

FDA ONCOLOGY CENTER OF EXCELLENCE
Public Workshop - Product Development in Hemophilia

December 6, 2018

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<p style="text-align: right;">Page 6</p> <p>1 C O N T E N T S (continued)</p> <p>2 AGENDA ITEM PAGE</p> <p>3 Panel Discussion 313</p> <p>4 Wrap up</p> <p>5 Jay Lozier, MD, PhD, FACP 330</p> <p>6 Lori Ehrlich, MD, PhD 339</p> <p>7 Adjournment 340</p> <p>8</p> <p>9</p> <p>10</p> <p>11</p> <p>12</p> <p>13</p> <p>14</p> <p>15</p> <p>16</p> <p>17</p> <p>18</p> <p>19</p> <p>20</p> <p>21</p> <p>22</p>	<p style="text-align: right;">Page 8</p> <p>1 to be getting together because there are quite a</p> <p>2 number of products now in development, not just</p> <p>3 novel protein therapeutics, but also gene therapy,</p> <p>4 which has been on the horizon for more than two</p> <p>5 decades for hemophilia, may finally be becoming a</p> <p>6 reality.</p> <p>7 Really, from the evolution of hemophilia</p> <p>8 for us in the Center for Biologics is pretty</p> <p>9 impressive because this is something that went from</p> <p>10 blood transfusions in the 1920s; to the use of</p> <p>11 cryoprecipitate in the mid-1960s; to the use of</p> <p>12 crudely purified factor concentrates in the 1970s;</p> <p>13 to the use of recombinant concentrates in the 1990s</p> <p>14 after the hemophilia community was particularly</p> <p>15 badly hit by the HIV epidemic.</p> <p>16 Now, we're on the horizon of novel protein</p> <p>17 therapeutics that are either bispecific monoclonal</p> <p>18 antibodies, conjugated proteins, and as I've</p> <p>19 mentioned, gene therapy.</p> <p>20 So really, I think, today, it will be a</p> <p>21 great discussion around aspects of product</p> <p>22 development ranging from appropriate surrogate</p>

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1 endpoints, to patient-reported outcomes, to
2 appropriate clinical trial designs, and that
3 discussion is really quite timely.
4 With that, to try to keep us somewhat on
5 time, I will shorten my opening remarks a little
6 bit and just thank you once again for coming today
7 either, again, here in the room or online, and I
8 will introduce Dr. Al Deisseroth, who will talk
9 about the FDA 101. Thanks very much.
10 Presentation - Al Deisseroth
11 DR. DEISSEROTH: Thank you, Peter.
12 So as Peter indicated, my name is Al
13 Deisseroth, and I'm going to provide some
14 background information for the standards used by
15 FDA for the approval of marketing applications and
16 the ways in which FDA can expedite review and
17 approval of applications for new therapies. I have
18 no conflicts to report and the views that I will
19 discuss are my own.
20 In 2018, the FDA carried out 32 approvals
21 in hematology; 12 new molecular entities,
22 5 biosimilars, and approval of 2 products for

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1 hemophilia, recombinant pegylated hemophilic factor
2 for hemophilia A and one of the bispecifics,
3 emicizumab, for prophylaxis in patients originally
4 with inhibitors and now without.
5 The top half of this diagram includes the
6 14 approvals of non-malignant indications;
7 2 therapeutic antibodies; 3 agonists of the
8 thrombopoietin receptor; 2 ESAs; 3 filgrastim
9 products; 1 anticoagulant; 1 TKI; and the
10 2 hemophilia-related products. And the bottom
11 summarizes malignant hematology.
12 So as you can see, drug development and
13 product development in the area of hematology has
14 been quite active, recently. The basis for all of
15 these approvals is a demonstration of efficacy with
16 acceptable safety, and adequate well-controlled
17 trials, and the ability to generate chronic
18 labeling, which defines a patient population and
19 enables safe and effective use of the drug product.
20 For a full or regular approval, evidence of
21 the clinical benefit is required as measured by
22 increased survival or improvement in the quality of

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1 life through ameliorations of symptoms.
2 FDA, however, has the authority to exercise
3 flexibility in the application of these standards.
4 One way that the FDA exhibits flexibility in its
5 regulatory activities are the programs that provide
6 for expedited review and approval of products.
7 There are several methods that the FDA is
8 entitled to use. Fast track applies to products
9 that have preclinical or clinical data that suggest
10 that there's a potential to fulfill an unmet
11 medical need.
12 Breakthrough therapy relies on clinical
13 data showing substantial improvement over available
14 therapy as measured by clinically relevant
15 endpoints.
16 Priority review is applied if the product
17 would provide significant improvement in safety or
18 effectiveness.
19 The fourth method of expedited review is
20 accelerated approval, which uses a surrogate
21 endpoint other than one that can equate immediately
22 to benefit, which must be reasonably likely to

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1 predict clinical benefit.
2 This slide shows the difference between
3 regulated and accelerated approval. As I
4 mentioned, endpoints for regular approval equate to
5 clinical benefit, whereas for accelerated approval,
6 there is a surrogate endpoint reasonably likely to
7 predict clinical benefit.
8 This slide is an example of an approval in
9 the hemophilia area, emicizumab. And as shown on
10 this slide, emicizumab is a bispecific antibody,
11 which stimulates the functional effects of
12 factor VIII by bringing together factor IXA and 10.
13 The endpoints that were used for this product
14 analyzed bleeding rate and a patient-reported
15 outcome instrument.
16 This slide summarizes the landscape for
17 therapies; as Peter said, factor replacement by
18 passing agents and applying specific antibodies in
19 gene therapy. And the available endpoints can
20 apply to each of these types of therapy.
21 One of the problems that the field
22 encounters is when different factors or different

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1 assays get discrepant assays, and I think this will
2 be the topic of discussion today, to which we're
3 looking forward.

4 The last method of expediting review that
5 applies to cell-based therapies is the RMAT
6 program, which is sort of a mixture of fast-track
7 and breakthrough therapy, but doesn't have the
8 requirements for demonstrating a substantial
9 advantage over available therapy. I think CBER has
10 received 31 requests and has granted 11 in this
11 area, so it's quite a useful method for cell-based
12 therapies.

13 Well, these brief remarks, I hope have
14 convinced you that FDA is capable of exercising
15 regulatory flexibility to expedite the approval
16 process for promising therapies for which there is
17 an unmet need.

18 I'm looking forward to the presentations
19 today, which may lead to identification of ways of
20 optimally managing expedited product development
21 for hemophilia. I'll now give the floor to Dr. Jay
22 Lozier.

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1 Presentation - Jay Lozier
2 DR. LOZIER: Thank you, Al.
3 My task is to describe CBER's concerns for
4 hemophilia product development, and I am a medical
5 officer in CBER in the Office of Tissues and
6 Advanced Therapeutics. I have no relevant
7 disclosures, as you might imagine.

8 I will talk about CBER's mission and how we
9 regulate hemophilia-related products in CBER, how
10 we approach development of new products, and our
11 regulatory experience, and then point to some
12 special concerns, particularly for gene therapy,
13 and then talk about our goals for this workshop and
14 how they'll be addressed by our very capable
15 speakers.

16 So our mission is to ensure the safety,
17 potency, purity, and effectiveness of biologics and
18 particular blood products, and gene therapies. The
19 key words are "safety" and "efficacy," and that
20 applies to all CBER products. Biologic products
21 are defined as viruses, therapeutic serums, toxins,
22 antitoxins, or analogous products applicable to the

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1 prevention or treatment or cure of disease or
2 injuries of man in the CFR, which is where we find
3 all of our definitions. And the basis for our
4 regulatory review is based on Title 21, Section 601
5 of the CFR.

6 Biologic products are reviewed mainly at
7 CBER, but there are some that are reviewed in CDER.
8 We regulate plasma-derived, recombinant, and gene
9 therapy products for the treatment of hemophilia in
10 CBER.

11 So product development; this is the
12 standard product development at FDA, which applies
13 to the hemophilia products. Often, there is an
14 early interaction between people with particular
15 notions about how to develop a product. There's an
16 informal set of meetings, INTERACT meetings. And
17 then when you have preclinical data, animal data,
18 and in vitro data, and you think you're ready to go
19 into humans, we have a pre-IND meeting typically.

20 Then when you think you're ready to go into
21 humans, you submit an IND, which we have 30 days to
22 review. And if we don't raise objections or we

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1 iron out any differences we have about things, then
2 typically, after 30 days, sponsors start on phase 1
3 clinical trials to establish the safety of the
4 product. These may be first in human or those
5 kinds of studies, and there may be more than 1
6 phase trial.

7 Assuming safety is established and doses
8 are found, then you proceed to phase 2 studies of
9 efficacy. Then, once you feel like you have a
10 product that's ready to go and be tested, you do a
11 phase 3 licensure trial, where you try to find some
12 clinical endpoint and continue to demonstrate the
13 safety to merit licensure.

14 The BLA stands for biologics license
15 application, and that is when you come to us with
16 your clinical data and say we want to market this.
17 We then review this, and if you undergo an
18 approval, then it's not over. There's
19 postmarketing surveillance and postmarketing
20 commitments to study safety typically in -- and
21 this is particularly important for accelerated or
22 expedited approvals. But there is postmarketing

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1 surveillance of all products to some degree.
2 So when we regulate factor concentrates,
3 the population we serve are the patients with
4 severe hemophilia and bleeding risk. The natural
5 history of these patients will differ amongst
6 patients with severe hemophilia. For instance,
7 those who have pre-existing joint damage and severe
8 hemophilia may have a more severe bleeding
9 phenotype than those with mild or moderate
10 hemophilia.
11 We have used the average of the annualized
12 bleeding rate, or the ABR, as the usual primary
13 endpoint for efficacy for factor concentrates,
14 currently. It's a subjective finding. It's a
15 patient-reported outcome. And if we're going to
16 use the ABR rate to describe a product as offering
17 a benefit, you will have to enroll patients who
18 have some bleeding episodes on replacement therapy
19 to show a benefit for the new product or therapy.
20 Now, with widespread prophylaxes,
21 essentially the de facto standard of care, often we
22 have patients entering trials with ABRs on standard

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1 therapy of zero or near zero. This sometimes is
2 difficult for clinical trial design.
3 Factor levels are measured when we test
4 factor concentrates in the clinic and we look at
5 peaks and troughs. Seldom do we have a steady
6 state that's achieved. Most of the measurements of
7 factor levels for FDA clinical trials will be
8 limited to pharmacokinetics and pharmacodynamic
9 studies and determining the dose for routine
10 prophylaxis management or perioperative management
11 or control of bleeding.
12 There can be interpatient variability with
13 regards to the pharmacokinetics and
14 pharmacodynamics and there, as you will hear, are
15 issues with the assays themselves because there can
16 be discrepancies between chromogenic assays and the
17 one-stage factor assays, which look at the activity
18 via clotting methodology. The safety risk for
19 factor concentrates these days is really centered
20 on worries about inhibitor development.
21 There are some special concerns for gene
22 therapy with regard to efficacy. We expect that

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1 gene therapy will likely result in steady-state
2 factor levels. If we look at factor levels as a
3 surrogate endpoint for reduction in bleeding, we
4 have a limited understanding of the relationship of
5 factor levels and the reduction of bleeding risk.
6 More is better, but we can't necessarily
7 say that a particular factor level, factor VIII
8 level particularly, associated with a mild bleeding
9 phenotype will necessarily translate to the same
10 mild bleeding phenotype or no bleeding risk for
11 gene therapy.
12 We do have issues with discrepancies
13 between the chromogenic and one-stage factor
14 assays, and they're really markedly different than
15 our experience with recombinant products. In gene
16 therapy, we are particularly aware that
17 neutralizing antibodies in the vector may limit the
18 initial treatment or re-treatment with a vector.
19 So if you have an AAV vector, it's a very potent
20 immunogenic set of capsid proteins that will elicit
21 a very strong antivector response, so we typically
22 think of AAV gene therapy as a one-time event.

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1 We have an issue with whether we're going
2 to see long-term durability of steady-state factor
3 levels, and the jury is out on that because many of
4 the clinical trials are still ongoing, and we still
5 wait long-term data on the stability of the factor
6 levels.
7 With regard to safety, we have concerns for
8 liver-related toxicities. These now are, I think,
9 pretty well understood, and anticipated, and
10 managed in AAV gene therapy clinical trials, and
11 those are usually pretty well managed with
12 corticosteroids.
13 We have theoretical concerns about
14 insertional mutagenesis, and given some preclinical
15 studies in animals, we are certain that we will
16 need long-term surveillance with any of the gene
17 therapy vectors, whether it's AAV or lentiviral,
18 retroviral, or whatever may be proposed.
19 We used to worry that we couldn't get
20 enough factor VIII or factor IX to make a
21 difference, and I remember writing any number of
22 papers with everybody else in the room, saying, if

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1 we could just get to 1 percent, we would make a
2 difference, which we would. But now we have gene
3 therapy trials where we're getting suprathreshold
4 levels, and we have to be at least concerned to
5 some degree about the risk for thrombosis when you
6 see factor levels getting up in the high 100s and
7 200 percent level, which 20 years ago I never would
8 have predicted could have happened.

9 For pediatric patients, we need to know
10 whether liver growth and development will affect
11 the durability of the factor levels, and where we
12 think currently gene therapy will be a one-time
13 treatment, how do we design a treatment or can we
14 design a treatment for children that can be a
15 one-time treatment. That's an open question, and
16 we have to worry about the risks for insertional
17 mutagenesis and are these risks greater in children
18 than for adults.

19 So our goals for the workshop are to
20 address the efficacy issues. In session 2, we'll
21 be talking about the physiology of hemostasis from
22 an in vivo gene expression standpoint, the impact

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1 of joint damage on the annual bleeding rate. In
2 session 4, we'll be talking about factor assay
3 method discrepancies, and in session 5, we'll be
4 talking about the durability of factor level
5 expression and adolescent liver growth.

6 In session 5, we'll be addressing safety
7 issues for clinical trial design, particularly the
8 risks for insertional mutagenesis and
9 considerations for enrolling pediatric patients.

10 With that, I will end on time, and I will
11 turn the microphone over to Laurel Menapace, who
12 will talk about the CBER perspective on drug
13 development.

14 Presentation - Laurel Menapace
15 DR. MENAPACE: Good morning. I'm Laurel
16 Menapace, a hematologist and clinical reviewer in
17 the Division of Hematology Products at the FDA.
18 Before I begin my slide deck, which is relatively
19 short, I just really wanted to thank all our
20 patient advocates, physicians, scientists, and
21 investigators who have joined us today. Really,
22 without your participation, this workshop would not

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1 be here. It took a lot of months of preparation in
2 advance, and we greatly appreciate your input and
3 your feedback.

4 As my colleague, Dr. Lozier, talked about,
5 he briefly outlined the CBER mission and points of
6 interest from a biologics perspective at the FDA,
7 in terms of new product development and hemophilia.
8 My presentation is really going to complement that
9 and simply talk about drug development and were
10 notably some of the recent approval we had in
11 hemophilia. So without further ado, I'll get into
12 that.

13 I'll just have a brief introduction of
14 CDER's mission, again which complements the CBER
15 mission and our role in drug development, and then
16 bring up a few clinical and safety concerns we have
17 regarding novel drug development in hemophilia
18 patients.

19 Lastly and most importantly for me, I'd
20 like to highlight a new field in hemophilia,
21 patient-reported outcomes. Patient-reported
22 outcomes have been heavily emphasized in oncology

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1 and hematology trials, but we're beginning to see
2 increasing emphasis on patient-reported outcomes in
3 benign hematologic conditions, including
4 hemophilia.

5 We're seeking feedback about patient-
6 reported outcomes to guide us as we think about the
7 future of patient-reported outcomes and
8 incorporating them into clinical trial design
9 specifically for patients with hemophilia A.

10 So when we think about the CDER strategic
11 mission, there are two key points here. There are
12 actually a total of three. I've only highlighted
13 two here. Really, we promote public health by
14 helping to ensure the availability of safe and
15 effective drugs, and we protect public health by
16 promoting the safe use of marketed drugs in the
17 postmarketing setting.

18 What I've outlined here is really that we
19 identify and develop new scientific methods,
20 models, and tools to improve the quality, safety,
21 predictability, and efficiency of new drug
22 development.

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1 The title of my slide demonstrates that the
2 field of hemophilia A in drug development is in
3 flux. It's changing and it's very dynamic. It's
4 no longer static. We've relied on typical factor
5 replacement products for many, many years, and now
6 we're beginning to see novel drug development. And
7 as such, the paradigm of treatment is shifting, and
8 we need to best understand this and interact with
9 our academic colleagues and investigators, as well
10 as patients, again, to develop new ways of
11 understanding these drugs, how these drugs should
12 be implemented in clinical trials, and how we
13 should approve these drugs.

14 Again, in the postmarketing setting, after
15 we've once approved a drug, we are looking for
16 early detection of new safety signals. We need to
17 understand emerging safety signals with these
18 drugs, and effectively manage these signals, and
19 communicate with the practicing community in terms
20 of mitigating these risks and how we should inform
21 our patients moving forward.

22 You've probably already seen a similar

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1 slide in Dr. Deisseroth's and Dr. Lozier's
2 presentations, but again, I just want to highlight
3 the fact that FDA and particularly my division, the
4 Division of Hematology Products, our reviewers,
5 which we have multi-disciplinary teams comprised of
6 physicians, chemists, pharmacologists,
7 toxicologists, and statisticians, as well as a
8 number of other experts in the field, are heavily
9 involved in the early process of drug development,
10 even in the pre-IND phase, and then again heavily
11 involved at each stage of clinical development, as
12 you can see outlined here, heading from IND
13 submission all the way to IND review, and then
14 phase 1 through phase 3 development, and then
15 ultimately submission of clinical trials for review
16 of the agency for regulatory approval.

17 Again, our job doesn't end once we approve
18 a product. We are constantly going through
19 postmarketing surveillance, and looking for new
20 safety signals with these drugs, and effectively
21 communicating with safety providers and the public.

22 Some may ask, okay, Dr. Lozier gave a great

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1 outline of some of the products the Center of
2 Biologics is reviewing and responsible for, so what
3 does CDER do in terms of hemophilia?

4 The two centers complement each other, and
5 I would simply say what Dr. Lozier didn't present
6 on his slides is what CDER is responsible for. But
7 in terms of our hemophilia pipeline drugs, I just
8 wanted to draw your attention to two.

9 The first is fitusiran, which is an
10 investigational antisense therapeutic target which
11 targets antithrombin. This has been in development
12 for the treatment of hemophilia A and B with and
13 without inhibitors and currently is in phase 3 of
14 development after a clinical hold was lifted
15 regarding some safety issues.

16 The other class of drugs that I want to
17 draw your attention to are the anti-tissue factor
18 pathway inhibitor antibodies, which we're beginning
19 to see at the agency. And this is a class of
20 drugs, and there are a number of drugs in various
21 stages of clinical development, most in early
22 stages of clinical development, including phase 1

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1 and phase 2.

2 In regard to our recent approval in
3 hemophilia A, most of you are familiar with
4 emicizumab-kxwh or also known as Hemlibra.
5 Emicizumab is a humanized monoclonal bispecific
6 antibody that binds both activated factor IX and
7 10, thereby bridging the two and restoring
8 effective hemostasis in patients afflicted with
9 hemophilia A.

10 It is administered via a subcutaneous
11 route, which is novel, and has a half-life of
12 approximately 4 to 5 weeks. So the initial
13 approval of emicizumab was in November of 2017,
14 where we approved emicizumab for a routine
15 prophylaxis to prevent or reduce the frequency of
16 bleeding episodes in patients with severe
17 hemophilia A with the presence of factor VIII
18 inhibitors.

19 In a short period of time, the sponsor then
20 submitted data from their pivotal HAVEN 3 and
21 HAVEN 4 trials, and this led to an additional
22 approval in October of 2018 where emicizumab was

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1 approved for prophylaxis in hemophilia A patients
2 without inhibitors, and additional dosing regimens
3 were incorporated into the prescribing information.
4 In terms of safety concerns regarding
5 emicizumab and questions for the agency as we move
6 forward with this newly marketing drug product,
7 some of these we're well familiar with and have
8 been discussed extensively at other conferences and
9 recently ASH. But most notably, with initial
10 approval, there were concerns regarding thrombotic
11 events, both arterial and venous, as well as the
12 incidence of thrombotic microangiopathy, which
13 occurred in patients who not only were receiving
14 emicizumab prophylaxis, but were receiving high
15 levels of bypassing products, high doses of
16 bypassing agents for the treatment of breakthrough
17 bleeding. This resulted in a black-box warning
18 and, again, we're continuing surveillance in these
19 patients.
20 More importantly, we didn't see any events
21 in the recent HAVEN 3 and 4 clinical trials, but
22 again, these trials enrolled patients without

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1 inhibitors, so they were not receiving bypassing
2 agents. They were receiving typical replacement
3 products for breakthrough bleeding.
4 Furthermore, another more recent safety
5 concern, which had been identified as a potential
6 safety concern by many of us early on, was the
7 development of antidrug antibodies. As we know,
8 these are common with this therapeutic class of
9 drugs, of antibodies, and they can result in
10 clinical loss of efficacy.
11 There recently had been a report of a
12 pediatric patient in the HAVEN 2 trial who
13 developed anti-drug antibodies with clinical loss
14 of efficacy. He was discontinued from the study
15 and returned to his prior prophylactic regimen, and
16 there were no other safety events. But moving
17 forward, we have to think about this potential with
18 emicizumab and monitoring in the clinic setting,
19 and how we're going to handle these events in the
20 future.
21 So just to highlight some overarching
22 themes and topics that we'd like to see addressed

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1 today and that many of our experts are going to go
2 into great detail about, again, these are some
3 questions we have for the future of emicizumab
4 therapy as a novel product in hemophilia A.
5 These include therapeutic monitoring of
6 patients receiving emicizumab prophylaxis,
7 treatment of breakthrough or acute bleeding with
8 factor VIII replacement products in patients
9 without inhibitors, as well as bypassing agents in
10 patients with inhibitors.
11 It's very important to note on the trials,
12 particularly after the events of thrombotic events
13 and TMA occurred, that the sponsor had redesigned
14 their trials so that patients were receiving the
15 minimally effective doses of replacement products
16 or bypassing agents. And again, that's provided in
17 guidance in the prescribing label.
18 This may not necessarily reflect a
19 real-world setting, where you have an acute or
20 serious bleed. This is something to think about.
21 We also have questions about emicizumab
22 prophylaxis in the setting of surgery or acute

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1 trauma, and as I previously alluded to, how we're
2 going to monitor for develop of anti-drug
3 antibodies, and the fact that, ultimately, even
4 patients without inhibitors have the potential for
5 delayed inhibitor development because they're still
6 relying on traditional factor VIII replacement
7 products in the setting of breakthrough bleeds.
8 So in the short term, we may be preventing
9 this dreaded complication of hemophilia A
10 treatment, but ultimately, they may still develop
11 inhibitors.
12 Now, switching quickly to patient-reported
13 outcomes, I just wanted to highlight, for those of
14 you who are not familiar, this is considered a
15 clinical outcome assessment. A patient-reported
16 outcome is a measurement that basically comes
17 directly from the patient about the status of a
18 patient's health condition without further
19 amendments or interpretation of the patient's
20 response by a clinician or anyone else. For
21 example, this may be a rating of pain on our
22 traditional pain scale.

