
16 audience, I might see a couple millennials and  
17 no Gen-Z around, so these patient-reported  
18 outcome tools have been developed by boomers  
19 and older. I think the technology is available  
20 to enable us to do a better job of collecting  
21 information, and I'll leave it at that.

22 DR. FEINGLASS: Shami Feinglass. The  
23 two things I'd add are from a diversity and  
24 inclusion standpoint in clinical trials. One

25 thing that was brought up by Dr. Basch, who we

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1 now know when he stands up at the mic, are the  
2 availability of language translations, I think  
3 is really important. And as you look at  
4 developing, those of you in the room who are  
5 developing more patient-reported outcome  
6 assessment tools, is there diversity and  
7 inclusion in the people that you're looking at  
8 when you're putting them, asking them those  
9 questions, are those questions relevant to them  
10 from a diversity and inclusion standpoint? So  
11 to be specific, gender, cultural, where are  
12 these people from, what do they identify as,  
13 what are their languages, can they actually  
14 answer your questions.

15 DR. GOSS: Tom Goss. I would just say  
16 that I would also suggest that CMS evaluate  
17 whether or not there are licensing fees for any  
18 of the measures that we recommend, I think  
19 there is some variability of some of them. And  
20 I would also say that it would be important as  
21 well that, for any of these measures that they  
22 would consider, clearly the validity of

23 translations is important as already noted, and  
24 I think the -- there was another one, and if I  
25 think of it, I'll come back to it.

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1 Oh, respondent burden. I think you  
2 should always have a sense of the time frame it  
3 will take to complete it, because the oncology  
4 patients may be fatigued or having other  
5 symptoms, so what seems like a short time, but  
6 it could be a long time, and certainly if  
7 someone were going through these symptoms and  
8 you were listing all of that, that would be, I  
9 think hard.

10 DR. GARRIDO: Melissa Garrido. I  
11 would add an adequate variation in the  
12 responses, so an absence of other floor and  
13 ceiling effects.

14 DR. ROSS: If we have no additional  
15 comments, we're going to move on to question  
16 three. How confident are you that each of the  
17 following assessment intervals are appropriate  
18 measurement periods for a valid PRO assessment?

19 DR. CUYJET: Al Cuyjet, question 3.a,  
20 answer one.

21 DR. CHENG: Joe Cheng, three.  
22 DR. CIVIC: Diane Civic, three.  
23 MR. FRANKEL: Naftali Frankel, three.  
24 DR. GARRIDO: Melissa Garrido, three.  
25 DR. ROSS: Pause, pause, pause, sorry.

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1 So we're talking about 3.a, the variable  
2 event-dependent frequency interval.  
3 MS. JENSEN: Yes, Garrido is three.  
4 DR. GOSS: Tom Goss, one.  
5 DR. JAMES: Tom James, three.  
6 DR. LAMON: Joel Lamon, one.  
7 DR. PERISSINOTTO: Carla Perissinotto,  
8 one.  
9 DR. FEINGLASS: Feinglass, one.  
10 DR. GOTTSCHALK: Steve Gottschalk,  
11 two.  
12 DR. OLSON: Doug Olson, three.  
13 DR. YANG: Jim Yang, four.  
14 DR. ROSS: Again on a scale of one to  
15 five, how confident are you in the fixed  
16 time-dependency frequency interval?  
17 DR. CUYJET: Al Cuyjet, four.  
18 DR. CHENG: Joe Cheng, four.

19 DR. CIVIC: Diane Civic, four.  
20 MR. FRANKEL: Naftali Frankel, four.  
21 DR. GARRIDO: Melissa Garrido, three.  
22 DR. GOSS: Tom Goss, four.  
23 DR. JAMES: Tom James, three.  
24 DR. LAMON: Joel Lamon, five.  
25 DR. PERISSINOTTO: Carla Perissinotto,

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1 five.  
2 DR. FEINGLASS: Feinglass, four.  
3 DR. GOTTSCHALK: Steve Gottschalk,  
4 four.  
5 DR. OLSON: Doug Olson, four.  
6 DR. YANG: Jim Yang, two.  
7 DR. ROSS: Okay, question four, again  
8 a scale of one to five. How confident are you  
9 that a PRO assessment over the course of the  
10 following study duration identifies a  
11 meaningful durable treatment effect with a  
12 valid PRO? A, six months.  
13 DR. CUYJET: Two, Al Cuyjet.  
14 DR. CHENG: Joe Cheng, two, but  
15 specifically for CAR T.  
16 DR. CIVIC: Diane Civic, two.