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1 Why is the FDA interested in
2 patient-reported outcomes and why are they so
3 important in hemophilia? Patient-reported outcome
4 instruments were utilized as secondary endpoints in
5 all HAVEN clinical trials to support our regulatory
6 approval for emicizumab prophylaxis in patients
7 with hemophilia. And we're beginning to see an
8 increasing interest from sponsors of drug
9 development programs in hemophilia interested in
10 patient-reported outcome measures and implementing
11 them in clinical trial design.

12 For the purpose to keep my presentation
13 brief here, I'm not going to go through this whole
14 slide, but basically, I just want to highlight that
15 patient-reported outcome assessments should be held
16 to the same standard as other outcome measures in
17 our trial, and that they should include a clear
18 statement of objectives, well-defined and reliable
19 assessments, and can distinguish the effect of the
20 drug from other influences.

21 In terms of regulatory goals for including
22 patient-reported outcome data, there are several

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1 paths that sponsors and pharmaceutical companies
2 can pursue. Sometimes, they're seeking just
3 supportive data for overall benefit-risk
4 assessment. Sometimes, they would just like to
5 provide descriptive patient experience in the
6 product label. Furthermore and lastly, some would
7 like to make a claim of treatment benefit in the
8 product label.

9 Just to highlight our CDER needs for the
10 workshop in regard to PROs, which we'll be
11 discussing in session 3, we'd like to introduce
12 some commonly implemented PRO instruments utilized
13 in the clinical trial setting, and we have invited
14 several patient advocates, who will discuss the
15 meaningfulness and utility of such instruments to
16 adequately capture the burden of disease.

17 This is really important. Something that
18 we're trying to highlight here at the agency is the
19 voice of our patients, and the impact of such
20 measures, and whether they actually have clinical
21 relevance for these patients who are afflicted with
22 hemophilia A.

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1 Finally, we would like to gain feedback
2 regarding the utilization of patient-reported
3 outcomes and hemophilia clinical trials to support
4 regulatory approvals from our colleagues. And at
5 this point, I'll conclude my presentation. Thank
6 you very much.

7 (Applause.)

8 Session 1

9 Moderator - Lori Ehrlich

10 DR. EHRLICH: Good morning. I'm Lori
11 Ehrlich. I'm one of the medical reviewers in the
12 Division of Hematology Products in CDER. It's my
13 pleasure to introduce Dr. Ragni. She joins us from
14 the University of Pittsburgh, where she's a
15 professor of medicine and clinical translational
16 science and the medical director of the Hemophilia
17 Center of Western Pennsylvania in Pittsburgh.

18 Her career's been focused on clinical and
19 translational research and novel therapy
20 development and hemophilia. She's just going to
21 provide an introduction for the rest of the day
22 with an overview of the progress and challenges in

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1 hemophilia.

2 Presentation - Margaret Ragni

3 DR. RAGNI: Good morning. Let's go through
4 my disclosures. You might say we're in a golden
5 age of treatment for hemophilia, considering how
6 far we've come from whole blood transfusion, plasma
7 prior precipitate, clotting factors, and
8 recombinant factors, and now with gene therapy and
9 some of these novel agents.

10 But with every advance, we've had
11 complications, and the new novel therapies are
12 certainly not alone here. Perhaps the biggest
13 complication of hemophilia today is inhibitor
14 formation, with about 30 percent incidence, both in
15 those on prophylaxis, the solid line, or those who
16 are on demand, the dotted line. There's a
17 T-cell dependent B-cell response to exogenous
18 factor VIII, and because it neutralizes your
19 factor VIII, the treatment is bypass therapy, but
20 it poorly controls bleeding with twice the
21 hospitalization, 10 times the cost, and 3 and half
22 times the mortality of standard therapy in a

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1 non-inhibitor patient.
2 While we can look at risk factors and
3 understand risks from race, genetics, family
4 history, and early factor exposure, we really
5 cannot predict who's going to develop inhibitors.
6 And the goal clearly is better hemostatic therapy
7 to prevent and eradicate inhibitors, which was the
8 topic of a recent NHBLI workshop, State of the
9 Science for Inhibitor Eradication.
10 But in addition to inhibitors, the burden
11 of treatment is high with 2 to 3 times weekly
12 treatment. Serious complications exist. Venous
13 access is difficult. Compliance as they become
14 adults is low, and breakthrough bleeds really limit
15 activity, and protection from joint bleeds and
16 joint damage is very limited. And finally, the
17 global disease burden is great and factor is
18 scarce, so we need novel therapies.
19 The three that I'm going to talk about are
20 emicizumab, fitusiran, and gene therapy, as you
21 heard recently, and these represent potential
22 paradigm shift with fewer infusions, less invasive

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1 route, longer protection from bleeds, improved
2 hemostasis, improved quality of life, and potential
3 for reduced immunogenicity, and even for potential
4 phenotypic hemostatic cure.
5 But complications continue to persist with
6 plasma-derived factor. We had hepatitis, HIV, and
7 inhibitors. With recombinant factor, we've had
8 inhibitors and a variable recovery. With bypass
9 therapy, bleeding is poorly controlled and
10 thrombosis may occur.
11 With extended half-life clotting factors,
12 we had higher doses and frequencies, but it raised
13 expectations. We ended up discussing the treatment
14 quite a bit with our insurance colleagues to allow
15 our patients to take what seemed to be working for
16 them.
17 With gene therapy, clearly there's the
18 capsid immune response, as well as other causes of
19 hepatotoxicity, and with some of our novel
20 therapies, hepatotoxicity and thrombotic
21 microangiopathy.
22 In addition, we need to be thinking about

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1 new measures of treatment response. Certainly,
2 with both plasma recombinant factor, we were able
3 to use factor VIII-IX assays as well as inhibitor
4 assays, and with bypass, we couldn't specifically
5 measure factors, but we use thrombin generation and
6 thromboelastography, not available in many clinics.
7 With extended half-life clotting factor
8 products, there have been variable peaks and
9 troughs and the evolution of a population
10 pharmacokinetic approach. With gene therapy, the
11 question is what level are we trying to attain and
12 discrepancies between chromogenic and standard
13 1-stage assays, and quality of life and its
14 importance in assessing outcomes, as well as some
15 of these patient and other core outcomes. With
16 novel therapies, thrombin generation has been used
17 as well as thrombogenic assays.
18 So let's talk a little bit about these
19 novel approaches. I'm going to talk about the AAV
20 gene therapy, emicizumab, as well as fitusiran.
21 Let's start with emicizumab.
22 Emicizumab is a bispecific antibody that

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1 binds factors IX and X. It's equally effective,
2 whether the factor VIII is missing or an inhibitor
3 is in place, and it basically mimics the
4 factor VIII action to bind IX and X to effect
5 hemostasis in a patient with hemophilia A or an
6 inhibitor.
7 In phase 1 and 2 trials, there was clearly
8 a dose-response curve, as you can see on the left,
9 with increasing doses, increasing levels of
10 emicizumab. This dose-dependent increase resulted
11 in improvement in thrombin generation as you can
12 see on the right. This was given once weekly
13 intravenously, so had the potential for a simpler
14 treatment.
15 As you can see here, this improvement in
16 thrombin generation really was acquainted to an
17 improvement in annualized bleed rate. And here you
18 see in blue emicizumab prophylaxis, and you're
19 comparing in pale blue no prophylaxis versus emi;
20 in green, factor VIIa or FEIBA versus emi; and in
21 yellow, factor VIII versus emi.
22 In every situation, there was improved

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1 reduction in analyzed bleed rate, as well as in the
2 large phase 3 trial comparing those with
3 prophylaxis on the left or no emi prophylaxis on
4 the right. There was a marked reduction in all
5 bleeds in blue; in joint bleeds, partially treated
6 bypass; as well as specific other bleeds. In each
7 case, there was a significant reduction in the
8 annualized bleed rate.

9 In these studies, other bypass was used for
10 breakthrough bleeds. FEIBA was used in 27 percent.
11 Recombinant factors VIIa at 33 percent or both in
12 12 percent. The most common adverse event was the
13 injection site reaction in 15 percent. But as you
14 can see, one of the most concerning findings was
15 thrombosis, which occurred in 5 patients, all 5 of
16 whom received FEIBA at a dose of 100 units per
17 kilogram per day for over 1 day, and was associated
18 with thrombotic microangiopathy.

19 So while emicizumab improves thrombin
20 generation and reduces bleeds, there are some
21 potentials for toxicity and also underscoring where
22 our knowledge is lacking in risks of clotting and

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1 risks of bleeding. And I'd mentioned, there were
2 5 deaths, all of which were thought not related to
3 the drug, 3 of which you can see were in
4 compassionate use; 1 in an expanded access program;
5 and another patient who died of bleeding related to
6 his hemophilia.

7 In terms of laboratory monitoring,
8 emicizumab doesn't require activation by thrombin.
9 It does artifactually shorten the APTT, so it would
10 affect any assay based on the APTT, including
11 single-factor VIII assays or the inhibitor assays.
12 In fact, the APTT may be normal and the anti-VII
13 may be zero in patients who are receiving this
14 drug, while it may not reflect their true
15 situation. But it is not affected by bovine
16 chromogenic reagents, and for that reason,
17 laboratory monitoring may use bovine chromogenic
18 Bethesda assay or a chromogenic factor VIII.

19 Other assays are being evaluated, including
20 thrombin generation, clot waveform analysis, and of
21 course you heard a little earlier about the
22 anti-drug antibodies in patients who seemed not to

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1 be responding to drug. They may have developed
2 anti-drug antibodies, 4 of the 18 in the HAVEN
3 trials. And this was associated with reduced
4 clinical efficacy and how best to manage that.

5 We don't all do ADA assays, but in a very
6 interesting study by Nogami, he looked in vitro at
7 anti-emicizumab monoclonal antibodies that compete
8 with emicizumab and seemed to eliminate the effect
9 of emicizumab in an APTT assay; so another approach
10 that one might use in addition to measuring the
11 assay.

12 So what are the issues about management in
13 patients with emicizumab? Breakthrough bleeding
14 should probably either minimize or avoid use of
15 FEIBA altogether. Standard factor VIII dosing is
16 quite reasonable, as is recombinant VIIa. And we
17 have instituted in our clinic, and I'm sure in
18 other clinics, that patients need to call the
19 hemophilia treatment center if they are requiring
20 continuing factor use for a bleed because we need
21 to evaluate what the cause may be or symptoms of a
22 blood clot. So we're making them aware, these are

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1 patients with bleeding disorders, what a blood clot
2 is.

3 Development of the anti-drug antibodies
4 clearly in patients who have loss of clinical
5 efficacy, increased breakthrough bleeds. We really
6 need to think about that, and these patients need
7 to be seen and discussed with us in clinic what
8 needs to be done, clearly suggesting that patients
9 who are non-compliant may not be candidates for
10 this drug or we might need to figure out better
11 ways to manage them.

12 Utilization of laboratory assays during emi
13 treatment, APTT and anti-VIII are normal, as we
14 mentioned, so we may want to use a chromogenic
15 factor VIII or a bovine chromogenic anti-VIII to
16 assess the status of our patients.

17 What do we do in surgery? It's clear that
18 emicizumab alone may not be adequate for major
19 surgeries. Certainly, we've used it alone in minor
20 procedures. Patients with hemophilia are more
21 likely to bleed than clot. We need to think about
22 scheduling the surgery around the time of the

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1 loading dose for hemostasis for emicizumab and then
2 giving factor VIIa or factor VIII at the time of
3 surgery, immediately before and after for several
4 days, and monitor them very closely for bleeding.
5 Just a reminder; bleeding complications
6 still outweigh thrombotic complications, so we need
7 to manage these patients very carefully, but how
8 you do that I think is not clear, and we're
9 learning as we go along.
10 Immune tolerance; will emicizumab be
11 efficacious if it's started before, or do we need
12 to wait until after immune tolerance induction?
13 There have been debates on both sides of this
14 question, and certainly, long-term follow-up is
15 necessary as are future trials of emi.
16 Cost-effectiveness, just to mention, the
17 Institute for Cost and Economic Research has looked
18 at the use of emicizumab in inhibitor patients and
19 shown -- looking at the cost of bypass therapy,
20 non-factor cost, long-term costs, including
21 hospitalization, which is one of the most costly,
22 and comparing it with bypass, with emicizumab, and

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1 showed that it was clearly much more cost
2 effective.
3 Is that true for patients who don't have
4 inhibitors? That math has not been done, but time
5 will hopefully tell, and we will be looking forward
6 to hearing more about that.
7 So in summary, emicizumab may improve
8 hemostasis, reduce treatment frequency. It may be
9 less invasive by the subcutaneous route, and my
10 patients love this drug, as I'm sure most of the
11 physicians here will tell you. It may have
12 comparable efficacy in inhibitor and non-inhibitor
13 patients, but it may be thrombogenic if it's used
14 concomitantly with FEIBA. We're very careful to
15 tell every patient that issue and avoid prescribing
16 it as much as possible.
17 It may be less immunogenic by avoiding
18 factor exposure, but breakthrough bleeds, as was
19 already pointed out, may still expose you to
20 factor, so that question is out.
21 Future questions are, what about the
22 treatment of acute bleeds? Surgery, how do we

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1 manage it? Trauma, when do we use it in children,
2 and do we use it in any other way in children?
3 Certainly, it's been used in very young with
4 excellent efficacy. And what about suppression of
5 inhibitors? So there are a lot of unanswered
6 questions.
7 We'll go on to the second drug, which is
8 fitusiran or an antithrombin III knockdown. This
9 works really by harnessing the RNA interference
10 platform. It targets antithrombin production, mRNA
11 in the liver. It interferes with its translation,
12 binding to it in the hepatocyte, degrading the
13 mRNA, and silencing gene expression, resulting in
14 reduced or prevention of antithrombin synthesis,
15 which clearly can be shown to be related in
16 subcutaneous dosing weekly here at 0.75, 1.5, and
17 3 mgs per kg in a dose-dependent reduction in
18 antithrombin level.
19 This is of course associated in the phase 1
20 study in hemophilia A with monthly dosing
21 subcutaneously to show a dose-dependent lowering
22 when it's given monthly, and that's associated with

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1 once the drug is stopped, it's reversible, as you
2 can see past day 80, 90, 100, and so on.
3 This reduction in antithrombin is
4 associated with increasing peak thrombin, as you
5 can see in this graph, and that's associated with
6 reduced annualized bleed rate. As you can see on
7 the far right, it is dose dependent.
8 This is also true in patients with
9 hemophilia A with inhibitors, again increasing
10 antithrombin lowering and is associated with
11 greater peak thrombin generation and reduction in
12 annualized bleed rate.
13 In terms of side effects and safety, I
14 would point out that injection site pain is the
15 most common, but in this particular study, there
16 was cerebral sinus thrombosis, and this occurred in
17 a single patient who used multiple doses, high
18 doses of factor VIII, which were contraindicated in
19 a study and for which the study was stopped.
20 I would also note that the fitusiran also
21 is associated with hepatotoxicity primarily in
22 patients who had hepatitis C and who are HCV RNA

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1 positive. That is not treated with antiviral
2 therapies. This drug is degraded by plasma and
3 intracellular nucleases, targets the liver, but
4 does not seem to be an inducer of P450.
5 So why did this happen? Fitusiran
6 certainly may cause stress signals in HCV damage to
7 hepatocytes. If this is the potential mechanism,
8 we're not sure. It may lead to increase in LFTs,
9 and the LFT elevation occurred only in those who
10 were HCV viral-load positive who had not received
11 treatment.
12 Going forward, patients must receive
13 antiviral therapies, and that is part of this
14 mitigation procedure; that they must first be
15 treated with anti-HCV therapies before on studies.
16 For breakthrough bleeds, we ask them to keep
17 diaries, use low doses of factor VIII, IX, VIIa,
18 APTT, and to call if they need continuing dosing.
19 For surgery, if there's a major surgery, we
20 try to schedule it at the nadir; that is, 2 weeks
21 after the dose; and use factor VIII or IX or VIIa
22 as needed. If it's a minor procedure, we've been

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1 able to just dose at the time of the nadir with no
2 additional dosing with patients who refused to take
3 any other agents, and we found that to be the case
4 in small minor dental and port procedures.
5 It's important to educate our patients
6 about the symptoms of thrombosis so that they are
7 well aware of those things. I will finish with
8 hemophilia gene therapy.
9 As you know, hemophilia is really a model
10 disease for gene therapy because it's monogenic,
11 and there's a wide range of factor levels affected.
12 It is a one-time potential cure, and what it really
13 offers is potential global treatment for many who
14 were affected for which there are no treatments,
15 and they are shunned in their society or die young.
16 You've seen this graph many times at ASH
17 and here, but in general, we really don't know what
18 the level that we would like to see here is. What
19 we want to do is avoid bleeds entirely, and as time
20 has gone forward, we know that, at least with the
21 12 or 15 percent level, we can do that.
22 Are higher levels better? Are we getting

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1 into a range in which we're worried more about
2 thrombogenesis? But what we really want to do is
3 to convert a severe phenotype to a monophenotype
4 and avoid bleeds altogether.
5 As you know, there are multiple approaches
6 and strategies for gene therapy, but the AAV is the
7 strategy used in hemophilia. The wild-type AAV is
8 minimally pathogenic in humans. There are many
9 different serotypes which offer tissue specificity.
10 But there are some potential cons with a small
11 packaging capacity, and pre-existing immunity is
12 known in at least 30 or 40 percent.
13 In general, the strategy is that you load
14 the cargo into this AAV vector with factor IX cDNA
15 of up to 1.3 kilobases or factor VIIIb
16 domain-deleted CDNA of 4.7 kilobases. And
17 basically, the gene is inserted into a vector,
18 infused intravenously into the patient, goes into
19 the hepatocyte as expressed in the circulation. We
20 draw those pictures for our patients. They seem to
21 understand that quite well.
22 Once you've inserted this genetic material

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1 into the wild-type genome, you use the capsid for
2 tissue specificity. And here you can see AAV 8 is
3 specific for the liver, as is AAV 5, and some for
4 the musculoskeletal and heart.
5 I'm going to just talk very briefly about
6 4 gene clinical trials. There were two more and
7 several more talked about at the ASH meeting, but
8 in general, we have two here, University College of
9 London, St. Jude. It looks at an AAV Factor IX and
10 BioMarin and Spark with a factor VIII AAV vectors.
11 As you can see in this University of
12 College of London study, one of the first in 3 dose
13 ranges, you can see that the mean factor level was
14 5.1 percent, but it was fluctuating, but even at
15 that level offered a 90 percent reduction in
16 annualized bleed rate and over 90 percent reduction
17 in factor use. So the major limitation was AAV
18 capsid T-cell response, which seemed to be
19 responsive in many cases to steroids.
20 Here, you can see that you can actually
21 increase that efficacy, that is that factor level,
22 even to a 33 percent steady state in this factor IX

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1 gene therapy using the Padua gene, which is at an
2 increased 8- to 12-fold higher factor IX, and this
3 also results in greater than 90 percent reduction
4 in bleeds and in factor use.
5 There were capsid-immune responses. They
6 seemed to be steroid responsive, and the gene
7 therapy was well tolerated, and these levels seemed
8 to persist.
9 In the factor VIII BioMarin AAV 5
10 factor VIII trial, you can see that there was a
11 wide range of factor VIII. These patients, many
12 were started on steroids empirically to avoid
13 immune response, and these levels ranged between 12
14 and 219 percent with marked reduction in both
15 annualized bleed rate and factor use.
16 In the Spark study, which is still ongoing,
17 the dose ranges were 11 to 14 percent, as you can
18 see here. These patients had also marked
19 reduction -- from the ASH meeting, a marked
20 reduction in annualized bleed rate and in factor
21 use, and still had some capsid-immune responses,
22 suggesting that maybe empiric steroids may be an

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1 improvement. They offer an improvement and longer-
2 lasting higher levels.
3 What are the problems with gene therapy?
4 Certainly, there is hepatotoxicity, transient liver
5 function elevation noted in some patients to not
6 just capsid-immune response, but also interactions
7 with other hepatotoxic drugs. One hemophilia A
8 patient receiving efavirenz, or Sustiva, as part of
9 a highly active anti-retroviral heart therapy for
10 their HIV, developed a grade 3 liver toxicity after
11 AAV gene therapy.
12 Efavirenz has a black-box warning. It is
13 one of the most highly hepatotoxic drugs, and it
14 can induce oxidative stress and endoplasmic
15 reticulum stress.
16 The mechanism of the liver
17 function/dysfunction in AAV gene therapy is
18 unknown. The temporal onset a few weeks after gene
19 therapy and rapid reversal on stopping this drug
20 certainly suggests that there may have been some
21 synergistic hepatotoxicity, and we really need to
22 learn more about this. But caution is urged to all

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1 patients who want to do gene therapy to avoid
2 potentially hepatotoxic drugs, and this is really a
3 critical message to all our patients and treaters.
4 Finally, we talked a little bit about assay
5 discrepancies. We know there are discrepancies
6 between the 1-stage and the chromogenic assay.
7 Which one should we use? Do we need to do both?
8 There's also inverse discrepancy between factors
9 such as the B domain-deleted Xyntha and gene
10 therapy results.
11 The mitigation is to either use both assays
12 or to standardize chromogenic assays. One of the
13 questions, of course, is, are most hemophilia
14 centers now going to adopt chromogenic assays?
15 What is the gene therapy's success? Is 10
16 to 15 percent a sufficient measure of success? Is
17 greater than 15 percent better, and who will
18 decide? Where does thrombosis fit into this
19 picture? How high do we need to go, or do we need
20 not to worry about it?
21 Is more better? Does getting to greater
22 than 100 percent make you stronger, able to do more

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1 work, et cetera, et cetera, activities? And are
2 alternate measures of success a reasonable
3 approach?
4 This is quality of life, some of these very
5 important core outcomes, freedom from fear,
6 happiness factor, as one of my patients told me, or
7 even looking at outcomes from liver transplant
8 patients as a yardstick to measure how patients do
9 once their levels are corrected.
10 Certainly, for mitigation, more data are
11 needed to assess factor levels after gene therapy,
12 understand the discrepancy between factor and gene
13 therapies, and determine what optimal therapies
14 there are for gene therapy.
15 We should mention that a cost-effectiveness
16 analysis has been done using a more cost-safe
17 transition model looking at quality-of-life years
18 gained. And clearly, as we compare gene therapy
19 with factor VIII and model using literature and
20 Medicare reimbursement measures, using a one-way
21 and probabilistic sensitivity analysis over a
22 10-year time frame, and doing over hundreds of

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1 thousands of simulations, gene therapy was clearly
2 dominant in 92 percent of those simulations, and
3 it's likely to be cost effective in severe
4 hemophilia A as compared to factor VIII
5 prophylaxis. This was one study. More need to be
6 done.

7 In summary, what we're seeing with these
8 novel therapies is improvement in hemostasis, both
9 in hemophilia A and hemophilia with inhibitors.

10 We're noting issues and questions that arise with
11 1-stage versus chromogenic and whether thrombin
12 generation and TEG are the ways to monitor some of
13 these.

14 These require less invasive administration
15 subcutaneously. Patients love it, and it is an
16 amazing change for these patients; reduced bleed
17 frequency, looking at annualized bleed rate,
18 improve clinical measures, whether you use quality
19 of life or these core outcomes, as we mentioned.

20 There's an improvement in laboratory
21 measures, but clearly discrepancies exist. It may
22 reduce factor VIII or IX immunogenicity just by

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1 avoiding factor VIII exposure, but breakthrough
2 bleeds may still remain a problem. And it may
3 induce potential toxicity such as the
4 hepatotoxicity and thrombotic microangiopathy we
5 talked about, and future considerations are really
6 understanding these drugs long-term, real-world
7 use, and use in ITI or with surgery and in
8 children. Thank you.

9 (Applause.)

10 DR. EHRLICH: Thanks, Dr. Ragni.

11 MR. COSSENTINO: I just want to make one
12 announcement real quick. After the break, we're
13 going to be doing some interactive audience
14 questions and polls using a website called
15 slido.com, and we encourage everybody to log onto
16 Slido during the break so you become familiar with
17 it, and we have a test poll up right now.

18 Just go to slido.com on your phone or
19 laptop, and enter event code 3355. It doesn't
20 require any login or personal information, and
21 you'll be able to ask questions and answer polls in
22 real time. I'll display the directions on the

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1 projector during the break in case you missed any
2 of that, and there are handouts as well that have
3 the directions. Thank you.

4 (Whereupon, at 9:36 a.m., a recess was
5 taken.)

6 Session 2

7 Moderator - Najat Bouchkouj

8 DR. BOUCHKOUJ: In order to stay on time,
9 we're going to go ahead and start. I'm Najat
10 Bouchkouj. I am a pediatric hematologist/
11 oncologist and a clinical reviewer at the Office of
12 Tissues and Advanced Therapies at CBER. I will be
13 the moderator for session 2, which is titled
14 "Clinical Endpoints in Hemophilia."

15 Before I introduce our speakers, I just
16 want to give you an outline about this session.
17 We're going to have two speakers, two
18 presentations, 20 minutes each, followed by a panel
19 discussion. We will leave the questions to the
20 end, and we'll take questions from the audience who
21 are present in person and online as well.

22 So if you can submit any questions you have

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1 online, we'll try to go through them as time
2 permits.

3 Just before I introduce our speakers, I
4 just wanted to pose a couple of questions for the
5 audience, and I hope you have joined Slido already
6 so we can get your feedback about a couple of
7 questions. There might not be a hard right or
8 wrong answer, but we'll ask the questions right
9 now, and then we'll ask them again after the
10 presentations.

11 The first question is about a 30-year-old
12 male with severe hemophilia B, who is currently on
13 prophylaxis therapy with factor IX product. He has
14 moderate activity, swimming and brisk walking
15 3 times per week. He is considering to be enrolled
16 in a gene therapy trial.

17 What target factor level at steady state,
18 which is a constant level, would be optimal to
19 reduce his risk of bleeding; 1 percent, 5 percent,
20 15 percent, 35 percent, or 40 to 100 percent?

21 (Audience responds.)

22 DR. BOUCHKOUJ: We have about 32 answers,

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1 and about 48 percent says 1 percent, and that goes
2 down. And no one said -- 1 percent is the low. So
3 no one said zero percent.
4 Okay. Let's go to the second question.
5 The second question is about a 16-year-old boy with
6 severe hemophilia A, who's currently on prophylaxis
7 therapy with a factor VIII product. He has two
8 target joints and he plays soccer. He wishes to
9 consider gene therapy treatment.
10 What target factor level at steady state
11 would be optimal for him to reduce the risk of
12 bleeding? Again, 1 percent, 5 percent, 15 percent,
13 35 percent, or 40 to 100 percent.
14 (Audience responds.)
15 DR. BOUCHKOUJ: As I said, there is
16 probably no correct answer, but we will go through
17 the presentations, and then we will ask the
18 questions again and see if you change your mind.
19 I have the pleasure of introducing our
20 first speaker for this session, Dr. Bob Montgomery
21 from the Medical College of Wisconsin. He is a
22 senior investigator at the Blood Research Institute

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1 at the Blood Center of Wisconsin and professor of
2 pediatric hematology at the Medical College of
3 Wisconsin, Children's Hospital of Wisconsin in
4 Milwaukee. He's a physician scientist who has
5 studied von Willebrand factor and its relationship
6 with factor VIII.
7 Presentation - Robert Montgomery
8 DR. MONTGOMERY: Thank you very much, and
9 thank you for the invitation to speak today. These
10 are my disclosures.
11 When we're dealing with normal hemostasis
12 and we have circulating levels of von Willebrand
13 factor, factor VIII platelets, in this cartoon,
14 when we have vascular injury, we expose the
15 subendothelium, which becomes a nidus for
16 von Willebrand factor binding. And that
17 von Willebrand factor binding organizes itself and
18 has the recruitment of platelets.
19 When those platelets are adhered, they
20 activate, and it's that activated surface that
21 factor VIII will in fact bind to. I show
22 factor VIII coming from the fluid phase, but as we

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1 know, factor VIII is carried in plasma on
2 von Willebrand factor. Once that happens, we have
3 the factor VIII that brings together the factor IXa
4 and X with the ultimate formation of the clot. And
5 after healing fibrinolysis, hemostasis is restored.
6 We'll be talking a bit about von Willebrand
7 factor and its impact on factor VIII and also
8 touching on some issues with factor IX.
9 There are two cells in the body that make
10 von Willebrand factor, and one of those also makes
11 factor VIII. There is no factor VIII in platelets.
12 In the megakaryocyte, in the formation of alpha
13 granules, von Willebrand factor is produced and is
14 stored along with a host of other proteins.
15 If you don't have von Willebrand factor
16 such in a type 3 patient, you actually still have
17 alpha granules in platelets. So therefore, it's
18 not that those platelets are dependent upon
19 von Willebrand factor, as we'll see different in
20 endothelial cells.
21 These megakaryocytes ultimately form
22 platelets, and it's these platelets that have the

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1 stored proteins, including von Willebrand factor,
2 in the circulation. There is a secretory pool of
3 von Willebrand here that's in platelets. There is
4 no factor VIII unless it was put there genetically.
5 In the endothelial cell, we have the
6 formation of Weibel-Palade bodies, which are the
7 secretory granule of the endothelial cell. These
8 Weibel-Palade bodies are actually formed because of
9 von Willebrand factor. And if you don't have
10 von Willebrand factor, you actually don't have
11 Weibel-Palade bodies either. So it's a very
12 different relationship.
13 This is also a secretory pool of
14 von Willebrand factor, but when you secrete
15 von Willebrand factor, as I'll show in a bit, you
16 also secrete factor VIII, and that's different from
17 platelets. In addition, we use DDAVP as a way of
18 releasing these Weibel-Palade bodies to increase
19 von Willebrand factor and factor VIII so that those
20 storage pools are clearly different.
21 Both von Willebrand factor and factor VIII
22 are acute-phase proteins and are increased with

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1 surgery, with pregnancy, with physical stress, with
2 mental stress, and with aging. All of these
3 phenomena result in changes of the secretory pool,
4 and it's something that we'll come back to, that at
5 least current approaches to either replacement
6 therapy or gene therapy don't necessarily replace
7 this part of the process.
8 Von Willebrand factor can acutely be
9 released by DDAVP, which also releases factor VIII,
10 and this can be used if patients have mild or
11 moderate deficiency.
12 A number of years ago, we actually asked
13 the question, based upon secretion, where do these
14 two proteins first meet. To make a long story
15 short, here we see a patient with mild hemophilia
16 who was treated with DDAVP. You can see that
17 factor VIII goes up and the von Willebrand factor
18 goes up, and both can be elevated into a
19 therapeutic range.
20 However, if you take a severe hemophilia
21 patient who's on prophylaxis and receiving factor
22 VIII -- in this case, it actually was every

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1 6 hours, for a variety of reasons -- but give that
2 patient DDAVP, the von Willebrand factor goes up as
3 expected, but there's no budge of factor VIII.
4 What's important there is that, therefore,
5 you can't replace the stress pool or the secretory
6 pool of factor VIII by infusion even though you can
7 definitely stop bleeding.
8 If we look at the von Willebrand patient,
9 again, DDAVP will release both proteins. These
10 will be similar in a stress response.
11 Interestingly, if you take a type 3 von Willebrand
12 patient who makes no von Willebrand factor and has
13 a baseline level of factor VIII usually around
14 5 percent of normal, and now you prophylax with
15 von Willebrand factor concentrate that has no
16 factor VIII in it and now give DDAVP, what's
17 interesting is the von Willebrand patient's
18 factor VIII has now been normalized because of
19 changing the survival in the presence of
20 von Willebrand factor. So factor VIII level is now
21 normal and that's endogenous factor VIII.
22 Yet, if you give DDAVP, even though there's

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1 endogenous VIII made in all the places, it doesn't
2 create a secretory pool, and I think that's
3 something that we'll touch on.
4 Two laboratories recently were able to show
5 somewhat the same thing in a single issue of blood,
6 and that is to study the amount, or the relative
7 amount, of factor VIII that's in fact produced in
8 endothelial cells. This was done by two different
9 approaches -- I'll talk a little bit more about our
10 own -- in which we floxed the factor VIII gene,
11 which meant that if we took that animal and crossed
12 it with an animal that was making, let's say, we'll
13 say albumin Cre, the albumin Cre would cut out the
14 factor VIII so that every cell that was making
15 albumin would stop making factor VIII.
16 This actually can be shown. Here is the
17 floxed factor VIII mice. Here are the ones in
18 which we knocked out the factor VIII in albumin-
19 synthesizing cells, and there was no effect.
20 In contrast, if we move to the cadherin and
21 the TIE2, or the TEK Cre, you can see that
22 factor VIII is essentially eliminated just like the

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1 knock-out, suggesting at least it doesn't say what
2 endothelial cell is making it, but it is saying
3 that virtually all factor VIII is made in
4 endothelial cells in mice.
5 More recent studies have suggested that the
6 different beds of endothelial cells can have a
7 dramatic difference, such that it may be that
8 vascular endothelium may contain both VWF and
9 factor VIII. Sinusoidal endothelial cells have
10 factor VIII but may not have von Willebrand factor,
11 and lymphatic endothelial cells are similar.
12 Recognize, though, that if we don't have
13 von Willebrand factor, the only place in these
14 models would be the peripheral vascular system that
15 you had a secretory or stress pool of factor VIII.
16 Factor IX is less controversial, maybe, and
17 factor IX is made in the liver by the hepatocyte.
18 Here is a recent paper showing the various organ
19 systems in the body, and the only one in which
20 there was an identified factor IX mRNA was in the
21 liver, not surprisingly.
22 If we went within the liver and now looked

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1 at the cells within the liver itself, you'll see
2 that LSECs, or sinusoidal endothelial cells, do not
3 make any factor IX, and it's only made in the
4 hepatocyte, not surprising.
5 Some other recent studies, however, by
6 Darrel Stafford and his coworkers at Chapel Hill
7 have demonstrated the importance of factor IX
8 binding to subendothelial collagen-4. This bound
9 factor IX provides an important extravascular pool
10 of factor IX. Certainly, it's the intravascular
11 that is physiologically important, but the
12 extravascular may be able to support that in the
13 long run.
14 Circulating levels of factor IX do not all
15 predict the full hemostatic potential, and as shown
16 using a K5A mutation in a mouse in which collagen-4
17 binding was eliminated, there was normal in vitro
18 clotting, but reduced in vivo clotting, so that the
19 fluid phase effect was easily measured even though
20 the systematic effect of collagen-4 is not binding
21 in a traditional clotting assay.
22 Now, great strides have been made that have

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1 significantly affected gene therapy, and we'll hear
2 a lot about that from other speakers today and some
3 of the problems with the assay. But really,
4 factor IX Padua has changed the field of producing
5 a protein that has increased specific activity and
6 is genetically modified, and along with some other
7 modifications can produce many-fold higher levels
8 of factor IX expression based on a mole-to-mole
9 basis.
10 Here's a model of the assembly of the Xase
11 complex. It's relatively straightforward that
12 VIIIa binds to form the Xase complex. But this
13 step may actually be more complex than that. I put
14 in here von Willebrand factor because of the
15 benefit of von Willebrand factor to increase the
16 local concentration of factor VIII, something that
17 doesn't necessarily happen unless von Willebrand
18 factor is present.
19 There are a number of binding sites, the
20 one that's been traditionally known for a long time
21 as the GP1b/IX binding site on platelets that bind
22 to the a1 domain of von Willebrand factor. It's

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1 also been known for many years that 2b3a on
2 platelets binds to the RGDS sequence that's present
3 in von Willebrand factor. And therefore, that,
4 along with the binding of factor VIII to VWF, could
5 in fact facilitate the local delivery of factor
6 VIII.
7 We now know, both in studies that have been
8 published by Veronica Flood and another one
9 presented at ASH this year on myosin, that these
10 are also extra platelet binding proteins at the
11 local vascular injury site that can augment,
12 number one, the binding of von Willebrand factor;
13 and number two, the delivery of factor VIII to
14 formation of the Xase complex.
15 We also know that IXa here can bind to
16 collagen-4 so that even von Willebrand factor is
17 brought into close proximity with its factor VIII
18 to factor IX that might be bound to collagen as
19 well.
20 Great strides have been made through
21 emicizumab. Emicizumab clearly can take over this
22 function of bringing IXa to X, to the formation of

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1 thrombin generation. If we think about it, that's
2 a fluid phase protein and not necessarily something
3 that's necessarily delivered with increased
4 concentration.
5 I think there are still issues that need to
6 be worked on where you need to think about
7 comparing what is the local delivery of factor VIII
8 to the systemic delivery of factor VIII and things
9 that might augment clotting and regulate function.
10 What questions remain concerning
11 factor VIII or factor IX? For factor VIII, is the
12 site of synthesis important? Is a storage pool of
13 factor VIII important? If it is, the site of
14 synthesis becomes important since you won't have a
15 secretory pool if you synthesize the factor VIII in
16 cells other than the endothelial cell.
17 Does stress increase factor VIII or just
18 release it from stores? Is there a problem with
19 uncoupling factor VIII from von Willebrand factor
20 as far as the physiology of local hemostasis?
21 Does von Willebrand factor actually serve
22 as a protein that delivers factor VIII to the

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1 evolving thrombus? This is something that one can
2 speculate on but is only evolving better proof of
3 that phenomenon.
4 For factor IX, does IX need to be made in a
5 hepatocyte? There are certainly studies of it
6 being well-made in muscle as well as other cells,
7 and as we heard in ASH by Qizhen Shi, also,
8 factor IX can be made in megakaryocytes in
9 platelets. But if made in another cell, there
10 needs to be both adequate furin and adequate gamma
11 carboxylation.
12 The final issue is, is Padua safe? There
13 are issues around its specific activity and its
14 immunogenicity. Everything seems to be very
15 favorable, but there are things that we just need
16 to continue to be aware of.
17 How important is subendothelial collagen-4
18 binding as a store? What Darrel Stafford's group
19 showed is that infusing high levels of factor IX
20 actually can have a binding to the collagen-4 and
21 actually caused sustained benefit over a longer
22 period of time than necessarily measured in plasma.

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1 With that, I'll thank those that worked
2 with me, and thank you for listening. Thank you.
3 (Applause.)
4 DR. BOUCHKOUJ: Thank you, Bob.
5 Our next speaker is Dr. Marilyn
6 Manco-Johnson from the University of Colorado.
7 She's the director of the Hemophilia and the
8 Hemostasis Center and the Children's Hospital of
9 Colorado. She will be talking to us today about
10 factor VIII and IX correlation with breakthrough
11 bleeding and optimal joint endpoints of new
12 therapies.
13 Presentation - Marilyn Manco-Johnson
14 DR. MANCO-JOHNSON: Thank you, and thank
15 you very much for the opportunity to present today.
16 Here are my disclosures.
17 I'm here talking about therapies for
18 hemophilia A. I've tried to compare this to what
19 we in hem-onc are more familiar with in the cancer
20 world; that is, a complete response, a partial
21 response, and no response. But a complete response
22 would be normal biochemical and clinical outcomes,

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1 while a partial response would include reduced
2 bleeding, reduced factor consumption, and reduced
3 morbidity with things like intracranial hemorrhage,
4 hospitalizations, and other severe bleeding events.
5 A partial response may be desirable, particularly
6 in the short term, regarding the risk of excessive
7 levels with a thrombotic potential.
8 When we look specifically at the important
9 outcome of hemophilic arthropathy, what outcomes
10 can we have? Well, certainly, I think we can never
11 get away from the restoration of plasma factor
12 activity; so factor VIII and IX both have ranges,
13 ranging from 50 to 150 percent of a population
14 mean. You can look at their activity or look at
15 the protein content in the blood.
16 Certain surrogate markers for factor
17 activity that are important to be applied to
18 non-factor therapies would be looking at correction
19 of the partial thromboplastin time, the normal
20 thrombin generation, thromboelastography, and more
21 recently, interesting markers of bone metabolism,
22 which have shown to be altered in the absence of

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1 factor VIII or factor IX and restored by the
2 replacement.
3 Clinical effects of protein restoration, we
4 have focused primarily up until now on no
5 spontaneous bleeding. Bleeding has been used to
6 consider clinical or determined to recognize
7 bleeding; no bleeding beyond what a normal person
8 would experience in trauma or surgery because,
9 obviously, we all bleed given enough of a stress,
10 and normal bone density, which is a more subtle and
11 refined indication of thrombin generation. And
12 we'll talk a little bit about no or reduced onset,
13 or reduced progression of joint disease.
14 The benefits of direct and indirect
15 outcome, if you look at factor VIII levels, we
16 widely understand what that means. A normal level
17 is normal. There's no reason to expect that if any
18 therapy got someone within the normal range, that
19 it wouldn't translate to normal clinical
20 hemostasis.
21 Indirect evidence on bleeding and joint
22 damage is more relevant to the patient. It's a

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1 functional marker of efficacy. And the con, a very
2 important con to this, is that all indicators of
3 outcomes on joint damage and joint bleeding are
4 going to work better in young patients with normal
5 or minimal pre-existing arthropathy, because
6 patients with damaged joints may experience
7 variable outcomes relative to joint pain and
8 bleeding depending on how they came into the trial.
9 I think this is very important because in
10 all therapies for hemophilia, through the FDA, we
11 do start with adult patients, who are better able
12 to give consent and we feel are less vulnerable as
13 research subjects; but on the other hand, they have
14 developed and fixed cartilage and bone structures.
15 If you look at the effects of hemophilia, I
16 want to argue as a pediatrician very strongly, that
17 the effect of blood is much more severe on growing
18 cartilage and growing bone. And we know that most
19 of this damage is not reversible, so if we're going
20 to come out with good adult outcomes, we need to
21 start with the very young children and protect the
22 cartilage and bone as it's growing.

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1 So our functional outcomes are the
2 prevention or stabilization of arthropathy, and we
3 have physical joint scores such as the Hemophilia
4 Joint Health Score, and we have imaging scores
5 using both ultrasound and MRI. We have very
6 important patient-reported outcomes, including
7 quality of life, activity, participation, and pain,
8 and these are going to be discussed later by Dr.
9 Kempton.
10 This is a presentation that we made
11 actually in 2013 by Tom out of Glorioso and
12 colleagues, and it looks at joint outcomes with
13 age. And very interesting, at a very young
14 age -- so for all of these images, looking at joint
15 bleeding, joint physical exams, and joint MRI
16 scores, you can see that hemophilia is marked by a
17 huge heterogeneity, with a huge variability in
18 scores among patients. And of course that makes
19 our registration trials with relatively small
20 numbers of patients difficult. But bleeding gets
21 to about a mean of 20 bleeds per year, and you've
22 reached that very early in life, and it's about the

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1 same throughout life.
2 Physical exam scores, while very variable,
3 peak out in the young adulthood and don't really
4 change much, whereas MRI changes are consistent
5 throughout life as long as they've been measured.
6 When we look between soft tissue and osteochondral
7 changes, this is primarily the osteochondral
8 change.
9 We looked at changes in the Hemophilia
10 Joint Health Score, and this was presented at the
11 World Federation this year, at individuals who
12 started prophylaxis before 3, between 3 and 6, 6 to
13 10, et cetera. And we found that you could only
14 blunt the curve of physical damage over time if you
15 started below 3. And among all these other ages of
16 starting, there was no difference.
17 On this scale, you see the Hemophilia Joint
18 Health Score. We do these annually in Colorado,
19 and looking at the positive score means you're
20 worsening; negative score is improving. This is
21 severe, moderate, and mild hemophilia. Right is on
22 prophylaxis; blue is on demand.