17 MR. FRANKEL: Naftali Frankel, two.  
18 DR. GARRIDO: Melissa Garrido, three.  
19 DR. GOSS: Tom Goss, two.  
20 DR. JAMES: Tom James, two.  
21 DR. LAMON: Joel Lamon, one.  
22 DR. PERISSINOTTO: Carla Perissinotto,  
23 two.  
24 DR. FEINGLASS: Feinglass, two.  
25 DR. GOTTSCHALK: Steve Gottschalk,

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1 two.  
2 DR. OLSON: Doug Olson, three.  
3 DR. YANG: Jim Yang, three.  
4 DR. ROSS: Hold on one second. Okay,  
5 question 4.b, 12 months?  
6 DR. CUYJET: Al Cuyjet, three.  
7 DR. CHENG: Joe Cheng, four.  
8 DR. CIVIC: Diane Civic, three.  
9 MR. FRANKEL: Naftali Frankel, three.  
10 DR. GARRIDO: Melissa Garrido, two.  
11 DR. GOSS: Tom Goss, three.  
12 DR. JAMES: Tom James, four.  
13 DR. LAMON: Joel Lamon, four.  
14 DR. PERISSINOTTO: Carla Perissinotto,

15 four.  
16 DR. FEINGLASS: Feinglass, three.  
17 DR. GOTTSCHALK: Steve Gottschalk,  
18 three.  
19 DR. OLSON: Doug Olson, four.  
20 DR. YANG: Jim Yang, four.  
21 DR. ROSS: Question 4.c, 24 months?  
22 DR. CUYJET: Al Cuyjet, five.  
23 DR. CHENG: Joe Cheng, five.  
24 DR. CIVIC: Diane Civic, three.  
25 MR. FRANKEL: Naftali Frankel, four.

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1 DR. GARRIDO: Melissa Garrido, one.  
2 DR. GOSS: Tom Goss, four.  
3 DR. JAMES: Tom James, five.  
4 DR. LAMON: Joel Lamon, five.  
5 DR. PERISSINOTTO: Carla Perissinotto,  
6 five.  
7 DR. FEINGLASS: Feinglass, three.  
8 DR. GOTTSCHALK: Steve Gottschalk,  
9 four.  
10 DR. OLSON: Doug Olson, four.  
11 DR. YANG: Jim Yang, five.  
12 DR. ROSS: Great. It was my mistake,



13 I forgot to ask after question three so I'll do  
14 them together, questions three and four, I want  
15 to give panel members an opportunity to explain  
16 their voting if they would like to state for  
17 the record anything they took into  
18 consideration. That's questions three and  
19 four. Dr. Yang.

20 DR. YANG: Jim Yang. For question  
21 number three, I interpreted that as being based  
22 on the individual investigator in the study if  
23 you can pick the cogent times for intervals,  
24 versus automatic fixed times regardless of  
25 treatment. Is that a correct interpretation?

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1 DR. ROSS: Well, my understanding, and  
2 other members can contribute, is that it's a  
3 fixed time interval as sort of prespecified at  
4 one week, at four weeks, at eight weeks, not  
5 necessarily that you could pick it.

6 DR. YANG: Not necessarily picked for  
7 every study.

8 DR. ROSS: Correct.

9 DR. YANG: But the other one, that  
10 would be something where the investigator would

11 decide what time intervals were the cogent

12 ones, for 3.a?

13 DR. ROSS: Yes, the investigator would

14 decide that this is the right time to ask the

15 PRO.

16 DR. GOTTSCHALK: So for 3.b I

17 interpreted it could be like for the first

18 eight weeks it would be weekly, and then you

19 would go to monthly intervals; is that correct?

20 DR. ROSS: That is correct.

21 DR. GOTTSCHALK: All right.

22 DR. CHENG: Yeah. I interpreted it

23 with the variable event-dependent, it's just,

24 that's the real world situation where the

25 patient would come back to clinic at plus or

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1 minus X number of days or weeks based on the

2 follow-up time.

3 DR. GOSS: Yeah, I interpreted -- this

4 is Tom Goss -- I interpreted that 3.a has, you

5 define specific events and then you administer

6 the PRO only when those events occur, and if

7 the event doesn't happen you don't really need

8 the PRO. So the occurrence of an event, say

9 neutropenia for example, as opposed to  
10 standardized set times, and these are  
11 representative set times, but in any given  
12 protocol for any particular study, the  
13 intervals would be defined based on the  
14 research question at hand. You know, it  
15 wouldn't always be weekly, it could be  
16 variable --

17 DR. ROSS: As long as it's fixed.

18 DR. GOSS: -- at three weeks or four  
19 weeks, 12 weeks, you know, 26 weeks, 52 weeks.

20 DR. ROSS: Right. Do people have any  
21 other comments they want to make about question  
22 four, or additional comments about three?

23 DR. GARRIDO: Melissa Garrido. My  
24 diminishing scores with the greater time lines  
25 reflect a diminishing confidence that we can

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1 isolate a treatment effect from confounding  
2 factors over time.

3 MR. FRANKEL: On question four, my  
4 concern was just the lack of data that's  
5 available at this point in terms of durability,  
6 you know, it still remains to be seen on the

7 time tables that we're talking about if we're  
8 going to see positive or negative effects. So  
9 when we're talking about 14 months plus with  
10 dramatic potential responses, I just figured  
11 that a longer window of time at this point  
12 until we see data to say otherwise, is a  
13 prudent approach. But obviously, we're basing  
14 our opinions on a real lack of data, so I  
15 assume this will be reevaluated as more data  
16 comes in.

17 MS. JENSEN: Can you state your name  
18 just for the record, please?

19 MR. FRANKEL: Naftali Frankel.

20 MS. JENSEN: Thank you.

21 DR. ROSS: Any additional comments  
22 from the panel members for the record?

23 DR. CUYJET: I based my decision  
24 primarily on that slide that showed the  
25 longitudinal course for treatment over time, so

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1 we have to monitor these patients over the  
2 course, there's going to be a lot of variation  
3 in this patient population and their responses,  
4 so we have to look for the responses.

5 DR. ROSS: Would you please just

6 restate your name?

7 DR. CUYJET: Al Cuyjet, I'm sorry.

8 DR. YANG: This is Jim Yang, I would

9 just like to clarify again. I am not assessing

10 this integrating all units of times equally

11 like, it was mentioned that with a longer time

12 period the effects would diminish if equally

13 valued and weighted, that's not the way I was

14 interpreting it.

15 DR. ROSS: Great. We're going to move

16 on to question number five, again, confidence

17 on a scale of one to five, how confident are

18 you that PRO assessments can provide meaningful

19 results when studied with each of the following

20 control populations, 5.a, patient him/herself,

21 before and after intervention.

22 DR. CUYJET: Al Cuyjet, four.

23 DR. CHENG: Joe Cheng, four.

24 DR. CIVIC: Diane Civic, three.

25 MR. FRANKEL: Naftali Frankel, three.

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1 DR. GARRIDO: Melissa Garrido, three.

2 DR. GOSS: Tom Goss, four.

3 DR. JAMES: Tom James, three.

4 DR. LAMON: Joel Lamon, five.

5 DR. PERISSINOTTO: Carla Perissinotto,  
6 five.

7 DR. FEINGLASS: Feinglass, four.

8 DR. GOTTSCHALK: Steve Gottschalk,  
9 four.

10 DR. OLSON: Doug Olson, five.

11 DR. YANG: Jim Yang, three.

12 DR. ROSS: Question 5.B, usual care  
13 versus a protocol-driven intervention.

14 DR. CUYJET: Al Cuyjet, four.

15 DR. CHENG: Joe Cheng, four.

16 DR. CIVIC: Diane Civic, four.

17 MR. FRANKEL: Naftali Frankel, four.

18 DR. GARRIDO: Melissa Garrido, three.

19 DR. GOSS: Tom Goss, four.

20 DR. JAMES: Tom James, four.

21 DR. LAMON: Joel Lamon, five.

22 DR. PERISSINOTTO: Carla Perissinotto,  
23 three.

24 DR. FEINGLASS: Feinglass, three.

25 DR. GOTTSCHALK: Steve Gottschalk,

1 four.