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1 You can see that there's tremendous overlap
2 and the worsening of scores regardless of the
3 severity of hemophilia, so mild hemophilia is way
4 better than severe, but it's not great, and it's
5 not the goal that we aspire to.
6 In the joint outcomes study that we
7 reported at ASH in 2006, children given 25 units
8 per kilo of recombinant factor VIII, starting
9 before the age of 30 months, were found at the age
10 of 6 to have significantly less osteochondral
11 damage compared to children who use this on
12 prophylaxis, such that the relative risk of joint
13 damage was 6-fold if you did not use prophylaxis in
14 the preschool years.
15 These children using Kogenate had a mean
16 half-life of 12 hours and a mean 48-hour trough of
17 4 percent. So when you're looking at troughs, this
18 is a baseline for what you get for 4 percent.
19 In the outcome, we found that there are
20 many children who had relatively little bleeding,
21 but evidence of bony change, and conversely,
22 children who had lots of joint bleeds who had very

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1 little joint damage, such that MRI showed a modest
2 correlation with a number of hemarthroses so that
3 we could only account for 13 percent of joint
4 damage that could be explained by clinical or
5 recognized bleeding. And this drove me to come up
6 with a concept of subclinical, unrecognized, or
7 micro bleeding.
8 Now, I want to emphasize this is in young,
9 intensively treated children. It probably doesn't
10 hold to 4 years ago, when individuals had
11 relatively little treatment and big clinical
12 bleeds.
13 Looking at that population, at the lifetime
14 average of joint bleeds of individuals who started
15 prophylaxis at an average age of 1.3 years was 1.5 joint
16 bleeds throughout childhood until age 18, whereas
17 those who started at age 7 continued to experience
18 more bleeding, with an average of 4.3. And if you
19 considered only the time after they were on prophylaxis,
20 they still had 4 joint bleeds per year compared to
21 1.6 on the early prophylaxis.
22 So if we look at clinical joint bleeding,

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1 ABRs, in clinical trials, it depends if the patient
2 was on prophylaxis or not and how early they
3 started prophylaxis. So heterogeneous trials that
4 enroll individuals from different backgrounds are
5 going to be affected by bias.
6 We found that the odds ratio of joint
7 damage between early prophylaxis and delayed prophylaxis was
8 14 at the age of 6, but held up as still an odds
9 ratio of 6 at the age of 18. And I think 18's an
10 important cutoff because most growth centers are
11 fused and you have pretty full cartilage and bone
12 development by that age.
13 Well, when we looked at our clinical,
14 easily used surrogates for joint outcome, the
15 clinical exam score, the joint ABR, the total ABR;
16 unfortunately, none of them correlated with
17 osteochondral changes on MRI. So the indicators
18 we're using in our trials are not correlating with
19 long-term bone and cartilage outcome.
20 The only predictor of the MRI osteochondral
21 damage was the number of bleeds suffered before the
22 age of 6, and this so strongly correlated with

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1 whether you were on prophylaxis before the age of 2 or
2 on demand, that it really was a surrogate for early
3 prophylaxis.
4 Looking at the osteochondral changes over
5 time, those who had early prophylaxis unfortunately
6 continued to accrue some osteochondral damage, but
7 this was less than those whose prophylaxis was delayed
8 until age 7 and less than those who never had
9 prophylaxis. So at the age of 18 to 20, we had a total
10 6-joint MRI score of 7; if we started early prophylaxis,
11 13; if the prophylaxis was delayed, towards 7; and 20 if
12 you never had prophylaxis. So outcomes are dependent
13 very much on the age it's starting.
14 The physical exam scores trend exactly the
15 same way, that they do worsen over time, and at the
16 time we did the joint outcomes study, 25 units per
17 kilo every other day, this group had excellent
18 adherence over 90 percent that you still accrue
19 some damage, but it's less than then if you delay
20 prophylaxis until 7.
21 So going back to the lack of correlation,
22 with recognized bleeding and with physical exam

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1 scores, this again supports a subclinical
2 unrecognized bleeding in our current population of
3 young, intensively treated patients, and is very
4 important and is probably as or more important than
5 the clinical numbers of ABRs.
6 I'm not going to dwell on this because
7 Dr. Montgomery just gave a very eloquent
8 presentation of this. We know that factor VIII
9 ranges fivefold in healthy people, and we know that
10 both exercise and inflammation raise factor VIII,
11 and we know that continuous factor VIII will not
12 respond to physiologic stresses.
13 What is the optimal goal of factor
14 VIII therapy? Should we be aiming to mimic
15 physiologic levels or should we be attempting the
16 lowest level that results in no clinical symptoms
17 for the widest range of patients? And I've already
18 given some arguments why the clinical symptoms are
19 not necessarily the best.
20 But if you look at clinical bleeding, if
21 you were to choose a trough, the work of Den Uijl
22 with moderate hemophilia, looking at endogenous

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1 level and number of bleeds, suggested that about
2 20 percent factor VIII, you would have very few
3 bleeds without significant trauma.
4 These are negative binomial analyses. And
5 I just want to point out, with hemophilia studies
6 of joint bleeding, you have lots of people who have
7 zero bleeds, and then you have tail-outs to the
8 very high numbers. And this distribution makes it
9 the most difficult to get accurate statistical
10 modeling.
11 Well, I kind of edited the work of Mike
12 Soucie, presented at ISTH in 2015. He came out
13 with a conclusion, looking at factor IX in yellow
14 and VIII in the dashed black, that 15 percent would
15 be an optimal level. And 15 percent works pretty
16 well for the adults, but if you want to prevent the
17 joint damage while cartilage and bones are still
18 growing, you have to focus on those growing-aged
19 children, and 25 to 30 percent actually looks like
20 a much better level to be targeting.
21 This just happens to be WAPPs PK curve.
22 I'm not talking about inhibitor tolerance, but to

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1 show that in factor VIII replacement, you have
2 peaks, and you have troughs, and you have area
3 under the curve. And even with the extended
4 half-lives, the longer the interval between
5 infusions, the longer time you're at a very low
6 level.
7 If we are to consider unrecognized bleeding
8 or oozing into the joint as being a significant
9 pathogenesis of joint disease, then those curves of
10 long tails are not necessarily optimal. If you
11 were to consider that peaks are important for
12 trauma, for sports, for surgery, then a consistent
13 level at 15, 20 percent is also not going to work
14 well.
15 With a standard replacement, we can
16 manipulate this. This is a boy with a tolerized
17 inhibitor on 30 per kilo every other day, and to
18 play soccer, instead of taking 30 per kilo 3 times
19 a week, he devised the 1 30-per-kilo dose, while he
20 has 3 15-per-unit kilo doses, and has a daily
21 dosing for 5 days a week and none for 2. And he's
22 able to increase the area under the curve. He's

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1 able to reduce or elevate the level of the trough,
2 reduce the time in the shoulder and have no
3 bleeding.
4 So we know that the counterpoint down side
5 of this is that it's very frequent IV injections,
6 and that's very difficult to tolerate over time.
7 But it's more recreating the physiologic state of
8 being able to be high and low as you need it.
9 This is a really elegant work of Carolyn
10 Broderick from Australia, where she looked at
11 sports participations in people with hemophilia
12 using the NHF categorization of level 1, 2, or 3
13 sports, and 3 is the most vigorous. She found that
14 at a factor level of about 35 percent, your
15 increased risk of bleeding was very modest. It was
16 only 1 and a half to 2 times that of sitting in a
17 chair reading a book with severe hemophilia; so
18 that's a very acceptable rate.
19 Her work would suggest for an active boy
20 being 35 percent at the time of activity. Another
21 graph she showed was that almost all bleeding is
22 within an hour of the active participation.

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1 So is hemophilia in the 25 to 30 percent
2 range optimal for therapy to consider both safety
3 and efficacy? Our future projections are based on
4 our experience with the disease and with our
5 imperfect treatment, so we really don't have the
6 data to predict that.
7 I want to suggest that clinical bleeding
8 predicts the onset of joint disease. So whether
9 you'll have joint disease or not is very well
10 predicted by the number of bleeds, but not the
11 severity of the damage.
12 Again, this is the subclinical bleeding,
13 and talking a little bit between MRI and ultrasound
14 MRIs, the gold standard, very good with bone and
15 cartilage, excellent on soft tissue. It's a long
16 study, expensive, and not always available, while
17 ultrasound is a point-of-care test.
18 It's available in the clinic. It's
19 inexpensive, but you can't image the central joint
20 structures where the joint bleeds actually occur.
21 It's operator dependent. It's tricky to
22 distinguish synovial fluid from hemosiderin, and

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1 it's a very, very nice discussion of these pros and
2 cons by Dr. Soliman from Andre Durie's group at the
3 University of Toronto in sick kids.
4 Just to point out a little bit, these are
5 normal ankle, and this nice dome on the talar dome,
6 you see it flattens when you get a lot of bleeds.
7 And these little white dots are cysts in the bone.
8 It's also very good. The bright white is fluid and
9 this black is synovium.
10 So these chronic changes over many years
11 are very well-picked-up by MRI, but they're not
12 good for a 1-year or 2-year study to show you're
13 not going to get that interval change quickly.
14 In ultrasound, this is a clinical study
15 done on a little 5-year-old boy whose parent was
16 using extended half-life factor VIII twice a week
17 at the dose recommended on the package insert,
18 feeling that she was giving her boys cadillac
19 treatment, and yet this widening in the right knee
20 joint, compared to the contralateral joint, was
21 representative of fluid in the joint, and this soft
22 tissue in here is some clotted blood in the knee.

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1 These findings were present in both knees
2 and both ankles, so this little boy who had no
3 evidence of joint bleeding, obviously had imprints
4 on ultrasound that he was oozing or having some
5 bleeding into joints, and that was not an extended
6 therapy.
7 Just to show that extended half-life
8 products so far have not really been able to extend
9 the time without a significant time at a low
10 trough; whereas with factor IX, extended
11 half-lives, we've done a lot better and can
12 maintain a trough near the gold standard.
13 In conclusion, factor level is a key
14 endpoint, but there are differences, fundamental
15 differences in therapies that do or don't have
16 peaks. Longer-term secondary endpoints will be
17 better assessed in young patients with less
18 pre-existing damage.
19 We need patient-reported outcomes. For
20 factor IX at target level, as close as we can get
21 to the normal range is desirable, but I think
22 factor VIII, for all the reasons Dr. Montgomery

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1 discussed, requires more data accumulation, and we
2 don't know yet what the optimal therapy will be.
3 And I'll close right there. Thank you.
4 (Applause.)
5 DR. BOUCHKOUJ: Thank you, Dr. Johnson.
6 We're just going to put out the questions
7 again and just ask for your feedback to answer the
8 couple of questions that we asked before, and see
9 if you've changed your mind after the
10 presentations.
11 So again, this is a 30-year-old male with
12 severe hemophilia B, who has moderate activity, and
13 what would be his optimal constant factor IX level
14 to reduce his risk of bleeding.
15 (Audience responds.)
16 DR. BOUCHKOUJ: Okay. Following question?
17 This is the 16-year-old with severe hemophilia A,
18 who is active, and what would be his optimal factor
19 VIII level.
20 (Audience responds.)
21 Panel Discussion
22 DR. BOUCHKOUJ: Thank you.

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1 I guess what we can do; perhaps I can ask
2 our speakers what would be your answer to the
3 questions. Maybe Dr. Manco-Johnson, if you want to
4 comment on that.
5 DR. MANCO-JOHNSON: I would say, with
6 factor VIII in the second boy, probably I would say
7 40 to 100 percent, if we were confident that we
8 weren't going to 200 percent because this is in the
9 normal range, and he already has 2 vulnerable
10 joints.
11 DR. BOUCHKOUJ: And for the first question,
12 do you have a --
13 DR. MANCO-JOHNSON: Optimally, a cure is a
14 cure, and I would like to see people in the normal
15 range, although I think, from what we know, that
16 35 percent for most things, except surgery, would
17 be acceptable.
18 DR. BOUCHKOUJ: Thank you.
19 How about your thoughts, Bob?
20 DR. MONTGOMERY: I think on the first
21 patient, I would think 35 percent seems the ideal
22 level, and the second one, I think the

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1 normalization of a child to be able to do athletics
2 is important and think that it does carry with it
3 an added burden of need of clotting factor. I
4 think that really probably is over 35 percent, but
5 I'd probably shy away from 100 percent.
6 I suppose 100 percent, without having any
7 acute phase response.
8 DR. BOUCHKOUJ: Maybe I can ask
9 Dr. Montgomery, does the result circulating
10 factor VIII or IX level after gene therapy result
11 in the same physiological thrombotic risk as with
12 endogenous factors?
13 DR. MONTGOMERY: Say that again.
14 DR. BOUCHKOUJ: The result in circulating
15 factor VIII or IX level after gene therapy, do they
16 have the same effect of thrombotic effect as the
17 endogenous factors?
18 DR. MONTGOMERY: I think there's still a
19 lot to be known, so I don't know that I have the
20 answer for that. I think that, ideally, you'd like
21 to produce the protein in its physiologic cell, and
22 that hasn't been done for factor VIII for a variety

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1 of reasons, and certainly has been done for IX.
2 But how important that is I think is an
3 issue. We probably have for years planned surgery,
4 trying to correct patients at the time of surgery
5 to 100 percent, not recognizing that the normal
6 patients that have surgery probably have
7 250 percent factor VIII at the time of surgery.
8 So I think the physiologic importance of
9 that stress response is more intuitive than it
10 necessarily is highly driven by science.
11 DR. MANCO-JOHNSON: I was going to say, one
12 problem we're dealing with today is that the range
13 of motion in functional outcomes of joint
14 surgeries, which are heavily used by adults with
15 hemophilia, is less than patients who don't have
16 hemophilia, and the musculoskeletal community of
17 the World Federation believes this is due to an
18 intense inflammation related to lifelong bleeding.
19 So again, if we're going to improve adult
20 surgeries, we have to start in childhood and remove
21 that early inflammation and damage.
22 DR. EHRLICH: Can I ask you a question,

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1 Dr. Manco-Johnson, about the idea of starting early
2 in childhood? So in light of novel therapies,
3 keeping in mind that you can show that early
4 prophylaxis is better, but we haven't yet shown for
5 the novel therapies if those actually reduce joint
6 damage, when do you start to think about using
7 something like Hemlibra in a child? Would you
8 start with standard prophylaxis, or are you as a
9 clinician considering moving Hemlibra earlier?
10 DR. MANCO-JOHNSON: So we have two issues,
11 the highest rate of intracranial hemorrhage and
12 epidural spinal hemorrhage. These life-altering
13 hemorrhages are in infancy and early childhood. So
14 I think Hemlibra does offer the opportunity to
15 prophylax a child before they're weight bearing
16 with a delivery route that's very possible.
17 So we don't have data on doing that yet,
18 how effective it is, but theoretically, I think
19 it's very attractive. And then, in terms of later
20 childhood, I think the subclinical bleeding -- I
21 like to call it micro bleeding -- probably starts
22 when you're weight bearing.

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1 So while Hemlibra could be a bridge in very
2 early weight bearing, we don't have data yet if the
3 current doses are high enough to really prevent the
4 kinds of stresses on joints that need to be
5 measured and need to be studied, and possibly
6 factor VIII therapies could be more effective then.
7 DR. EHRLICH: Do you, in light of the
8 development of antidrug antibodies, even though the
9 experience so far is that those are rare, consider
10 the possibility, once you develop an emicizumab
11 antidrug antibody, then you've sort of lost the
12 ability to use that later in life, that you should
13 consider maybe saving that for later, when you've
14 exhausted other therapies?
15 DR. MANCO-JOHNSON: I like to front-load
16 therapies to get children to grow in a healthy
17 structure and function. And it's not that I don't
18 worry as much about adults, but I think the
19 morbidities of adults can be better managed if you
20 enter adulthood with a good body.
21 DR. SHARMA: I have a question for
22 Dr. Manco-Johnson. Could you comment on how can we

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1 best capture the subclinical or microbleeds in the
2 context of a clinical trial?
3 DR. MANCO-JOHNSON: Yes. I showed that
4 picture of ultrasound. I'd like a show of hands
5 here. How many thought that looked like
6 mumbo jumbo?
7 (No response.)
8 DR. MANCO-JOHNSON: No? Well, they're not
9 as black and white, clearly beautiful, as the MRI
10 image is. And I think they are operator dependent,
11 and we're going to need a lot more training, a lot
12 more standardization, a lot more validation before
13 they're a good clinical tool.
14 On the other hand, with the ultrasound, you
15 can see fluid in the joint, and actually, that can
16 be pretty well characterized. My husband did a lot
17 of work in developing ultrasound, and with the
18 ultrasounds and MRIs, he used to look at the joints
19 of young children with hemophilia and say
20 10 percent of the joints have too much fluid. It's
21 very minor, but objectively, you don't see this in
22 healthy children.

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1 I know now that 10 percent of children had
2 subclinical bleeding in their joints, and that's
3 what he was seeing. And he kept feeling a
4 little -- he read the outcomes of the joint
5 outcomes study and he was apologetic about it. But
6 he said it's just more. I don't know what it is.
7 I don't know why, but this is more than you should
8 see.
9 But I think, for a clinical trial,
10 ultrasound can show are you having a little
11 bleeding now, because I don't think in a
12 registration trial, we have the time. You need
13 5-10 years to look at MRI outcomes. But if you're
14 accumulating fluid while you're on this therapy,
15 then this therapy is not effective.
16 DR. SHARMA: Thank you.
17 DR. BOUCHKOUJ: Just by a show of hands,
18 how many clinicians do we have with us in the room?
19 (Hands raised.)
20 DR. BOUCHKOUJ: In your practice, do you
21 use ultrasound as point of care to evaluate
22 bleedings on a regular basis?

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1 DR. MANCO-JOHNSON: Yes.
2 DR. BOUCHKOUJ: Thank you.
3 I guess one question for Dr. Manco-Johnson
4 I have, as we get better at improving, minimizing
5 joint bleeding in general, would you recommend that
6 measuring joint outcomes may be needed to assess
7 long-term impact on treatment, for long-term
8 treatment?
9 DR. MANCO-JOHNSON: Absolutely. And I
10 think something like MRI, if you had a standard
11 time at 18 years or 30 years, I think that that
12 would be a gold-standard outcome right now because
13 you can look at the effect on the center of the
14 joint.
15 In ultrasound, you can see cartilage and
16 bone abnormalities, but only in the periphery of
17 the joint, but an MRI has to be reserved to a few
18 time points and you need a good interval from
19 baseline to outcome.
20 DR. BOUCHKOUJ: Are there efforts among
21 healthcare providers to standardize the way these
22 are assessed, the joints are assessed, in terms of

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1 for recruitment of trials and so on?
2 DR. MANCO-JOHNSON: Yes. I think the
3 International Prophylaxis Study group that was
4 started and headed by Victor Blanchette at SickKids
5 has done a lot of work to develop and validate
6 physical joint scales for both adults and children,
7 and then took on MRI, and they're taking on
8 ultrasound.
9 I know Dr. von Drosky [ph] is also working
10 on that, but I think that Dr. Blanchette's groups
11 are multicontinental, multinational, and have a
12 very wide interdisciplinary input.
13 DR. BOUCHKOUJ: Thank you.
14 I think what we can do; maybe we open up
15 for questions. If you guys have any questions,
16 please come to the microphone, if you want to ask
17 the speakers and panelists.
18 We have some questions from Slido. You can
19 submit your questions on Slido as well if you are
20 listening online.
21 DR. EHRLICH: I just want to point out,
22 there are a couple questions already on Slido, but

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1 I think they'll be better addressed in a later
2 session. So we're not ignoring you. We'll just
3 bring them up in the appropriate session.
4 DR. BOUCHKOUJ: Question?
5 DR. GOLDING: I'm Basil Golding with FDA);
6 a question for Dr. Manco-Johnson. You alluded to
7 bone markers and bone disease in the hemophiliacs.
8 Could you expand on that and tell us what you
9 found, and whether you think that that is something
10 we should look at in clinical trials?
11 DR. MANCO-JOHNSON: Yes. Jason Taylor,
12 when he was at University of Oregon Health and
13 Sciences University, did a lot of work. And
14 although there were different patterns between
15 factor VIII deficiency and factor IX deficiency, he
16 generally found an increase in osteoclastic
17 activity and a decrease in osteoblastic activity
18 when the factor level was severely low, and then
19 after replacement, he found a reversal or
20 normalization.
21 For many years, we had known that people
22 with hemophilia have decreased bone density.

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1 Naively, I thought that because of joint disease,
2 individuals were not doing as much weight bearing
3 and this was a function-structure relationship.
4 But he then gave a biochemical explanation that
5 thrombin generation may also be necessary for the
6 deposition of calcium into cartilage, the cartilage
7 matrix.
8 This I think is a more subtle, maybe
9 shorter-term marker that we could follow in
10 clinical trials because, obviously, we would want
11 optimal mineralization of our bones.
12 DR. BOUCHKOUJ: Thank you very much for our
13 speakers, and we will move on to the following
14 sessions.
15 Laurel?
16 Session 3
17 Moderator - Laurel Menapace
18 DR. MENAPACE: Shifting gears, we're headed
19 into session 3, which will be an overview of
20 patient-reported outcomes as I previously discussed
21 in my introduction. It is my distinct pleasure to
22 introduce Dr. Elektra Papadopoulos, who serves as

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1 the associate director of the clinical outcomes
2 assessment staff in the Office of New Drugs in the
3 Center for Drug Evaluation and Research.
4 Her staff and office provide consultation
5 to CDER review divisions, as well as other FDA
6 centers on clinical outcome assessments regarding
7 their development, validation, interpretation, and
8 overall suitability to support regulatory approval
9 of labeling of new hemophilia drug products.
10 Dr. Papadopoulos, can you come forward?
11 She'll be providing a brief overview of patient-
12 reported outcomes, so sort of broad-sweeping
13 strokes before our other speakers present their
14 information. Thank you.
15 Presentation - Elektra Papadopoulos
16 DR. PAPADOPOULOS: Thank you very much,
17 Laurel, for the kind introduction. It's my
18 pleasure to be here this morning.
19 As Laurel mentioned, our group works across
20 therapeutic areas. We focus on measurement issues
21 with regard to clinical outcome assessments of
22 which patient-reported outcomes are one type.

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1 Without further delay, before I delve into
2 the details of clinical outcome assessments, I
3 always like to take a step back and remind
4 ourselves of, really, what are we trying to
5 accomplish. I think this really sets the stage
6 nicely in terms of what is a patient-centered
7 outcome. These are really outcomes that are
8 important to how patients survive, how they
9 function, and how they feel in the here and now in
10 their daily lives. In the case of patients who
11 can't express this, sometimes we have to rely on
12 caregivers and others.
13 Now, this was referred to in earlier talks,
14 but our mandate at FDA when we're making drug
15 approval decisions is to really weigh the clinical
16 benefit against the risks of a medical product.
17 Clinical benefit as described here is a positive
18 clinically meaningful effect of an intervention on
19 how an individual feels, functions, or survives,
20 and clinical outcome assessments are the tools that
21 we use to measure the clinical benefit of medical
22 products.

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1 Importantly, how we describe this clinical
2 benefit to patients, providers, and other
3 stakeholders is determined by what we call the
4 concept or the outcome that was measured. This
5 slide was shown earlier, but it shows the array of
6 types of outcome assessments that we use to assess
7 clinical benefit. Again, we call them clinical
8 outcome assessments.

9 Importantly, patient-reported outcomes are
10 not the only types of patient-centered outcomes,
11 and very often we have to rely on a variety of
12 clinical outcome assessments in a complementary
13 fashion to really demonstrate the evidence of
14 clinical benefit.

15 For example, if we need clinician judgment
16 to make an assessment, we would use a clinician-
17 reported outcome, or in the case of young children
18 or those who may have cognitive impairment and we'd
19 like to get a measure of how they're functioning in
20 their daily lives, we may need a caregiver
21 assessment called an observer-reported outcome
22 assessment. Oftentimes, we'd also like to observe

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1 patients performing specific tasks in a
2 standardized setting, and in this case, we would
3 use a performance outcome.