2 DR. OLSON: Doug Olson, three.

3 DR. YANG: Jim Yang, five.

4 DR. ROSS: And finally, question 5.C,

5 historical control.

6 DR. CUYJET: Al Cuyjet, one.

7 DR. CHENG: Joe Cheng, two.

8 DR. CIVIC: Diane Civic, two.

9 MR. FRANKEL: Naftali Frankel, four.

10 DR. GARRIDO: Melissa Garrido, two.

11 DR. GOSS: Tom Goss, three.

12 DR. JAMES: Tom James, two.

13 DR. LAMON: Joel Lamon, one.

14 DR. PERISSINOTTO: Carla Perissinotto,

15 one.

16 DR. FEINGLASS: Feinglass, one.

17 DR. GOTTSCHALK: Steve Gottschalk,

18 one.

19 DR. OLSON: Doug Olson, three.

20 DR. YANG: Jim Yang, one.

21 DR. ROSS: Great, thank you. Does any

22 panel member want to state for the record their

23 thinking behind their votes?

24 DR. CUYJET: Al Cuyjet. I'll just use

25 my experience as a clinical investigator in the

1 ALLHAT trial, you had to have elevated blood  
2 pressure to be enrolled whether you were on  
3 treatment of not. At the end of the study, 85  
4 percent of our study cohort was at (inaudible)  
5 blood pressure, so I am a firm believer in  
6 protocol-driven interventions.

7 DR. CHENG: Joe Cheng. For historical  
8 controls, I think only a few of the PROs like  
9 PROMIS are able to be cross-walked to other  
10 historical things like EQ-5D, and so I voted  
11 down low because some of the other ones we  
12 chose would not have an easy crosswalk ability.

13 DR. FEINGLASS: This is Dr. Feinglass.  
14 I agree with Dr. Cheng on that.

15 DR. ROSS: Great. So I believe we  
16 have come to the end of our votes. We now have  
17 an opportunity for a final open panel  
18 discussion and I have only 20 minutes. Each  
19 panel member has an opportunity to give their  
20 final remarks in a maximum of two minutes if we  
21 could just go in order, and you can decline,  
22 you don't have to take advantage of this  
23 opportunity.

24 DR. CUYJET: This I think is my last  
25 MEDCAC meeting, I think I have to take a year



1 break, but it's been a very interesting  
2 experience.

3 DR. ROSS: Don't forget your name.

4 DR. CUYJET: Al Cuyjet.

5 DR. ROSS: I think Dr. Basch has left.

6 DR. CUYJET: But it's been great  
7 participating in all these discussions because  
8 it's such a wide variety of opinions regarding  
9 whatever the topic is that we discussed, and  
10 it's been very refreshing to be engaged and  
11 involved in it, so I want to thank the MEDCAC.

12 DR. CHENG: Joe Cheng. I echo that  
13 and thank you for all the insight that you've  
14 given me across the various spectra of this  
15 topic.

16 DR. CIVIC: Yes, this is Diane Civic.  
17 I really learned a lot today and am glad I  
18 participated. Just in terms of my own  
19 experience and the questions, I think I really,  
20 you know, put a lot more effort into answering  
21 the first set of questions and looking at the  
22 specific instruments, and I think, you know,  
23 the other ones were much harder maybe for a lot

24 of us, and based on a lot less data, but we all  
25 did the best we could.

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1 MR. FRANKEL: Naftali Frankel. I just  
2 want to first thank everyone for the great  
3 presentations and the great discussion amongst  
4 the panel members. The only thing that I just  
5 wanted to mention in closing is that when we  
6 talk about patient-reported outcomes that it's  
7 really in the singular that we're talking about  
8 patients as individuals rather than a  
9 homogeneous population, the patients have  
10 independent needs and comorbidities and  
11 different responses. And it's very important,  
12 I think, that when discussing this general  
13 topic of patient-reported outcomes, we have to  
14 always focus on the patient as an individual  
15 rather than just as a population, and I trust  
16 that based on the conversations that we had  
17 today and the discussion that CMS will take  
18 note of that when evaluating PROs moving  
19 forward, that obviously, that it's going to be  
20 considered in that light for patients to be  
21 empowered with information as well as the

22 clinician through that transparent process, but  
23 the patients can learn from each other, but  
24 with keeping in mind both from the clinical  
25 side as well as the patient side, that

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1 individuals vary greatly from each other.