4 Now, of course the focus of this session is
5 on patient-reported outcomes, but we should not
6 forget our youngest patients who may not be able to
7 provide self-report.

8 How do we review clinical outcome
9 assessments? Essentially, we ask the question,
10 does the instrument measure the outcome of
11 interest? Our regulatory standard is, is the
12 instrument well defined and reliable? Is it
13 appropriate for the target population, for the
14 target indication, and does it have adequate
15 measurement properties? I'll get into that in a
16 little more detail.

17 The 2009 FDA PRO guidance defines good
18 measurement principles to consider when we use
19 these tools to provide evidence of clinical
20 benefit, but importantly, all clinical outcome
21 assessments can benefit from these good measurement
22 principles, so they don't really differ

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1 fundamentally.

2 Important to remember is that this guidance
3 provides an optimal approach, but other approaches
4 may also be considered and used depending on the
5 situation, and we always need to exercise
6 regulatory flexibility and judgment to meet the
7 practical demands of medical product development.

8 Now I'll go through some of the key
9 characteristics that we evaluate when we're looking
10 for adequate and well-controlled assessments.
11 First is content validity, and this is really
12 critical from a regulatory perspective because it's
13 important for labeling claims.

14 Our labeling claims must be accurate. They
15 must not be false or misleading, so content
16 validity is critical because it really tells us are
17 we measuring what we set out to measure; are we
18 measuring the concept that we think we're
19 measuring.

20 This measurement property is supported by
21 qualitative and quantitative evidence, so very
22 often, we'll do qualitative research with patients

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1 in the target population to document this
2 measurement property.

3 Other measurement properties are largely
4 quantitative in nature, and importantly, these
5 can't be really interpreted unless you first have
6 evidence of content validity. Measurement
7 properties such as reliability or how reproducible
8 the measure is, construct validity, which
9 essentially is the measure associated with other
10 variables as we would expect, an ability to detect
11 change, these are all critically important, of
12 course, but they tell us really how well we are
13 measuring. They don't necessarily tell us exactly
14 what we're measuring unless we have that content
15 validity piece first.

16 Now, I'd like to just highlight some common
17 issues that we encounter when we're reviewing
18 clinical outcome assessments for their use in drug
19 development. First, we ask ourselves, is there
20 input from the relevant stakeholders, and if not,
21 we may be omitting what is most important and
22 relevant to those patients. We may include

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1 irrelevant questions in our measures; the
2 instructions, questions, and response options may
3 not be well understood.
4 We next consider is the instrument
5 appropriate for the study design, the population,
6 or the research question. If we don't have this
7 piece, the measure may be poorly matched to the
8 severity of the patients, so that may hinder
9 ability to detect change.
10 It may not be a reliable, valid, or
11 responsive to change, and it may capture something
12 that's important to patients, but not really what
13 the drug is targeting or what's expected to change
14 in a clinical trial with a therapeutic
15 intervention. We also ask is the instrument's
16 concept clear and well-defined, and this is of
17 course important for labeling considerations.
18 I just wanted to highlight this meeting.
19 It was a public meeting, part of the 21st Century
20 Cures patient-focused drug development meetings,
21 and it occurred not only with hemophilia A but also
22 other heritable bleeding disorders in 2014. You

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1 can find online a Voice of the Patient report,
2 which faithfully summarizes the input that we
3 received from that meeting.
4 I've shown on this slide some of the very
5 important concerns that patients experience, of
6 course including unpredictable bleeding; joint soft
7 tissues, muscles, and brain; limited mobility due
8 to joint pain and deterioration; and the
9 participation in social and work life are extremely
10 important. All the psychological issues of course
11 are critical.
12 This slide I won't go into detail, but all
13 three medical product centers here at FDA have a
14 multitude of ways that we can engage with our
15 stakeholders, not only in the context of a drug
16 development program, but also we have meetings, and
17 there's also a qualification pathway where we can
18 provide advice on the development of tools for drug
19 development.
20 I just have some closing thoughts, and that
21 is a clinical outcome assessment development and
22 implementation, it's not an easy endeavor, and it's

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1 really a multi-stakeholder, multi-disciplinary
2 endeavor. We have pathways for review and advice,
3 and we're very importantly open to multiple
4 approaches to instrument development or
5 modification. Very often, we need to consider how
6 do we leverage existing measures, or if we don't
7 have appropriate existing measures, we may consider
8 modification or development of new measures.
9 With that, I thank you for your attention.
10 (Applause.)
11 DR. MENAPACE: Thank you, Elektra.
12 It is my pleasure now to introduce
13 Dr. Christine Kempton, who is an associate
14 professor in the Department of Hematology and
15 Medical Oncology at Emory University School of
16 Medicine, where she is the director of the
17 Hemophilia Center of Georgia Center for Bleeding
18 and Clotting Disorders of Emory.
19 She also serves as the regional medical
20 director for the southeastern region of the
21 Hemophilia Treatment Center Network, and her clinic
22 and research focus is on hemophilia and its

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1 complications.
2 Dr. Kempton is going to speak about
3 specific patient-reported outcome instruments and
4 tools that have been utilized in hemophilia studies
5 as well as recent clinical trials. Thank you.
6 Presentation - Christina Kempton
7 DR. KEMPTON: Thank you. I appreciate the
8 invitation to be here today and to speak with you,
9 and here are my disclosures as well. Before I get
10 started into the specific instruments, I want to
11 talk just briefly about why we might care about
12 PROs with maybe a little bit of my editorialization
13 that brings together some of the discussion here
14 today and adding into the overview of selecting
15 PROs for clinical trials.
16 Then I'm going to dive into the SF-36 and
17 Haem-A-QoL tools that have been used recently, and
18 I'll talk about them in more detail, with some
19 comment of using these two tools as well in
20 clinical practice.
21 Just looking at kind of why we might think
22 about using PROs, this is where I think about

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1 hemophilia and what we're doing in the context of
2 Maslow's hierarchy of needs and that there are some
3 parallels with how we're talking about hemophilia.
4 We long ago have gotten done with treating
5 major bleeds and then more recently done a pretty
6 good job at preventing bleeds. Now, we're talking
7 more about how to impact disability, moving up in
8 this hierarchy, how we're preventing disability by
9 things that maybe we can't see exactly in our
10 subclinical bleeding.
11 But I would also submit there is an even
12 higher level to that, even when we get the function
13 down, that contributes to that anxiety and
14 depression, and that's where we meet these
15 patient-reported outcomes and quality-of-life
16 measures to really understand the full impact to
17 the patient. And even when we've got good levels
18 that are preventing disability, if we're not curing
19 the disease in its entirety, we will still have
20 impact of the disease.
21 So PROs in clinical trials can be used for
22 a variety of endpoints. They can inform clinical

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1 decision making. Clearly, they can be part of
2 pharmaceutical labeling claims, which is what I'll
3 focus on some here today, and could impact product
4 reimbursement and influence healthcare policy.
5 To support these activities, we need to use
6 the appropriate PRO instruments, and ideally these
7 PRO instruments are supported by a conceptual
8 framework. The conceptual framework helps to
9 illustrate how concepts and instrument domains
10 really hang together, and this really supports the
11 face validity. This should make sense to a content
12 expert how all these domains interact with each
13 other.
14 As already mentioned, it's important for
15 the instruments to be validated to be reliable,
16 meaning they have retest reliability. There's
17 internal consistency questions within a domain and
18 looking at the same construct. Both content and
19 construct validity is measuring what we want it to
20 measure and it also fits in with other tools that
21 we already know. If another tool is measuring the
22 same quality of life, they should be going

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1 together. If they're measuring something that's
2 totally there that should be different, we should
3 be seeing them divergent, and that's divergent
4 validity.
5 It's also nice that they're able to detect
6 change. If we can't detect change as we make
7 changes in medical treatment, they're not going to
8 be all that useful in our clinical trials.
9 Ideally, they'll have limited respondent and
10 administrator burden, which is another important
11 component, not just in clinical trials, where we
12 accept a lot more respondent and administrator
13 burden, but as we move into clinical practice as
14 well, that's more key.
15 Ideally, they're able to impact clinical
16 care. I think we're missing opportunity if we're
17 using PROs in clinical trials that can never
18 translate into clinical care.
19 So PROs can be generic versus disease
20 specific, and there are some advantages and
21 disadvantages to each of these. With generic PROs,
22 the advantage is maybe that they capture more

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1 common health-related, quality-of-life domains and
2 really allow comparisons to a normative population;
3 how close are we getting to a normal quality of
4 life? Disadvantages are that they might not be
5 sensitive to changes over time.
6 With disease-specific quality-of-life
7 measures, they may be more sensitive to specific
8 symptoms experienced by patients. However, they
9 may miss domains affecting the patient, but
10 unrelated to the disease under study.
11 Before I move into specific measures of
12 health-related quality of life, I thought it
13 worthwhile just to touch on the conceptual
14 framework and illustrate it here, the conceptual
15 framework for health-related quality of life.
16 In this framework, we see that there is a
17 cascade of impact of biological function, impact
18 systems, impact functional status, general health
19 perception, and then overall quality of life. All
20 of these domains are then impacted by
21 characteristics of both the individual and the
22 environment. This is what our health-related

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1 quality-of-life tools are trying to understand, how
2 these work together and impact the overall quality
3 of life.
4 I'll transition to more specifics on the
5 SF-36. It was a product of the medical outcomes
6 study that was conducted in the 1980s and was a
7 4-year study examining specific influences on
8 outcomes of care. There are originally 149 items.
9 They ultimately then reduce down to a short survey,
10 tried to include just 20 items, but there were
11 significant floor effects.
12 In conjunction with the RAND Corporation,
13 the SF-36 was then published in 1992 and has gone
14 through several different versions. In use, you'll
15 see version 1 and version 2 as well.
16 It's considered a general measure, and it
17 has 8 health concepts: physical functioning,
18 bodily pain, role limitations due to physical
19 health problems, role limitations due to personal
20 or emotional problems, emotional well-being social
21 functioning, energy fatigue, and general health
22 perceptions. It has asked patients to evaluate the

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1 specific questions over the past 4 weeks.
2 It scored on a scale of 0 to 100 for each
3 of the domains, 8 domains and 3 summary scores.
4 The higher the score, the better the health.
5 Scoring does require recoding and averaging in a
6 specific domain, so it's not something that you can
7 just add up as you're just looking at the
8 responses. As I stated, there are 8 domain scores
9 and 3 summary scores, a physical component score, a
10 mental component score, and an overall health
11 score.
12 It's been well-validated and translated in
13 over 50 languages, and again, it's validated in
14 numerous disease states. However, it's only
15 recently been actually validated in hemophilia
16 specifically in the PFIX [ph] study.
17 This demonstrated good internal
18 consistency. You want to see a Cronbach's alpha of
19 greater than 0.7 to demonstrate good consistency.
20 It has good test/retest reliability. It
21 demonstrated known group validity as well as
22 content validity with correlations greater than

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1 0.6.
2 It has been used as part of labeling in the
3 Advate clinical trials. It's definitely used in
4 lots of other clinical trials in studies as well,
5 but I'm just going to focus on what's been used in
6 the product labeling here.
7 We can see that with Advate prophylaxis,
8 there was improvement in bodily pain domain and the
9 physical component score in patients receiving
10 prophylaxis compared with those on-demand therapy.
11 And this is what we would expect to see as we're
12 reducing joint bleeding and improving our
13 short-term functioning.
14 I think it's relevant, and what is part of
15 the benefit of this quality of life is that you
16 might be able to then evaluate maybe some balance
17 measures as we're getting more and more aggressive,
18 particularly with prophylaxis, and the demands of
19 the care may be more complicated or there are some
20 other downstream effects.
21 Although this wasn't clinically relevant, I
22 do think it's just notable that the mental

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1 component score has a point estimate that was in
2 the negative direction; again not clinically
3 significant, but this is maybe a way that one can
4 look at balancing or are therapies actually having
5 some downstream negative effects that maybe we
6 didn't quite understand.
7 Typically, quality of life is a secondary
8 outcome in clinical trials. This is an interesting
9 meta-analysis that looked at the concordance of the
10 primary outcome with changes in health-related
11 quality of life as measured by the SF-36.
12 We can see here there were 21 studies that
13 had a primary outcome that was significant with the
14 SF-36 that was significant. So that was a
15 concordance of about 65 percent, whereas 25 percent
16 had a non-significant SF-36 in the face of a
17 significant primary outcome. So they don't always
18 jive together, which I think is probably, then, one
19 of the challenges of interpreting the results and
20 what it means and challenges for you guys at the
21 FDA.
22 So of the 33 studies that had

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1 non-significant results as well, about 69 percent
2 of them also had a non-significant result in the
3 SF-36. So about two-thirds or so are concordant
4 with the primary outcome.
5 Shifting gears to the Haem-A-QoL A, which
6 is a disease-specific measure, it was developed in
7 2004 in adults with hemophilia, and there is a
8 corresponding questionnaire in children as the
9 Haem-A-QoL. The measure was developed using
10 qualitative interviews of patients and physicians,
11 and the initial draft contained 159 items. Pilot
12 testing took place in 10 Italian hemophilia
13 treatment centers.
14 The current measure has 46 questions in
15 10 domains, including physical health; feeling; a
16 view of yourself; sports and leisure; work and
17 school; dealing with hemophilia; and treatment, and
18 it asks the participants to evaluate these areas
19 over the past weeks.
20 Raw scores are transformed to a score also
21 of 0 to 100, though lower scores indicate better
22 health. This is in contrast to the SF-36, where

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1 higher scores indicate better health and quality of
2 life.
3 So the Haem-A-QoL, again, it's been used in
4 more than two clinical trials, but they reported it
5 in some of the labeling with Eloctate, and then
6 more recently with the emicizumab. These two
7 clinical trials were what were used to document the
8 internal consistency, this is from the A-LONG and
9 B-LONG study. The Cronbach's alpha was greater
10 than 0.7 in 8 of the 10 domains. The two where
11 there was less internal consistency was dealing
12 with hemophilia and treatment.
13 In terms of validity, known-group validity
14 was good except for family planning and dealing
15 with hemophilia domains, and then convergent
16 validities showed strong correlations with the
17 EQ-5D-5 level, and the total scores physical health
18 and feelings domains of the Haemo-QoL-A. There
19 were moderate correlations with the HJHS with 5
20 domains and the total score.
21 The Haemo-QoL-A has also been used in the
22 emicizumab clinical trial that supported its label.

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1 We've been talking a lot about emicizumab today.
2 This is the baseline information for groups A, B,
3 and C, and I'll highlight here the physical health
4 domain and the sports and leisure, which were the
5 highest domains in these groups. And, again, a
6 higher score is worse report for the patient.
7 The next two that were poor were the view
8 of yourself and future, the next lowest scores.
9 View of yourself have questions like, "I envied
10 healthy people my age," with a report of a
11 frequency, or "I felt comfortable with my body."
12 Those were the types of questions that might be in
13 view of yourself.
14 This was recently published as a HAVEN 1
15 study, that the total score showed clinically
16 meaningful differences, which means there was a
17 7-point reduction in the total score. We saw that
18 started at about 5 weeks and continued out to
19 25 weeks with the top dashed line being those on
20 on-demand therapy. So we see clinically meaningful
21 reductions or improvements in health-related
22 quality of life as evidenced by reductions in the

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1 Haem-A-QoL score.
2 This was also matched with a physical
3 health score, where we see a 10-point reduction
4 that's considered clinically meaningful reduction;
5 and again, the same time frame. They were reached
6 by about 5 weeks and persisted through the study.
7 The physical health score was what made it
8 into the product label with the adjusted mean
9 reduction of 32.6 points, or mean of 32.6 compared
10 to no prophylaxis, which was 54.2. It's important,
11 again, as I said, that the health-related
12 quality-of-life measures can help us ensure that
13 gains in physical domains are not offset by losses
14 in other domains.
15 So although physical health was in the
16 product label, I think it's always worth taking a
17 look at the other domains. As we saw in the Advate
18 label, the mental health component didn't really
19 improve all that much, whereas we can see, at least
20 with this Haem-A-QoL, with emicizumab, the view of
21 yourself did improve, though clinically meaningful
22 differences for these domains haven't been

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1 established, and also the future also did improve
2 as a domain.
3 There are also significant improvements in
4 feelings in work and school, though again,
5 clinically meaningful differences are not known.
6 So just touching on PROs in clinical
7 practice, which Chris Guelcher will also talk on
8 further, when considering them in clinical
9 practice, to me, I like the idea of a value
10 compass. With this compass, we take a balanced
11 approach and consider not only clinical outcomes
12 that are the hard ones and easy to measure, but
13 also the functional health status, as well as
14 satisfaction and total cost. PROs are really best
15 suited to measure the satisfaction and the
16 functional health status.
17 In clinical practice, we can use them for
18 screening, monitoring, promoting patient-centered
19 care, supporting discussions about patient
20 priorities, promoting self-efficacy and adherence,
21 and also supporting multi-disciplinary team
22 communication and evaluating our quality of care.

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1 Now, turning specifically to the ones that
2 I've discussed today, the SF-36 and the Haem-A-QoL,
3 some have been used. The SF-36 has been used
4 pretty extensively in the orthopedic populations, a
5 lot by payers and accountable care organizations,
6 so these are really still looking at a population
7 level rather than an individual level.
8 Instituting these into clinical practice,
9 given the complexities with scoring, needing to
10 transform, reorganize, et cetera, really requires
11 informatics to support that on a real-time basis,
12 as well as clinically meaningful differences need
13 to be established in the hemophilia population to
14 really know what these mean.
15 With the Haem-A-QoL, I couldn't find any
16 reports of use in routine practice, and Chris may
17 have some differences for us. It's a pretty
18 burdensome questionnaire. You have to read very
19 carefully each of the questions. It's kind of hard
20 to scan through. The scoring requires
21 transformation and, again, preventing use in kind
22 of a paper format and requiring some level of

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1 informatics. The lack of meaningful change cutoff
2 outside of the total score and physical score limit
3 its use.
4 In conclusion, as our treatments get
5 better, we can expect more, not just functional
6 improvements, but also improvements in our
7 health-related quality of life and our psychosocial
8 status. It's important to have these measures to
9 assess these therapies and ongoing clinical trials.
10 As their use and importance in clinical
11 trials and labeling increase, it's important that
12 we move beyond really the ABR. Their use in
13 clinical care will require improvements in
14 informatics, identification of meaningful changes,
15 and instruments with minimal response burden.
16 Thank you.
17 (Applause.)
18 DR. MENAPACE: We'll now be transitioning
19 to the patient speaker part of our session. And
20 just to provide a little bit of background about
21 what we asked our speakers to discuss today, we
22 provided them the specific instruments that

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1 Dr. Kempton just introduced, the Haem-A-QoL, which
2 is a hemophilia measure as well as the more general
3 SF-36 form.
4 So all patient speakers and advocates were
5 given these surveys to review and look at the
6 content and also provide their interpretation of
7 the meaningfulness of these surveys as patients
8 themselves.
9 We have four patient advocate speakers
10 joining us today. Their biographies are listed in
11 their packets. I'd like to introduce all four
12 right now, including Mr. George Stone, Ms. Miriam
13 Goldstein, Mr. Christopher Templin, and Mr. Shelby
14 Smoak.
15 I believe Mr. George Stone has volunteered
16 to provide his first talk. Please come to the
17 podium. Thank you.
18 Presentation - George Stone
19 MR. STONE: Well, good morning. It's great
20 to be with you guys today. This is an exciting
21 time for those of you who are in the hematology
22 world as doctors and nurses and in the lab work and

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1 development. And it's a very exciting time for
2 those of us who are patients, particularly in the
3 developed world; maybe in the undeveloped world not
4 so much.

5 Briefly, I'm a 65-year-old severe
6 hemophilia A patient. I've gone through all the
7 things that you would normally expect someone in my
8 situation and age to go through. I'm the proud
9 owner of 5 artificial joints. It was fun going
10 through surgery to get here this morning. I was
11 beginning to wonder, is this going to happen today
12 or not.

13 The reason I'm going to kick this off is
14 we've talked quite a bit about emicizumab or
15 Hemlibra this morning, and I was a HAVEN 3 study
16 patient, between March of 2017 and October of this
17 year, so about 18 months. First of all, I'm very
18 pleased to tell you, zero bleeds, so that's most
19 important.

20 Now, with respect to these surveys, I
21 regret to inform you that my view of these surveys
22 is a little bit different. I had to complete these

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1 surveys as part of the Hemlibra HAVEN 3 study. At
2 first, I think it was monthly; then it was
3 quarterly. I had seen these surveys before in
4 hemophilia clinic. They aren't new.

5 I have to tell you, I realize these are
6 translated from Italian, but when you see awkward
7 language like, "Shelby, how are your swellings
8 today?" Come on. Right away, as a patient, I go,
9 "They can't be serious. Who designed this? Do
10 they know anything about what they're asking? No
11 hemophilia patient talks like that."

12 So that begins some skeptical view of the
13 whole thing, frankly. So I think my number one
14 observation is these need to be tweaked for the
15 United States. They need to be put in proper
16 English in America. Think about that.

17 Then the relevancy of these questions;
18 well, to get on to the HAVEN 3 study, I had to be
19 on prophylaxis 3 times a week with Advate for a year.
20 If you're trying to measure the difference that
21 emicizumab is making today, you need to know my
22 baseline. Am I coming in as a patient that's been

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1 on prophylaxis, or am I coming into the study as a
2 patient that's been treated on demand?

3 You need to know a little bit more of my
4 overall physical condition. I think it would be
5 helpful to know, have some background for these
6 questions that, in my case, I may not have a lot of
7 pain in my joints because, well, many of them have
8 been replaced.

9 A lot of this information that I would
10 think you would want to know isn't captured. And I
11 don't know whether it's captured by my hematology
12 team and provided to the surveyors or not. There
13 are many times when I'm trying to fill out the
14 questions, I go, "You know, I'd like to add an
15 explanation here," but I can't. You're limited to
16 answering the questions that are put before you.

17 I just don't know that any of these
18 questions are all that relevant when it comes to a
19 patient outcome with respect to Hemlibra, in my
20 case in particular.

21 What are the outcomes that I would think
22 would be important? Well, for one, ease of

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1 administration, is probably number one on the list.
2 I did get some additional questions from Genentech
3 during this study, and they were asking questions
4 about are you satisfied with this treatment, are
5 you okay with subQ?

6 One of the questions, which they didn't
7 even really have to ask, was would you rather stay
8 on Hemlibra or go back to factor? Really? I think
9 maybe 5 percent actually said they wanted to go
10 back to factor. I never quite understand that.

11 So I'm very good at one thing; maybe two
12 things. One of them is internet research. And I
13 found this little thing on the website,
14 "Genentech's Hemlibra, clinical outcome assessment,
15 data only partially swayed U.S. FDA.

16 "Hemophilia A drugs' labeling reflects data
17 on physical function improvement because FDA deemed
18 that portion of the Haem-A-QoL instrument fit for
19 purpose, while other questions were viewed as
20 insensitive to change or irrelevant. Review
21 documents suggest agency was unimpressed with
22 results from the health status instrument

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1 frequently used in economic analysis."
2 What I found on the Web was, especially for
3 the Haem-A-QoL, many countries are using it, more
4 to probably convince their governments that it's
5 worthwhile to help pick up the tab for factor for
6 their hemophilia population rather than much else.
7 So in sum, I think it's probably a good
8 idea that we revisit this issue, and I would say
9 that I believe that the national hemophilia
10 organizations, with a little prodding, probably
11 would be willing to sit down with the FDA and
12 industry, and maybe get a few hemophilia individual
13 patients as well, and see if we can come up with
14 something that's a little more direct, a little
15 more pinpointed, and probably a little more
16 accurate for what you all really need to know.
17 With that, thank you.
18 (Applause.)
19 Presentation - Christopher Templin
20 MR. TEMPLIN: Good morning, everybody.
21 Bear with me as I read off of my paper so I don't
22 go off the reservation.

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1 First of all, I'd like to thank FDA for
2 giving me the opportunity to speak today about my
3 thoughts and opinions on these patient-reported
4 outcome surveys. It's important that the patient
5 has a voice, so I'm pretty honored to be here.
6 come with sort of a different view, I think, being
7 old school, living with the way treatment was back
8 in the day. It's pretty amazing what it is today.
9 We sort of went from the stone age, where
10 treatment was I spent days, weeks, months in the
11 hospital. I remember spending a whole year there
12 once as a kid, and that was quite the year, to now
13 having product at home available at a moment's
14 notice and being able to pretty much infuse and get
15 rid of all the waste stuff in 15 minutes, and your
16 day really isn't impacted if I have the ability to
17 pay for it, which that's not a topic for today's
18 discussion.
19 But any day I wake up in a bed, not in a
20 hospital or prison, must mean that my clotting
21 factor is keeping me from bleeding, and my health
22 insurance company has done their job to keep me

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1 with medication because the Department of
2 Corrections takes good care of their prisoners.
3 I often get curious to the actual true
4 value and usefulness of survey-based data due to
5 the ability of a person to embellish or dramatize
6 how their hemophilia or bleeding disorder and/or
7 their medication impacts their daily life on a
8 minute-to-minute or day-to-day basis.
9 I believe that our needs to always group
10 people into a box is sometimes a disadvantage
11 because I don't think it tells the true story, sort
12 of as I know a lot of folks that have mild
13 hemophilia, and they're always told about how hard
14 it is to get prophylaxis, or how hard it is to get a new
15 script, or they can't really tell their doctors the
16 truth because they won't get factor. But somebody
17 with severe hemophilia, they seem to have the truck
18 delivering the product to their house every week if
19 they need it.
20 I actually know severes who bleed like
21 milds and milds that bleed like severes, so just
22 going by the factor level is sometimes a detriment.

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1 The goal should really be not to bleed. Whatever
2 factor level it takes for an individual is that
3 individual's factor level need. We're all
4 different. I have a brother; him and I, completely
5 opposites. We don't even look alike. Imagine
6 that. He must be the milkman's kid.
7 But my biggest fear is that I'm not going
8 to have access to my clotting factor because these
9 new treatments might cause a company that currently
10 makes a product to go off the market or reduce
11 capacity. There's actually been some shortages in
12 the factor IX space. Some folks I know have had
13 some issues getting some product, and they had to
14 switch to a different product, and it's sort of
15 scary to know.
16 At least they're in this country. It seems
17 like there's a lot of factor, but the price of it
18 determines everything. So I think between products
19 and even the level of care in the future, if the
20 centers go away, doctors don't know what they're
21 doing, try to give me factor VIII instead of IX,
22 it's not going to help too much.

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1 I believe that my feelings of pain,
2 physical ability, anger, discomfort, all the nice
3 stuff, changes on a daily basis, but is even made
4 worse when you have to worry about is my doctor
5 going to be there next week. The doctor I go to,
6 she's pretty old, and I know she's getting ready to
7 hand the center off to somebody else. Hopefully,
8 those folks are committed to that facility because
9 I don't want to have to travel further to get the
10 level of care that I get.

11 One of the big problems that I see is
12 people seem to inject factor, and they think that
13 it's some superpower agent, and it turns them into
14 the \$6 billion man or \$6 billion woman, because
15 women do bleed, too. I have a daughter with
16 hemophilia B. It's pretty crazy.

17 But I'm concerned that the level of benefit
18 from these agents isn't able to be determined by
19 checking a box because, like George said, maybe I
20 want to explain, but there's no place to explain,
21 or I think a little bit into the question. One was
22 can you walk like a mile. And I was like, "I can

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1 walk a mile if I maybe take a break like halfway
2 through or take a little time."

3 I walk my daughter to the bus stop every
4 morning, and it's funny, everybody else drives
5 their car, and it's like a half a mile walk. But
6 it's nice to get out in the morning, and get your
7 gloves on, get your hat on, put your scarf on.
8 While everybody else is driving, I get my exercise.

9 I get concerned that maybe we're moving a
10 little bit too fast. We're trying to put everybody
11 into the box. We're trying to really just make it
12 bigger, better, stronger, faster, but we really
13 need to think about the future a little bit more
14 and just put the brakes on a little bit.

15 We have product. We don't want to
16 substitute one expensive drug for another expensive
17 drug, and here again, I'm talking about cost. I
18 don't infuse. My daughter doesn't infuse this
19 product because we just want to stick needles in
20 our arms and cost the insurance companies money,
21 bother the doctors with writing scripts, and all
22 that stuff. We take it because it's a truly

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1 life-saving drug.

2 I think we all need to remember that factor
3 needs to be looked at as a life-saving,
4 life-sustaining, keep Chris out of the hospital,
5 out of the morgue, keep him at work so he can cause
6 trouble there. But it's not a lifestyle drug, and
7 I don't know of anybody with hemophilia that's
8 taking this stuff because they want to take it. I
9 mean, there may be, but that's few and far between.

10 So we just have to make sure that whatever
11 surveys are used is something that is really being
12 beneficial because I get a lot of surveys, and I
13 get a lot of questions. And sometimes you're in a
14 hurry, and you just check, yep, yep, everything's
15 great. You go to a meeting. You get the survey.
16 Everything's great. Here's your survey. See you
17 later. Got to go. You want the people to take the
18 time to put in the effort to do it, so you get the
19 best bang for your buck.

20 I actually think a conversation-based
21 method is better. When I go to the treatment
22 center and talk to the social worker, or the

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1 psychologist, or psychiatrist, they can actually
2 tell if you're sort of BS-ing a little bit. The
3 doctor might come in, "Yep, everything's great,"
4 bing-bang-boom, because it's 2 hours, 3 hours, and
5 I'd rather go somewhere else.

6 You can learn more by having a conversation
7 instead of just checking a box, especially as some
8 of the questions are sort of hokey, like how are
9 your swellings and stuff like that. So thank you
10 for your time.

11 (Applause.)

12 Presentation - Miriam Goldstein

13 MS. GOLDSTEIN: Thank you. My name is
14 Miriam Goldstein. My own disclosure is that I work
15 at the Hemophilia Federation of America, but I'm
16 here today in my personal capacity, and my views do
17 not necessarily reflect the views of HFA.

18 I should also note that my personal
19 experience with instruments like the ones that
20 Dr. Menapace circulated for us to review is as a
21 caregiver for now adult sons who are filling these
22 surveys out on their own. So I speak from a

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1 vantage point of a caregiver and a member of the
2 larger hemophilia community.
3 It was very interesting to get the history
4 of these tools because looking at them again in
5 preparation for the session, they are clearly very,
6 very dazed [ph]. They really seem to reflect a
7 period before prophylaxis was commonly used in
8 adults, and that seemed like a fundamental
9 shortcoming.
10 They also are not inclusive, so one obvious
11 area of omission is they omit questions that would
12 be relevant to women with bleeding disorders. They
13 take a one-size-fits-all approach to a community
14 that is highly diverse, so baseline differences
15 about age of patients, the stage of life, their
16 childhood experiences all seem to be omitted from
17 the survey.
18 Whether the clinician brings that in, in
19 their own review of the instrument, is obviously a
20 completely different issue. So personal goals and
21 life experiences, also a high degree of diversity.
22 And finally, the Haem-A-QoL was heteronormative, so

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1 kind of shocking to come across questions about
2 personal relationships and sexuality written in
3 that way.
4 So even when these tools are applied to a
5 very specific or limited demographic, it seemed to
6 me, as a potential respondent, that it was very
7 hard to tell what they were getting at. Are they
8 trying to get at the overall quality of life of the
9 respondent or to how someone is faring on a
10 particular therapy, and that confusion sort of
11 colored my reading of the entire survey.
12 In view of the complexity of hemophilia and
13 the diversity of the population, I would agree with
14 Chris and George that multiple-choice, check-the-
15 box questions really don't capture the patient
16 experience very well and that there's need for more
17 elaboration. I realize that's intention with
18 Dr. Kempton's remarks on how these have to be easy
19 for providers to administer, but some kind of
20 accommodation between those goals seems important.
21 I think George mentioned that patient
22 groups might be able to come up with more nuanced

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1 survey questions, and I will say from my work
2 experience, I know that HFA has experience in
3 working with patients to come up with
4 patient-centered as well as patient-reported
5 questions through CHOICE and CHOICE 2.0.
6 Finally, I'll just close by saying that
7 while I recognize that the survey instruments are
8 trying to capture a particular point in time, as a
9 patient or a caregiver, the longer view is also
10 really, really important to me; so some kind of
11 longitudinal or follow-up is really important in
12 terms of likely success, life outcomes on any
13 therapy.
14 Again, I am familiar because of my
15 employment with HFA's own patient portal, which
16 does provide a tool for tracking patients
17 longitudinally and even if they change providers.
18 So I think I will end there, and thank you very
19 much.
20 (Applause.)
21 Presentation - Shelby Smoak
22 DR. SMOAKE: Hey. I'm Dr. Shelby Smoake.

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1 Although I live in the world of Dante and Milton, I
2 think I understand most of this, so hopefully my
3 remarks will be adequate to your needs.
4 I am a severe hemophilia B. I'll just
5 start and say I've been in numerous clinical trials
6 my whole life. I've experienced all kinds of
7 therapies. Most recently, I was actually in a
8 hep C trial. Happily, I was able to clear the
9 virus, and that was a great, great day. I can't
10 even explain that.
11 One of the things that I think we should
12 think about -- and it was briefly mentioned, but
13 I've wondered about the venue of these reports. No
14 one has brought this up. But it seems to me you
15 might want to consider a variety of venues. And
16 I'll use myself. When I was in the hep C trial, if
17 you know anything about D.C. traffic, it's
18 horrific, and my PI in that study was only able to
19 meet at like 3:30 or 4:00. And I can remember
20 times where it was like I just needed to get on the
21 road so I could get home at a decent time, so I did
22 rush through them.

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1 On one particular occasion, even being a
2 PhD, they had "strongly agree," "strongly
3 disagree," that kind of thing, I quickly did it.
4 And they were switching them, and I didn't know
5 that. So I got a call the next day of deep concern
6 because I had answered the wrong way and I had to
7 correct that.
8 So there can be mistakes. So I've wondered
9 if trying to mix a virtual testing with what I do
10 think is important -- I do think you have to have
11 that face-to-face. I think sometimes the answers
12 are skewed when you don't have that. So that would
13 be a suggestion in that regard.
14 In terms of the therapy we have, I remember
15 growing up, having two products. So to be here and
16 to be experiencing the different available
17 therapies the way our biologics respond
18 differently, it's very valuable. It's very
19 important.
20 I'll just briefly mention the metrics that
21 are being used, we are engrained with factor level
22 studies, and I think gene therapy studies are good

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1 to use that, but I do like the movement of moving
2 to ABR. But I think this is going to fail the real
3 advantage of clinical trials because the real
4 advantage to me is you're moving away from a
5 rise-and-fall therapy, and it's really the troughs
6 that destroy us, and the vantage of a clinical or a
7 gene therapy drug is that that trough is removed.
8 So how do you capture the trough or how do
9 you capture the sustained factor level? Thinking
10 long term, how do you prove to the insurance
11 companies that you can have a normal replacement
12 factor product that is equal to a factor level at
13 certain points in the spectrum, but the other one's
14 going up and down, and gene therapy is not?
15 We have to figure out a way to make that
16 kind of data capture because that's going to be the
17 essence of selling this when it goes to market, and
18 it's the real advantage.
19 I also can tell -- we know our bodies very
20 well, and there's a certain point when you're in
21 that trough, I feel like a rusty machine. I know
22 that something's going on. I do like the idea of

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1 Dr. Manco-Johnson maybe doing the MRI, something
2 that's tangible, but there does need to be that
3 capture.
4 In terms of the QoL, I can't emphasize
5 enough the relationship between hemophilia and
6 stress. So I think there needs to be questions
7 that bring in stress. You need to look at how
8 stress is maybe impacting the product, but you want
9 a drug that's going to offer coverage during
10 stress.
11 So if you want to remove it as a factor and
12 say it was stress induced, that's one thing. But I
13 know when I had an undue year of stress, I went
14 from having an average bleed rate of 2 to 3 bleeds
15 to something like 15 bleeds in that one year, one
16 of which was a prolonged bleed of almost 8 weeks
17 that sent me to total knee replacement surgery.
18 That stress incidentally enough was related
19 to insurance. I ended up with \$18,000 out of
20 pocket that year. How does that happen? Well, you
21 start the year with the \$6,000 out of pocket. You
22 change jobs, so that's another \$6,000 out of

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1 pocket. And then you find out your employer is not
2 renewing on a January to January but an October to
3 October, and so you hit another \$16,000. So I have
4 the equivalent of a car payment without the
5 advantage of a car loan, and bleeds resulted.
6 I think those are some points to make. I
7 think as far as PROs, I'll second my colleagues and
8 say these really do need to be more specific. The
9 rhetoric, the language is off, and we just need to
10 utilize more appropriate language that is perhaps
11 more specific.
12 So those are my thoughts, and I want to
13 thank everyone for being here today and especially
14 FDA for including us in this process. It's a very
15 valuable thing. Thank you.
16 (Applause.)
17 DR. MENAPACE: I'd like to thank our
18 patient speakers and patient advocates. Your
19 feedback and input regarding these patient-reported
20 outcomes is truly essential to the mission of the
21 agency and the FDA, as well as the academic
22 community. So again, we greatly thank you for your

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1 participation.

2 Moving forward, I'd like to introduce Chris
3 Guelcher. Chris is a pediatric nurse practitioner,
4 who has been a hemophilia nurse coordinator at
5 Children's National in Washington since 1997.
6 Ms. Guelcher was promoted to lead advanced practice
7 provider within the Center for Cancer and Blood
8 Disorders at Children's National in 2017.
9 Christine will be providing some clinician
10 perspectives today regarding PROs and PRO
11 instruments and how we attempt to successfully
12 incorporate them into clinical practice. Thank
13 you, Chris.

14 Presentation - Christine Guelcher

15 MS. GUELCHER: So I want to echo previous
16 speakers by thanking FDA for inviting me, and I
17 will disclose that when Lori asked me, I said, "You
18 don't really want me." I'm not an expert, but I
19 think I've come to peace with the invitation in
20 that I am sort of representative of my peers who
21 probably aren't experts with patient-reported
22 outcomes, and that's an area, a gap, that needs to

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1 be addressed, so thank you for the opportunity.

2 I also want to apologize that I don't have
3 a disclosure slide, but I have been on advisory
4 boards for Genentech and Active Pharma and Novo
5 Nordisk. None of that is relevant to today's talk.

6 Probably everybody has seen this model,
7 which is the centerpiece of our model of care, with
8 the patient being at the center and caregivers
9 providing a multidisciplinary approach to address
10 multifactorial issues in patients with bleeding
11 disorders. And we know that that has reduced
12 morbidity and mortality, and in the pediatric
13 realm, less missed days of school, and for my
14 parents, less missed days of work.

15 So with that as the background, how can we
16 continue to include the patient's voice in the care
17 that we provide? I think starting with the boots
18 on the ground and where I think I can add to the
19 discussion today is what is going on in a
20 comprehensive clinic with a multi-disciplinary
21 team.

22 If you think about adding in the patient's

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1 voice to what's already at my center a 90-minute to
2 120-minute visit, and that's only with 5 core team
3 members there -- so we have a hematologist, a nurse
4 practitioner, a nurse coordinator, a physical
5 therapist, and a social worker.

6 I originally had 5 slides because if I list
7 everything that we all do, it takes up a whole
8 slide. But I've in the interests of time pared it
9 down just to highlight some of the more time
10 intensive but important aspects of the clinic
11 visit.

12 As Dr. Manco-Johnson mentioned, we do use
13 clinical ultrasound to look at joints, and that has
14 been a great tool to add to our visits and I think
15 has really solidified what we're talking about,
16 about joint changes and following bleeds over time
17 for our patients. So that's been an excellent
18 tool.

19 Our social workers, obviously, as alluded
20 to by our patients, have an insurmountable task
21 sometimes dealing with insurance issues and add
22 that to a basic mental health assessment, the

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1 impact psychosocially of this bleeding disorder
2 diagnosis on the family unit in the community.

3 Then looking at the nursing component,
4 traditionally, we've been looking at bleed
5 assessment. And yes, that's gotten better on
6 prophylaxis, but it's not absent. So it's
7 important to be looking -- not necessarily we don't
8 think of it in the clinical setting, at least at my
9 center, as an annual bleed rate. I think that's
10 more been a clinical trial definition, but it's
11 important to try to characterize bleeding and how
12 that's changed over time, and certainly with the
13 advent of new therapies.

14 We also spent a lot of time talking about
15 infusion teaching and home infusion, and that's
16 changing a bit with the advent of some of the new
17 therapies, and we're moving to what is an easier
18 administration. But I think, as I said, walking in
19 this morning with Miriam, we're going to have a
20 generation of patients who may not be able to
21 home-infuse factor when they have bleeds.

22 So how as nurses are we incorporating that

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1 into our care? Bleeds may happen less often on
2 these non-factor therapies, but it's that
3 disadvantage, that familiarity with what is a bleed
4 and how to treat it at home.

5 Then at the end of the visit, sort of tying
6 it all up in a bow with discussing research, which
7 has expanded exponentially, talking about new
8 therapies, which is growing exponentially as well,
9 and then recommending treatments. I think, as
10 you've heard from the patients, there's not a
11 one-size-fits-all approach. And while we may think
12 as clinicians something is the latest and greatest,
13 we have to respect the perspective and opinions of
14 our patients that may evolve over time.

15 So all of that is a pretty meaty clinic
16 visit. And not to belabor the point, there's a lot
17 of actually hands-on implementation that's going
18 on. We may be spending time going over any number
19 of clinical trials. Somebody might be looking at
20 consent for the CDC surveillance registry. They
21 may be looking at an authorization for the ATHN
22 data set. They may be eligible for industry

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1 studies. There may be some investigator-initiated
2 studies. All of that takes time to explain and
3 make sure that our patients are fully aware of
4 risks and benefits.

5 From a sort of practical standpoint, we
6 offer patient choice, so we need to know from our
7 patients if their insurance allows them what
8 product they want to use and what home care they
9 want to use. Our federal partners have some
10 mandates of us, so we have the Patient Engagement
11 Survey for our patients that are over 13.

12 At our center, we use transition
13 guidelines, sort of a quiz approach that we've
14 developed in our region to gauge where they are,
15 what their understanding is of their disease state,
16 and how that changes over time. Then for women
17 with bleeding disorders, we also might be doing the
18 Bleed Assessment Tool.

19 Either during or after clinic, the
20 providers have some pretty big tasks. Maybe we're
21 entering data into our clinical manager, which is
22 our tool to track our patient visits. That could

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1 translate into the 20 core elements that are part
2 of the ATHN data set, which then translates into
3 the hemostasis and thrombosis data set, which is a
4 responsibility to a federal partner.

5 Patients that are participating in the CDC
6 study, there is a CDC surveillance form that needs
7 to be completed, and any number of ATHN, 1 to 10,
8 that patients are participating in. Then of
9 course, industry studies may be ongoing throughout
10 the year with more frequent visits.

11 So all of that takes a lot of time and
12 effort by the clinicians, so it extends beyond
13 obviously that annual or biannual clinic visit.

14 Outside of just seeing our patients in
15 clinic, it's important for us as clinicians to be
16 aware of what's going on in the literature. And in
17 the hemophilia literature, this is just a
18 smattering of papers that are out there, many of
19 which were authored by some of the clinicians that
20 are here today.

21 We have lots of discussions of the
22 landscape tools that are measuring different

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1 aspects, and uniformly, everybody has said there
2 are great tools out there. They are reliable and
3 valid, but picking the right tool to meet your
4 needs can pose a challenge. And then, of course,
5 having so many tools then makes it difficult to
6 measure from one study to the next if we're using
7 different tools.

8 To echo what one of the patient speakers
9 said, I think in the literature, the use at HTCs of
10 these tools for investigator-initiated have been
11 more to sort of demonstrate a need. The advantage
12 of a tool like Haem-QoL-A is it's translated into a
13 number of languages. In these two cases, these
14 centers were able to take their data and compare
15 it, so that is an advantage of using a tool like
16 Haem-A-QoL, but it may be challenging to
17 incorporate that into the clinical setting, which I
18 think Dr. Kempton alluded to.