2 Thank you.

3 DR. GARRIDO: Melissa Garrido. Thank  
4 you to all of the speakers today for very  
5 informative and helpful presentations. I think  
6 improving PROs is a very worthwhile endeavor.  
7 I just think we should use extreme caution when  
8 trying to infer any causal relationship between  
9 PROs and the various treatments that may be  
10 considered.

11 DR. GOSS: Tom Goss. Thanks for  
12 letting me participate. It's been very  
13 interesting and I appreciate all the  
14 presentations made by the experts, they were  
15 very informative and helped us to really  
16 understand some of these issues in greater  
17 detail. I think our work is helpful but  
18 probably not sufficient, because there's some  
19 open questions remaining, so I hope CMS will

20 remain open to any additional information as it  
21 becomes available, but I love the concept of  
22 really including the patient voice in patient  
23 decision-making and assess access to treatment.

24 DR. JAMES: Tom James. This is my  
25 first MEDCAC, so I really appreciated the

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1 presentations and the opportunity to be here.  
2 We all come with our own experiences to this  
3 kind of forum. As a primary care physician  
4 working with the insurance industry, I work  
5 with both individuals and populations, but my  
6 experience is in working with Picker Institute  
7 and we talk in terms of patient focus, not  
8 patient centered, because patient centered is  
9 what is being done to them, patient focus is  
10 their own preferences. This is a terrific  
11 first step for CMS moving toward patient  
12 preferences.

13 DR. LAMON: It's my pleasure being  
14 here. Reading these questions ahead of time  
15 put me out of my comfort zone, and I appreciate  
16 all the information. Just as an aside as a  
17 practicing physician, I trust that medical

18 education is still training physicians to treat  
19 one patient at a time, and all of this needs to  
20 come up to conform those decisions to that  
21 care. So I would make a comment to CMS or  
22 whomever, to say that leaning always on more  
23 data for people giving services, we need to  
24 lean on the electronic health record people to  
25 deliver a record that will allow a seamless way

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1 that will allow us access to this data, so  
2 we're no longer in silos buying all this  
3 equipment that's replaced frequently because  
4 that is no longer adequate. We've defined what  
5 we need and now we must demand that it be  
6 provided for us.

7 DR. PERISSINOTTO: Carla Perissinotto.  
8 I want to echo the comment from my colleague  
9 here about more use of the EHR in information  
10 gathering. It's a privilege to be here today,  
11 I'm very impressed with just the breadth of  
12 expertise and I think that helped to have a  
13 very balanced discussion coming from multiple  
14 viewpoints. I also want to acknowledge that  
15 it's great to include someone who deals

16 specifically with older adults at the moment,  
17 so thank you for including me.  
18 DR. FEINGLASS: I wanted to thank the  
19 patients that are on the panel and in this  
20 room. It's important to have your view, it's  
21 important to ground us with that view, so thank  
22 you for your time and your efforts. In  
23 addition, I found it very interesting when we  
24 were talking to our colleague at the FDA about  
25 the fact that at least in the oncology space

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1 today, we've heard that no PRO has been used to  
2 drive a negative decision related to oncology  
3 at the FDA, so that was interesting.

4 Again, I think PROs have promise, real  
5 promise, no pun intended there. I think it is  
6 a field that has more development to happen in  
7 it. We are encouraged in industry by the  
8 development of the patient-reported outcomes.  
9 As you've heard, many in industry have used  
10 PROs in their trials, we think they have a  
11 purpose, and as we see going forward how these  
12 are used, we're certainly interested in seeing  
13 how this field moves forward, so thank you.

14 DR. GOTTSCHALK: Yeah, I would like to  
15 echo the other panel members' comments, I also  
16 really enjoyed being here, participating, and I  
17 would like to thank also the speakers. I  
18 probably have three comments.