19 From my perspective, having the
20 patient-reported outcomes in labels is an
21 opportunity but it's also a challenge. One of the
22 things that I spend a lot of time doing in clinic

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1 is interpreting. Historically, it's been what is
2 recovery study in a half-life? What is the area
3 under the curve and how do you explain that? Now,
4 I'm trying to explain how a level is not a factor
5 level, but it might be on par to hemostasis and
6 does that change the area under the curve?
7 So adding interpretation of patient-
8 reported outcomes is just another way to try to
9 meet a patient where it might be meaningful. So a
10 patient that goes cross-eyed when I start talking
11 about peaks and troughs, this may speak to someone.
12 So it's important that we have that as an
13 opportunity, but I think it may also be missing the
14 mark. So I don't know that we want to put too much
15 emphasis where it's not relevant. I guess we'll
16 know more as these discussions happen in clinic.
17 I can say from just my current clinical
18 use, this hasn't been the focus for most of our
19 patients. They're really intrigued about the more
20 classic reduction in bleeds currently.
21 I'll end echoing what Dr. Kempton said,
22 that I fully respect that the patient is the center

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1 of care, and I went into nursing because that's all
2 I ever wanted to do. So I feel very responsible to
3 hearing the voice of the patient, but I want to be
4 realistic that in order to administer these tools,
5 there has to be a way to present it where we're
6 going to get meaningful information.
7 If my clinic's on Monday afternoon and I'm
8 in D.C., so that same traffic. I have parents that
9 need to get out of clinic, and pick up kids from
10 school, and make dinner, so I need to be respectful
11 that in order to get meaningful results, they need
12 to have time to complete it.
13 Because there is so much going on in
14 clinic, are patients just going to check boxes, and
15 are we going to see results that are really based
16 on survey fatigue? Then the impact on the
17 resources at the treatment centers; we have a lot
18 of -- I guess it's not fully fair to say unfunded
19 mandates, but we have a lot of responsibilities to
20 our partners.
21 So entering that data and incorporating the
22 data, more importantly, into our plan of care, how

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1 do we do that? If we're seeing patients once a
2 year and they're filling out a survey, are they
3 going to see that as valuable if I can't turn
4 around and tell them how that's making a difference
5 in their care or in the care of the community?
6 Ultimately, I think Chris alluded to this,
7 patients that participate in clinical trials -- and
8 George I think gave the other perspective -- may be
9 coming at this use of clinical-reported outcomes
10 differently.
11 If you're a patient that wants to be in a
12 clinical trial and you've taken that approach, are
13 your answers the same as somebody who's not in a
14 clinical trial and coming to clinic? So I think we
15 need to be cautious about the differences in why
16 patients might be responding.
17 So with that, thank you very much for your
18 attention.
19 (Applause.)
20 DR. MENAPACE: Thank you, Chris, for
21 providing some real-world pearls of wisdom in terms
22 of how we think of patient-reported outcomes in the

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1 clinical setting, particularly for patients with
2 hemophilia.
3 Moving forward, we're going to have more of
4 a panel discussion with four of our internal
5 reviewers at the FDA. We all have different job
6 aspects in terms of how we review patient-reported
7 outcome data, but basically, we're all interacting
8 with stakeholders, whether it be pharmaceutical
9 companies or patient advocacy groups, academic
10 investigators who have questions about patient-
11 reported outcomes and how best to utilize them in
12 their own clinical studies or clinical trials.
13 I'd like to introduce two reviewers.
14 Virginia Kwitkowski is the associate director for
15 labeling in the Division of Hematology Products.
16 In this role, she advises review team members and
17 division leadership on methods for developing
18 clear, meaningful, and scientifically accurate
19 prescription drug labeling that conforms to
20 regulations, guidance, and policies issued.
21 She is also a patient-reported outcomes
22 lead for the Division of Hematology Products, and

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1 we heavily rely on her expertise in this area, and
2 she certainly has helped guide me in a number of
3 challenging situations.
4 Ms. Kwitkowski completed her master of
5 science degree at the University of Maryland
6 graduate program, with a certification as an acute
7 care nurse practitioner in oncology.
8 The second reviewer I'd like to introduce
9 is Dr. Belinda King-Kallimanis. She is a
10 psychometrician working in the Office of Hematology
11 and Oncology Products, and she provides support to
12 the three oncology divisions with respect to
13 clinical outcome assessments as well as patient-
14 reported outcomes.
15 She works on advancing science with respect
16 to understanding how current clinical outcome
17 assessment strategies in cancer clinical trials can
18 be improved. Belinda has been working the field of
19 COAs in patient-reported outcomes for the past 10
20 years across both academia and industry.
21 So I would invite Gini, as well as
22 Dr. King-Kallimanis, to come up to the podium if

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1 they would like to provide some further comments or
2 thoughts about their reviewer's perspective. Thank
3 you.
4 Presentation - Virginia Kwitkowski
5 DR. KWITKOWSKI: Thank you, Laurel.
6 I really appreciate being here, and I just
7 want to thank, again, the patient representatives
8 here. The information they provided regarding the
9 clinical outcome assessment instruments that we
10 shared with them are really meaningful and helpful.
11 I just want to start by saying that we
12 expect that these instruments are developed with
13 patient participation, and if they're not, if
14 they're initially developed with clinicians, expert
15 clinicians, they would be reviewed with patients.
16 So it's disappointing to hear that we've managed to
17 collect patients here that don't agree with the
18 items, and that's very interesting for us.
19 So I when I'm looking at an
20 instrument -- and again, I've been a clinical
21 reviewer in the past and now I focus mostly on
22 labeling and patient-reported outcomes -- we're

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1 always taking into consideration our previous
2 experience as clinicians and whether or not the
3 instruments and the items in the instruments appear
4 to be relevant to the patient's feelings and the
5 experience that they have with their disease.
6 So we're looking at content validity from a
7 very high level, but we're expecting that the
8 development of the instrument actually looked at
9 that in a very focused way, with patients, with
10 clinicians who are experts in the disease area.
11 So those are some things that we look at as
12 clinicians, is to sort out whether or not content
13 validity has been established because that's the
14 most important part of the instrument evaluation.
15 Other things that are really important, and
16 sometimes where our regulatory goals may counteract
17 what the patients want to see in an instrument,
18 would be, there are some disease symptoms that are
19 not really mobile, so you may have a permanent
20 injury that is really important to you as a patient
21 and that you would want that captured in any
22 instrument that was drafted for a patient with

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1 hemophilia.
2 However, if it isn't mobile, if it won't
3 move with treatment, it isn't important from a
4 regulatory standpoint because if you're rating it
5 on a scale of 0 to 5, and you're rating it as a 3,
6 and there's no chance of moving that, whether it be
7 the mechanism of action of the drug or whether it's
8 just a fixed deficit, we would not be able to see
9 movement in that particular item, and that would be
10 problematic, especially if it were incorporated
11 into a total score. So we have issues with those
12 as well.
13 I think that what's really important,
14 sometimes we get submissions where we have
15 instruments used to collect data, and there's
16 actually no real good evidence of what the
17 clinically meaningful change is; so when they say,
18 "Look, our patients had a 3-point change on this
19 scale of 0 to 5," and we have no data to support
20 that a 3-point change is important to patients.
21 That information can be established in
22 multiple ways, but if it's not established at all,

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1 or it's not established in an adequate way, we have
2 difficulty deciding whether we should put it in
3 labeling at all because we really don't want to put
4 non-useful information into labeling.
5 Those are my thoughts, and I'll just turn
6 it over to Dr. King-Kallimanis.
7 Presentation - Bellinda King-Kallimanis
8 DR. KING-KALLIMANIS: Thanks, Gini.
9 I think what we heard from patients a lot
10 in this session has been that the items have to be
11 relevant, and I think this goes back -- if you look
12 at the Haem-A-QoL questionnaire, you can see that
13 there is evidence that it has reasonable
14 measurement properties. But what we're hearing is
15 that the questions are not relevant and that they
16 may not map to a relevant research question.
17 So one of the things we've been pushing for
18 a lot in IND applications that are coming in today,
19 that the PRO questions being asked are actually
20 being thought out a little bit more carefully. In
21 the past, it's just been we want to investigate
22 health-related quality of life, but how and what

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1 elements of that are important and when is it
2 important to measure that.
3 So we start to develop more clear and
4 concise research questions, and we can then go and
5 look for the right instrument versus put an
6 instrument in that maybe captures a lot of the
7 concepts that are interested, but not particularly
8 well, and then try and fit a question to it after
9 the fact. It's difficult, and we often then find
10 ourselves asking questions that are not relevant.
11 So it's this balance between capturing
12 concepts that are relevant and overburdening
13 patients and having something at the end that we
14 want to have an answer to. So I think that's where
15 we're needing to move, and we've heard a lot of
16 that today.
17 I think some of it's just that we're in a
18 time period where patient-reported outcomes have
19 become very popular, and we want to be able to
20 include that information more in the label, but the
21 trials were designed 5 years ago or something like
22 this, and it wasn't such an important outcome at

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1 that time. So we're sort of in this growing pains
2 period, and I hope to see that change as we start
3 to move forward.
4 (Applause.)
5 DR. MENAPACE: Thank you.
6 I think we've reached the end of session 3,
7 and we're going to be opening up the discussion for
8 a panel discussion. We do have a couple of Slido
9 questions that we'd like to pose to the audience to
10 kind of get the conversation rolling. But anyone
11 within the panel or from the audience who has
12 questions, feel free to come up front to the
13 microphones once we're done with the question
14 aspect of this segment.
15 DR. EHRLICH: I think the first question
16 should be on your Slido on your phone, but I don't
17 think we're going to display it here, but we'll
18 display the responses when they become available.
19 The question is, prior to today's
20 presentations, describe your baseline knowledge of
21 PRO instruments and their use in hemophilia
22 clinical trials.

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1 DR. MENAPACE: Can you repeat that question
2 again? Here we go.
3 DR. EHRLICH: Are the results there?
4 They're displayed here.
5 (Audience responds.)
6 DR. EHRLICH: I think it looks like most
7 people have answered now, so I'm going to close
8 this poll. It looks like a significant number of
9 people in the audience have had at least some
10 experience and some extensive experience with PROs.
11 The next question should be coming up now.
12 This next question that should be now on your Slido
13 I think is perhaps a little bit of a loaded
14 question. But the question is, is it useful to
15 have patient-reported outcome information included
16 in the prescribing information for specific
17 hemophilia products?
18 (Audience responds.)
19 DR. EHRLICH: It looks like we have most of
20 the responses. It definitely tilted towards the
21 yes, but some nos. I think it would be interesting
22 if we could break this down by people's roles in

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1 product development, whether it's sort of patients
2 versus industry versus FDA. There might be a
3 different answer to this question.
4 Our third question is here now, so which of
5 the following patient-reported information would
6 you consider most important to include in the
7 prescribing information? There's functioning,
8 emotional health, ability to go to work or school,
9 side effects, or other.
10 (Audience responds.)
11 DR. EHRLICH: All right. I think we have
12 most responders now, physical functioning being the
13 clear winner on this one. I think our next
14 question is sort of the flip side of this. What do
15 you feel is the least important to be included in
16 the prescribing information? And "write other" is
17 a little bit of a tricky one here.
18 (Laughter.)
19 (Audience responds.)
20 DR. EHRLICH: I think we have the bulk of
21 responders now. Perhaps a surprising response
22 here, and maybe this will come up some in our panel

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1 discussion, but side effects seem to be the winner
2 here. Just one more question before we go to the
3 panel discussion.
4 How much time are you willing to devote to
5 the PRO surveys that include relevant items during
6 each study visit?
7 (Audience responds.)
8 Panel Discussion
9 DR. EHRLICH: I think we have most
10 responders now, so a pretty decent spread here. It
11 seems like 5 to 10 minutes is the winner, but a
12 decent kind of bell curve on the amount of time
13 being devoted here.
14 I think we can move to the panel
15 discussion. There's one question on Slido that we
16 can maybe start off the discussion with, and then
17 we can maybe move on to other questions. But the
18 question on Slido is does the FDA consider ABR as a
19 PRO; and if so, how does one assess the reliability
20 and validity? If not, how does it not meet the
21 criteria of a PRO?
22 I can actually start answering this

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1 question also, unless anyone else has comments. I
2 think at least in CDER, which is where my
3 experience is, this ABR as a PRO is shifting from
4 what used to be kind of a clinician-reported
5 outcome and is now shifting more towards a patient-
6 reported outcome.
7 Our most recent experience has been with
8 emicizumab, as you probably know, and in this case,
9 they were developing a new electronic tool to sort
10 of better capture bleed-related data as a
11 patient-reported outcome.
12 This is an example that as the technology
13 moves ahead, then the data that we're getting and
14 how we review that data is changing. But
15 certainly, in this trial, it was a patient-reported
16 outcome.
17 In the development of this drug, there were
18 a lot of discussions between the commercial sponsor
19 and the FDA clinical review team as well as the COA
20 team to develop this tool and make sure that it was
21 answering the question that we needed it to answer
22 to ensure that the tool was functioning as we

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1 needed it to.
2 An interesting outcome, which was also
3 presented at ASH this past weekend, was that I
4 think it was a little bit surprising that what we
5 had previously seen as a clinician-reported outcome
6 was generally treated bleeds. And now with this
7 tool, there was a much bigger report of untreated
8 or all bleeds.
9 There was an improvement in this all-bleed
10 category, but I think the rate of ABR with all
11 bleeds was a little bit surprising, and we did a
12 better job of capturing that with a
13 patient-reported outcome.
14 DR. MENAPACE: Thank you, Lori, for
15 responding to that question.
16 Just to follow up on the information you've
17 already provided, in some ways, it was almost a
18 little bit of a hybrid with electronic diaries that
19 they used most recently in the HAVEN 3 and HAVEN 4
20 studies, where patients were essentially able to
21 log and bleed-related and treatment-related data
22 for a period of, I think, approximately 7 days they

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1 logged, or every 8th day.
2 Then at each subsequent study visit, the
3 investigator or clinical nurse investigator who was
4 working with the patient had the opportunity to
5 review that data with the patient. And if there
6 was an error or an omission of a significant
7 bleed-related event, go back and amend those
8 diaries.
9 So it is interesting in the sense that
10 we're heavily relying on patients to report their
11 own bleed-related outcomes, which I think is novel
12 and an important advancement in this field. But at
13 the same time, they were still relying on
14 physicians and other providers to help them
15 translate bleed-related data and also help them if
16 they had forgotten or omitted any bleeds in their
17 electronic diaries.
18 MS. GOLDSTEIN: I just wanted to add
19 something that I didn't mention when I was up there
20 that is kind of on par with that. I think the
21 opportunity to discuss patient-reported outcomes
22 can't be understated and to get the context that

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1 Chris was talking about, not just the checking the
2 box.
3 I think something else to think about is
4 if, for instance, the advocacy groups like HFA and
5 NHF are opening up patient portals, how is that
6 information going to be communicated, if at all,
7 with clinicians?
8 I was a former board member of ATHN, and I
9 am no longer on the board, but I've always been a
10 proponent of having tools that communicate with our
11 clinic EMRs, so that if a patient is documenting
12 bleeds, that that's able to be communicated with
13 the clinicians who can then put it in the context
14 of the clinical picture and communicate with the
15 patient about how that's impacting on things like
16 missing school, and work, and their prophylaxis
17 regimen.
18 So to not have double data entry and to
19 have patient portals communicating with clinical
20 manager, to have study forms that we can
21 incorporate, I think all of that in the advent of
22 EMRs is something -- there are opportunities there

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1 that would make things much more smooth.
2 DR. MENAPACE: Great. I think we have a
3 question from the audience.
4 DR. PIPE: Steve Pipe, University of
5 Michigan. One of the themes I heard this morning
6 so far was, within the clinical trials and the need
7 to demonstrate some patient report outcome
8 measures, the sponsors are limited to the validated
9 tools that are currently in existence.
10 At least I would assume to see that those
11 PROs end up perhaps in the label, but if we have
12 some agreement that these tools aren't necessarily
13 capturing the kind of information we need,
14 particularly on the patient experience side, what's
15 the agency's position on the ability to elicit that
16 kind of patient experience in the context of a
17 clinical trial, even if a validated tool isn't
18 actually used to collect that?
19 So if we feel like we all need to get
20 better patient experience as part of these clinical
21 trials, sometimes the questions that need to be
22 asked may be fairly specific. And I think

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1 Mr. Stone gave a good example from his experience,
2 where he felt that the validated instrument tools
3 weren't really getting at what he was feeling for
4 his participation.
5 So if experiential questions are collected
6 in the context of a clinical trial, how are we
7 going to see this information brought forward at
8 the regulatory level?
9 DR. EHRLICH: I think that highlights an
10 important question that got brought up throughout
11 this panel discussion, and it's a difficult
12 question. We certainly do have pathways available
13 where sponsors can propose a new tool, a novel
14 tool, and there are pathways to validate those
15 tools. However, that can be challenging, that
16 takes time, and you can't really validate the tool
17 just within your own trial. They have to be
18 validated in a larger perspective. So it is
19 challenging.
20 I think we've presented these two surveys,
21 and we actually don't have any allegiance to these
22 two surveys other than that's what's been presented

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1 to us, that we've only been able to review the data
2 within the context of what's been presented to us.
3 I think we've highlighted here that these
4 tools perhaps have problems that are insurmountable
5 that maybe we weren't even internally fully aware
6 of throughout the review. But I think we've also
7 highlighted that what we were trying to do within
8 the context of these tools that were presented was
9 differentiating between what metrics are important
10 on a more global lifestyle or lifelong perspective
11 for patients, and what we can capture within a
12 clinical trial, and what can be modified by
13 treatment, as Gini also pointed out.
14 So for example, we included the physical
15 functioning metric because that seemed to have a
16 reasonable expectation that both represented
17 patients' outcomes that could be sort of modified
18 within the context of a 24-week trial and could be
19 modified by a drug, where things like partnership
20 and sexuality either couldn't be captured in a
21 short period of time or couldn't be modified by the
22 drug.

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1 So we were able to use those tools and
2 parse out some of what could be contextually
3 validated.
4 DR. PIPE: I would also suggest that the
5 tools that we have at our disposal right now are
6 covering a very broad range of levels of care or at
7 least how they're applied. So for instance, many
8 of these instruments can be used in countries that
9 don't even have patients on prophylaxis.
10 So to be able to use these tools and move
11 the needle, so to speak, when you introduce a
12 prophylactic therapy, et cetera, is not nearly as
13 difficult as in a context where you might have
14 access to more complete therapies. And going
15 forward, if you look at where the field's heading,
16 where you're going to get into gene therapy later,
17 what the comparison is going to be against is
18 really against optimized prophylactic therapy, and
19 the ability to move the needle on that background
20 with the tools that we have available would seem to
21 be particularly challenging.
22 So I think, now even more than ever, the

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1 patient experience and maybe drilling down into
2 elements that are not even captured properly by
3 these tools is going to be, practically, really
4 important going forward.
5 DR. EHRLICH: Yes, I agree. I think some
6 of the issues that were brought up such as ease of
7 use, obviously, is going to be important to capture
8 with the subQ administration. And then with gene
9 therapy, obviously, it's a one-time administration,
10 so maybe ease of use is not the right terminology
11 for that but also can be important.
12 I think at the FDA, we look at things a
13 little bit more globally, that we can take into
14 context both the factor level bleed rate that's
15 been captured as well as some patient-reported
16 information, whether or not it's captured with
17 these tools or other tools, to make our
18 benefit-risk analysis.
19 DR. PAPADOPOULOS: I just have something to
20 add, and that is I think patient advocacy groups
21 are well-positioned to undertake either development
22 of instruments or optimization of existing

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1 instruments that could be used across medical
2 product development, so that we would have
3 standardized measurements that have been adequately
4 tested with patients and have had that patient
5 input piece.
6 The patient advocacy groups can really help
7 foster that in a pre-competitive setting so that
8 each medical product developer doesn't have to do
9 that by themselves. And we do have a pathway for
10 that to occur, where we can provide advice on tools
11 that are being developed for unmet medical needs
12 within a qualification program. And ultimately,
13 these tools we expect to be made publicly available
14 so that they can be used in medical product
15 development broadly. So I think that's a really
16 key opportunity.
17 MS. GUELCHER: I would just caution that
18 advocacy groups are great, but they don't
19 necessarily represent all of the patients.
20 Hemophilia treatment centers see patients that may
21 not be part of those advocacy groups, and we don't
22 want to miss those voices.

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1 DR. MENAPACE: Thank you, Elektra and
2 Chris, for your comments. I believe we have one
3 more question from the audience, and we are running
4 into our break for lunch. So with this last
5 question, we'll wrap up and conclude the panel.
6 Thank you.

7 MR. SKINNER: Mark Skinner, patient with
8 hemophilia, but also someone who does extensive
9 research in the health outcomes field. I wanted to
10 pick up on Steve's comment and then the last
11 remark.

12 There was a core outcome set developed in
13 hemophilia that identified a series -- at least 3
14 of the 6 elements were specifically patient-
15 reported outcomes. We've covered ABR, but the two
16 others were pain and mental health, the
17 transformative aspect. Dr. Ragni mentioned the
18 transformative piece earlier this morning.

19 Within the pain domain, I think that the
20 group identified -- and it was the number one
21 concern of patients coming out of the patient-
22 focused drug development last year. Two-thirds of

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1 the patients reported pain as the dominant outcome.
2 It really hasn't been discussed today within the
3 context of outcomes, nor within the pluses or
4 minuses of SF-36 or Haem-A-QoL, both of which are
5 deemed to be, at least by a lot of individuals,
6 deficient and being able to differentiate between
7 chronic and acute pain.

8 So now that we have a core outcome set,
9 we're live, we're in the real world -- but that
10 outcome set was developed in the pre-competitive
11 space that was mentioned; but we're now in the real
12 world and we're needing to collect that data with
13 pain being the dominant outcome that the FDA was
14 informed about -- what are the opportunities to
15 bring in other instruments that would pick up the
16 other elements of that core outcome set, to have
17 them concluded?

18 Specifically pain, something that's more
19 sensitive in terms of its occurrence frequency,
20 differentiating how the drugs would change, and
21 then bringing in the transformative piece since we
22 now have those at least identified as core

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1 important outcomes. Thank you.

2 DR. EHRLICH: I think within the FDA, there
3 are always opportunities to have these discussions.
4 We have mechanisms where commercial sponsors as
5 well as patient advocates can just come and meet
6 with us, and we can sit down and try to figure out
7 a pathway to move these things forward. I know the
8 COA staff does a lot of the earlier work in
9 validating these tools and helping to incorporate
10 these into clinical trials, but there certainly are
11 mechanisms where we can meet and figure out a path
12 forward.

13 DR. PAPADOPOULOS: The core outcome set
14 that you referred was one that was developed in the
15 context of use of gene therapies. My understanding
16 of that is that the first stage of development was
17 really having an agreement consensus around what
18 are those concepts, what are those outcomes that
19 are important to be measured in all gene therapy
20 trials at a minimum, basically. It doesn't
21 preclude other things from also being included.
22 But at a minimum, those were the outcomes that were

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1 decided upon. And my understanding is, then, now
2 the next stage is to identify the actual
3 instruments that will be measuring those outcomes.

4 So that's just a reflection on your
5 comment. It's not complete yet. It hasn't been
6 complete yet.

7 DR. MENAPACE: Thank you, everyone, for
8 your comments. Just to echo everyone's sentiments,
9 I think the FDA and the Division of Hematology
10 Products, in general, is willing to engage with
11 patients and patient advocates, and physicians, and
12 physician investigators, as well as industry, to,
13 as we previously referenced, move the needle
14 forward in terms of patient-reported outcomes and
15 clinical trials.