19 First, my kind of take-home message is  
20 that PROs are probably not ready for prime time  
21 to be mandated for experimental therapies like  
22 CAR T-cell therapy. The second thing, I would  
23 really encourage that you really take advantage  
24 of CIBMTR. At least if you look in the stem  
25 cell transplant arena that really is the most

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1 robust database to glean outcomes and the  
2 infrastructure is there, so that would be at  
3 least a starting place, especially since most  
4 treating physicians are transplant physicians,  
5 of CAR T-cell patients, so they're very  
6 familiar with the data requirements and the  
7 reporting requirements in this.

8 DR. OLSON: It's been a unique  
9 privilege to be able to participate in  
10 something like this today and I certainly  
11 learned a lot, and it was particularly

12 gratifying to hear so much focus on the  
13 patients and what that patient is experiencing,  
14 and it's, as I said, gratifying to hear that.

15 DR. YANG: I'd like to thank everyone  
16 who presented. I learned that PROs are  
17 extremely valuable instruments for acquiring  
18 information that cannot be acquired any other  
19 way. The follow-on is just as important,  
20 though, what interventions will eventuate and  
21 can we demonstrate that those have benefits  
22 back to the patient who generated those data,  
23 and that's the piece that I'm looking for  
24 still.

25 DR. ROSS: Then I will conclude by

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1 just extending my appreciation to all the panel  
2 members and speakers who volunteered their time  
3 today. Chairing a meeting like this is  
4 actually quite exciting in many respects. It's  
5 the science of really two emerging fields  
6 coming together. The science of PROs has  
7 really exploded in the past decade, in no small  
8 part thanks to PCORI and the efforts of  
9 investigators who appeared here today, as well



10 as the science of cell-based therapy, which is  
11 due in no small part to the industry colleagues  
12 who are here, and the scientists at NIH who  
13 spent, you know, decades doing this work. I  
14 think both are now sort of coming to the cusp  
15 of actual clinical practice, which is exciting  
16 for us. And now as a general interest here  
17 among others and the geriatricians, we have to  
18 figure out how is this going to, how can we  
19 best generate evidence that's going to inform  
20 decisions not just in very specialized  
21 treatment centers but much more broadly.

22       So I appreciated the opportunity to  
23 help steer the conversation, keep everyone on  
24 time. Thank you very much.

25       MS. JENSEN: So, let me conclude on

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1 behalf of CMS and the team, the national  
2 coverage determination team that's in the front  
3 row, thank you. Thank you for your  
4 participation, thank you for all of your  
5 comments, they are very appreciated.

6       And Dr. Cuyjet, let me tell you, you  
7 don't know yet this is your last MEDCAC,

8 because we might have scheduled another one yet  
9 and haven't told you.

10 DR. CUYJET: The sentiment won't  
11 change.

12 MS. JENSEN: We do appreciate all that  
13 you have done as well on your tenure here. And  
14 Dr. Ross, thank you for chairing this. This is  
15 your first MEDCAC ever, and we threw him into  
16 the deep end to chair it as well, and you have  
17 done a fabulous job, so thank you for that.

18 So just for next steps, very quickly,  
19 so this is part of our process, part of our  
20 national coverage determination process. I  
21 don't know if anyone has heard, but we opened  
22 up a national coverage determination on CAR T,  
23 so this is part of that process. You can go to  
24 our website to know, we have a tracking sheet  
25 of what the next step is, and our next step is

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1 the proposed national coverage decision which  
2 is due in February, end of February, like  
3 February 27th, right? Many of you may know the  
4 date. So I think it's due, the proposed is due  
5 the end of -- there are several pending but I

6 think the end of February this one is due, so  
7 it will be public on or before that date, so  
8 that is the statutory due date and so we will  
9 meet that. The final, then, will be due 90  
10 days after we make the proposed public, so  
11 those are our next steps.

12 Now we're going to take all this back  
13 and we're going to review everything that the  
14 panel has said as part of our analysis, this is  
15 one part, it is not the entire part, and we  
16 will then start drafting our coverage  
17 determination and make that public before the  
18 statutory due date or on the statutory due  
19 date.

20 So again, thank you very much, and  
21 anything else?

22 MS. ELLIS: I just need to collect the  
23 pre-score sheets from all of the panel members.

24 MS. JENSEN: So with that, we're  
25 concluded, so thank you very much. Safe

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1 travels, everybody.

2 (The meeting adjourned at 3:10 p.m.)

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