16 We'd be happy to answer any questions from
17 any additional individuals over lunch or later on
18 this afternoon, but thank you, everyone, for your
19 attention, and we'll now break for lunch.

20 (Whereupon, at 12:26 p.m., a lunch recess
21 was taken.)
22

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1 AFTERNOON SESSION
2 (1:20 p.m.)
3 Session 4
4 Moderator - Mikhail Ovanesov
5 DR. OVANESOV: Good afternoon, everybody.
6 Welcome back and please be seated. Let's get
7 started.
8 My name is Mikhail Ovanesov. I work for
9 the Center for Biologics, Evaluation, and Research,
10 also known as CBER. My office is the Office of
11 Tissues and Advanced Therapies, OTAT, and my
12 particular job at the Food and Drug Administration
13 is the review of coagulation factor activity
14 assays. I will facilitate this session today, a
15 session on the use of coagulation factor
16 measurements as surrogate endpoints in clinical
17 trials.
18 Our agenda for today, just to go over it
19 really quickly, there will be two presentations.
20 The first one is on the analytical assays and
21 reference standards, and the second presentation is
22 on the clinical perspective on the assays used in

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1 clinical trials. Then there will be a panel
2 discussion. That's the second part of our session.
3 Our two presenters will be joined by three
4 panelists. And together, the five panelists will
5 represent the experts from the clinical labs in the
6 United States and the European regulatory agencies.
7 There will be no questions and answers
8 after each of the presentations. If you have a
9 question to a presenter, please write it down and
10 join us at the end of the panel discussion because
11 we want to hear from you. We want our audience to
12 participate in these questions.
13 Now that I went over the housekeeping
14 items, I can proceed to introduce our first
15 presenter today, Dr. Elaine Gray from the United
16 Kingdom. Dr. Elaine Gray is working for the
17 National Institute for Biologic Standardization and
18 Control, NIBSC, with the Ministry of Product Health
19 and Controls within the United Kingdom.
20 Elaine is an international expert in
21 biological standards. She was personally involved
22 in the development of the WHO international

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1 standards for factor activity, many of which are
2 used now for hemophilia diagnosis and treatment
3 today. Elaine came to us from across the pond, and
4 without further ado, welcome, Elaine. Thank you.
5 Presentation - Elaine Gray
6 DR. GRAY: Thank you, Mikhail, for this
7 very kind introduction and also for the invitation
8 to come here to speak. As my title indicated, I'll
9 be talking about analytical perspective on methods
10 and reference standards. This is my disclaimer.
11 Factor concentrates are biological
12 medicines, and as we all know, it's dosing
13 international units. There are a lot of advantages
14 of the international unit. As we know, one
15 international unit is typically found in 1 mL
16 normal plasma, and that's how we define the
17 international unit in the first place. This is
18 equivalent to 100 percent normal in plasma.
19 Although we lay this international unit to
20 normal plasma, the activity of normal plasma pool
21 can change, and that normal pool from different
22 labs are not the same. And even if you collect a

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1 pool of plasma from the same lab, using the same
2 donor over time, you'll find that actually would
3 not be the same.
4 How do we know that it's not the same?
5 That's because we have the international standard
6 and the international unit. By comparing the
7 different local pool to that, we find that there
8 can be some differences.
9 For the international unit, once it's
10 defined for the first standard, it is then fixed
11 for subsequent replacement preparations. It is
12 recommended that the local pools should be
13 calibrated against the international standard or
14 other reference preparation traceable to the
15 international standard. This allows the laboratory
16 to compare the level of activity.
17 It also allows us to potency label products
18 in international unit and this international unit
19 for the products that link to the plasma
20 international unit. Therefore, this allows us to
21 normal and deficient levels and helps the
22 calculation of target levels for therapy.

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1 Just to give you a quick example on how
2 useful this is, this is data from the value
3 assignment of the 2nd international standard for
4 blood coagulation factor XI in plasma. First of
5 all, this shows that this particular candidate was
6 assayed against different local pool normal plasma,
7 and you can see that overall geometric mean here
8 shown, that 0.72 units per ampoule.
9 However, if this sample's assay by these
10 3 labs, as shown by the red circle there, you get
11 about 0.65 unit per ampoule. However, the same
12 sample assays in these other 2 labs, the value they
13 have obtained were about 0.85. So you can see
14 there's quite a wide spread of activity.
15 When we assay that same sample against the
16 first international standard for factor XI, you can
17 see that we get much better agreement, and the
18 overall geometric mean, although not too different
19 to that against the local pooled normal plasma, the
20 actual GCV, the variability of the assay, came down
21 to about 2 percent as opposed to about 7 percent.
22 So this is really showing how good it is to improve

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1 the laboratory agreement when we assay against a
2 common standard.
3 So the role of the international unit is
4 that it anchors down the potency labeling. This is
5 very important in terms of ensuring the consistency
6 of production. It is labeled in international unit
7 and it's linked to dosing international unit. We
8 know that for the products that are on the market
9 right now, any of the products, in general, you can
10 give more or less the same unit per kilogram body
11 weight to raise activity by a very similar manner.
12 So for factor IX, it's usually one unit of the
13 product per kilogram body weight to raise activity
14 by 1 IU per deciliter.
15 Ideally, the same type of assay method
16 should be used for potency labeling and clinical
17 monitoring. However, this isn't always the case.
18 An example of that would be the factor VIII product
19 in Europe has been potency labeled using
20 chromogenic assay method. However, in the clinical
21 lab, they're being monitored using 1-stage clotting
22 assay.

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1 The way that we prepare this standard, of
2 course they have to be replaced from time to time.
3 And you can see the history of the factor VIII
4 concentrate standards here, which the first one was
5 established in 1970, and now we are on the 8th
6 international standard that was established in
7 2009. The characteristic of these standards tend
8 to go with the availability of a product available
9 at the time, so we went from intermediate purity to
10 high purity material.
11 At the moment, the potency labeling of
12 factor VIII and factor IX products, the
13 plasma-derived and recombinant modified products
14 are all traceable to the WHO international standard
15 in international unit.
16 We talked a lot about functional activity
17 assay today. We talked about the one-stage
18 clotting assays, which is based on APTT. I don't
19 want to go into detail about that, but we know that
20 there's a lot of different APTT reagent with
21 different phospholipid composition activators.
22 For the chromogenic assay, this is based on

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1 using purified reagent, but we also have a lot of
2 variations. For factor IX, there are two
3 commercial assay kits, which is C-marked in Europe,
4 but I understand that it's not registered in the
5 U.S. yet. There are at least 6 commercial assay
6 kits for factor VIII, plus there are a number of
7 in-house assay methods.
8 I think we need to consider these two types
9 of assays, as really within each assay type, there
10 are a number of different variations, and they can
11 be considered different assays.
12 These types of factor activity assay
13 determinations require bioassays, which are
14 actually relative potency assays. So it's not like
15 a mass balance, where you just wait out something
16 that we know what it is or it's not determined in
17 terms of microgram or milligram. We require a
18 reference standard.
19 The potency estimated for the test sample
20 is relative to reference standard and based on the
21 principle of assaying like against like.
22 In these assays, the reference standard and

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1 test sample should have a similar characteristics,
2 and the test dilution should behave as though it is
3 the dilution of the standard. For us to do that,
4 we have to minimize the matrix effect. We used a
5 concentrate standard for assay of concentrated
6 product, and for plasma standards for assays of
7 patients sampled, especially for the congenital-
8 deficient patient plasma sample.

9 The choice of the reference standard should
10 be based on how well a candidate compares with all
11 the product that it needs to cover. This is a huge
12 challenge for the primary standard, as it needs to
13 cover a product type with wide diverse
14 characteristics.

15 Even for the plasma-derived material,
16 although they're supposed to be native
17 factor VIII/factor IX molecules, the excipient also
18 will make a difference to the way that it's being
19 assayed. This is something that we have to take
20 into consideration.

21 Just to give you an example of how it can
22 work, this is a von Willebrand factor concentrate

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1 looking at collagen-binding activity. In this
2 particular set of results, this particular
3 concentrate has been assayed against the fourth
4 international standard for VWF plasma, so this is a
5 concentrate assay against a plasma standard.

6 Consider that we have two types of collagen
7 reagent, type 1 and type 3, but even within type 3,
8 collagen reagent, you can see we get a wide spread
9 of results. It can be somewhere between 8.5 to
10 about 16 or 17 units per ampoule, and the GCV came
11 out to be 40 percent.

12 When the same sample is assayed against the
13 first international standard for VWF concentrate,
14 you can see immediately that we harmonized the
15 results we get from all the collagen reagents, and
16 the GCVs came down to about 7 percent.

17 Assaying like against like, the concentrate
18 against concentrate, improved the interlaboratory
19 agreement. It's also true that when we look at the
20 actual factor VIII activity -- and here's some data
21 where we assayed a concentrate against the plasma
22 standard, you can see that the blue boxes are

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1 1-stage clotting assays and the pink and the yellow
2 boxes are neither the 2-stage clotting assays or
3 chromogenic assays.

4 It's quite clear that we have assay
5 discrepancy there. When we assayed this
6 concentrate against another concentrate standard,
7 you will find that here, as shown, the histogram
8 outcome shows that they're all coming together; we
9 have good agreement of values.

10 Even when we're looking at plasma-derived
11 material -- this candidate is a plasma-derived
12 material -- it's still important for us, in
13 accounting [indiscernible], whether you assay
14 against the plasma standard or a concentrate
15 standard. We do have different WHO international
16 standards for the measurement factor VIII and
17 indeed factor IX for plasma and concentrates.

18 Assay discrepancy is nothing new. The most
19 famous example is the B domain-deleted factor VIII,
20 and we know that their clotting and chromogenic
21 ratio is approximately 1.4 and that clotting
22 activity is higher than the chromogenic activity.

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1 Now, we're moving into the extended
2 half-life factor VIII product, and I don't need to
3 tell this audience how many we have. We have at
4 least 3 extended half-life products for factor IX
5 currently licensed. For some of these materials,
6 they offer better yield, and they're longer acting,
7 so it's better for the patients, but it creates a
8 substantial standardization challenge.

9 We're now moving also into the gene
10 therapy, and we have seen presentations on
11 factor VIII and factor IX gene therapy. So again,
12 do we expect that that's issued in terms of assay
13 discrepancy? I think we know the answers to that.

14 The regulators are very concerned over the
15 issues of assay discrepancy, and in 2013, the EMA
16 ran a workshop to discuss the categorization of new
17 clotting factor concentrates. I think that also
18 showed there are issues related to the potency
19 labeling as well as post-infusion sample
20 monitoring.

21 The professional organizations like ISTH
22 and SCC also came up with recommendations on how to

<p style="text-align: right;">Page 197</p> <p>1 deal with these new products. This is a very well- 2 cited decision tree, where it's based on 3 statistical assessment of the assay of this new 4 product against the WHO international standard for 5 concentrate. 6 The idea is if you assay your product 7 against the WHO international standard, you have to 8 decide whether it's valid or not. If it's valid, 9 you then go down one route and, if it's not, you 10 can go down another route. It is based on 11 statistical assessment. So I'd like in the next 12 couple of slides talk about how we do this. 13 The estimation activity potency; you can 14 use a single-point estimation for tests. To do 15 that, you carry out a multiple dilution for your 16 standard and create a standard curve. You test 17 your test sample at 1 dilution. You can just read 18 off the standard curve and you find out what's the 19 concentration of that test sample. 20 This is a very common practice in clinical 21 labs, although it is changing, especially in the 22 U.K. The reason why it's a problem is that</p>	<p style="text-align: right;">Page 199</p> <p>1 range, and the mean is shown as the black line 2 within the box. 3 We set out the acceptance criteria for 4 slope ratio as 0.8 to 1.25, and this is represented 5 by the two red dashed lines. This is based on 6 historical data, what we understand from these 7 types of assays that will give us good parallelism. 8 So we can see that this is a plasma-derived 9 factor VIII against plasma-derived factor VIII 10 concentrate, so this is the comparison best 11 scenario. We only found that only 3 assays gave 12 ratio outside 0.8 to 1.25 acceptance criteria. I 13 think that what is also important to note is the 14 boxes are very small, if you'd like, so that shows 15 there's hardly any variability in terms of slope 16 ratio for all these reagents. 17 When we look at the same picture for 18 extended half-life product, you can see that, 19 actually, for the majority of the reagent, the 20 means are actually still quite close to 1 for the 21 slope ratio, but the boxes are somewhat wider. And 22 with the 2 reagents here, APTT-S local and the</p>
<p style="text-align: right;">Page 198</p> <p>1 single-point estimation for potency can be 2 misleading when the dose-response relationship of 3 the standard test samples are not parallel. It can 4 see that when it's not parallel, in this particular 5 case, the slope of the standard curve is less than 6 the slope of the test curve, so this gives a slope 7 ratio of less than 1. 8 However, when the test sample perfectly 9 parallels each other, the slope ratio will be equal 10 to 1. We need to do multiple dilution of both 11 tests and standards in order to assess their 12 parallelism. 13 In an ideal situation, the ratio of slope 14 for standard and test should be 1, and I'm going to 15 illustrate this in the next couple of slides. This 16 is the results from the recent study that NIBSC 17 carried out on the extended half-life factor VIII 18 product. 19 Here I'm showing the results of the slope 20 ratio, the standard to the test ratio for 15 APTT 21 reagent and 6 different chromogenic assays. The 22 boxes illustrate the 75 percent interquartile</p>	<p style="text-align: right;">Page 200</p> <p>1 APTT-automated local, the actual boxes themselves 2 are actually outside the acceptance criteria. 3 However, out of the 350 assays for APTT 4 assays -- I think there are about 170 chromogenic 5 assays there -- we only have 8 assays that gave a 6 ratio outside the acceptance criteria. This 7 indicates and justifies that this product should be 8 potency label against a factor VIII concentrate, 9 international standard, and labeled in 10 international units because, by statistical 11 analysis assessment, the comparison against the 12 international standard is valid. 13 However, just because the assays are valid, 14 it doesn't mean that we're going to get the same 15 potency. Here is another pegylated full-length 16 factor VIII product. This is the results from an 17 NIBSC in-house study, and it's quite clear that 18 with APTT-SP and PTT, we're getting real low 19 results. I think there were about 0.4 units per 20 mL. But if you're using Actin-FS, you getting 21 14 units per mL. So this is a huge assay 22 discrepancy despite the fact that we have</p>

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1 statistically valid assays.
2 The same kinds of pictures, you can see
3 from a lot of field studies, and I think that all
4 the extended half-life products have a few studies
5 out there now. Just using Afstyla an example, you
6 can see quite clearly that, for panel A, I think
7 this is a sample at 4 percent and panel D is
8 100 percent.
9 If you're using a silicon dioxide based
10 activator APTT region, you get a lot lower results.
11 However, overall, I think that the studies have
12 shown and have come to the conclusion that,
13 overall, the results are quite consistent from the
14 chromogenic to 1-stage clotting discrepancy, where
15 overall, for all the range particularly tested,
16 they gave very similar discrepancies, about twofold
17 difference there.
18 So in the packet insert, this is
19 recommended that for this particular factor VIII,
20 it should be monitored using a chromogenic assay,
21 which reflects the accurate determination of the
22 activity of this particular product, or if you use

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1 a one-stage clotting assay, you should use a
2 conversion factor of 2, so this is quite clear.
3 However, in this same paper, which is great
4 because it will also show the chromogenic assay to
5 one-stage clotting ratio for 3 other products, for
6 these particular products, you can see that we have
7 some kinds of dilutional linearity issues with the
8 chromogenic to 1-stage ratio, where, for example,
9 with NovoEight and Eloctate there, the increase in
10 the chromogenic to a 1-stage ratio with increasing
11 activity, whereas for Adynovate, it's the other way
12 around.
13 So we do need to rethink a little bit about
14 these dilutional linearity issues, especially when
15 you're measuring peaks and troughs.
16 The same kind of story can be seen with the
17 factor IX. Here are field study results, and this
18 time, I think it's with factor IX, Fc fusion
19 protein, which shows quite clearly we have
20 overestimation or over-recovery at low level.
21 Interestingly, the same kinds of results were
22 obtained for BeneFIX, which is the recombinant

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1 product.
2 For the recombinant longer half-life
3 product, we know that, statistically speaking, they
4 give you valid results, and according to the
5 decision tree, if it's valid by both methods,
6 clotting and chromogenic, you need to look at
7 discrepancy and then agree on a single method.
8 However, what we haven't talked about is
9 that this discrepancy so far, taking 1 stage to
10 chromogenic discrepancy, but will happen when
11 there's discrepancy within the method. So we know
12 that this is an issue with APTT or 1-stage clotting
13 method.
14 The next couple of slides are actually on
15 gene therapy, which I'm not going to go through
16 because I think Steve is going to talk about those
17 in much more detail, but enough to say that we see
18 the assay discrepancy for the gene therapy
19 products.
20 So where are we now? Recombinant and
21 modified recombinant product potency label against
22 international standard, or in-house standard

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1 calibrated against the international standard,
2 using the manufacturer's own in-house assay and
3 reagent. This international unit for these product
4 anchors the relationship between the label potency,
5 dosing, and recovered activity in the patient using
6 these products.
7 For us, it is really important to keep the
8 continuity of the international unit specific to
9 each product, which after all, has been verified or
10 supported by clinical trial data.
11 I'm going to run out of time soon, so I'm
12 going to skip this one, but I would like to point
13 out that, again, in the collaborative study that
14 established a 5th international standard, factor IX
15 concentrate, we put in a recombinant factor IX
16 product, and we looked at the results against two
17 other recombinant reference preparations.
18 Here at the top line, with this particular
19 product assay against a 4th international standard,
20 there's clear clotting and chromogenic assay
21 discrepancy, where the clotting typically was 8.9
22 IU per mL but 7.1 IU per mL.

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1 But when we assay this particular product
2 against the recombinant preparation A or
3 recombinant preparation D, we minimize the clotting
4 chromogenic discrepancy. It also showed that we
5 have improved interlab agreement. It's also
6 important to note, with this particular set of
7 data, that we obtained the same estimates for this
8 particular recombinant factor IX product relative
9 to all 3 reference preparations used.

10 So if we have done de-calibration of the
11 standard correctly, it doesn't necessarily mean
12 that we will actually shift into international
13 units by using a recombinant standard. A
14 recombinant factor IX international standard would
15 have minimized assay discrepancy and provide
16 interlaboratory agreement for pooling recombinant
17 factor IX products.

18 Product specific standard can help solve
19 assay discrepancy. This is actually old data shown
20 by Mikaelsson in 2001. This is a post-infusion
21 sample measured by chromogenic assay and clotting
22 assay. You can see the arrow shows that there's

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1 clear clotting and chromogenic assay discrepancy,
2 when assay gets a plasma standard. However, when
3 the same samples were assayed against the
4 product-specific standard, we get perfectly good
5 agreement between the two different type of method.

6 I think there's an advantage of having a
7 product-specific standard. It does ensure and fix
8 the traceability of international units as defined
9 by the international standard and allowed
10 interchangeability of the products because we know
11 that currently the similar dose of these different
12 products raises a similar level of activity in the
13 patient.

14 This standard will also help the long-term
15 stability of the product-specific unit. It will
16 allow method independent testing assay, minimizing
17 assay discrepancy because we will be assaying like
18 against like. It reduces risks related to assay
19 reagent and kit withdrawal, which is a real risk
20 because the kit manufacturer can just drop the
21 reagent when they think that it's no longer
22 appropriate or they feel there is not enough people

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1 using that particular reagent. It can definitely
2 improve interlaboratory agreement.

3 So I think that a publicly available,
4 stable, product-specific standard calibrated
5 against the IS by manufacturer's method and reagent
6 would support the safety and efficacy of these
7 products.

8 I'd like to acknowledge our team at IBSC
9 and also Mikhail for a very stimulating helpful
10 discussion always. Thank you for your attention.

11 (Applause.)

12 DR. OVANESOV: Thank you very much, Elaine.

13 I would like to invite to the microphone
14 our second presenter, Dr. Steven Pipe, from the
15 University of Michigan. Dr. Pipe's
16 biography -- and biography of our presenters can be
17 found on the FDA website. But I just want to note
18 that he has served on the board of directors for
19 the Hemostasis and Thrombosis Research Society, as
20 the chair of the board of directors for the
21 American Thrombosis and Hemostasis network, and
22 currently, he is the chair of the Medical and

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1 Scientific Advisory Committee, MSAC, to the
2 National Hemophilia Foundation. Thank you very
3 much, Dr. Pipe.

4 Presentation - Steven Pipe

5 DR. PIPE: Thank you, Mikhail, and thank
6 you for the invitation to participate in this great
7 workshop. I'm going to be discussing the clinical
8 laboratory perspective on assays with a particular
9 focus on replacement therapy as well as gene
10 therapy.

11 Why do we measure factor levels to begin
12 with? They are certainly critical for clinical
13 diagnosis, both diagnosing hemophilia, we assign
14 severity based on the assay readouts and we depend
15 on these assays for highlighting patients who have
16 inhibitors and tracking their progress and
17 treatment for their inhibitor.

18 We also use these in the clinical
19 management of hemophilia for dose-adjustment,
20 factor replacement, and monitoring factor levels
21 during treatment in prophylaxis and even optimizing
22 factor dosing for PK-guided prophylaxis. But there

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1 are some important principles here, even talking at
2 the diagnostic level, of why we need two types of
3 assays to fully characterize our patients.
4 The assays are available in almost all
5 healthcare settings. They're the activated partial
6 thromboplastin time rate, TPT. You also have a
7 mixing study that can be used to exclude the
8 presence of the inhibitor. And we have the
9 factor VIII and factor IX activity assays, which
10 are based on this one-stage APTT-based assay. This
11 has allowed accurate diagnosis of hemophilia and
12 accurate disease severity assignment, at least for
13 severe versus non-severe in almost every clinical
14 practice setting.
15 But we do need additional assays to have
16 full diagnostic precision. We need the chromogenic
17 2-stage factor VIII activity assay for accurate
18 phenotyping of patients with hemophilia A in
19 particular and to clarify discrepancies that exist
20 between 1-stage and chromogenic assay results.
21 In some cases, factor VIII and factor IX
22 genotyping is critical to fully understanding

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1 patients' underlying disease mechanism. In some
2 cases, we need factor VIII von Willebrand factor
3 binding assays to sort out distinguishing against
4 other presenting bleeding disorders. And we have
5 even used molecular analysis of the VWF gene to
6 help tease out so we're not misdiagnosing patients
7 who may have type 2 and von Willebrand disease.
8 This is an often-presented schema of
9 correlation of average annual number of joint
10 bleeds based on a patient's underlying residual
11 factor activity. This is looking at patients
12 comparing severe hemophilia, those with factor VIII
13 activity that is below 1 percent, the precipitous
14 reduction in expected joint bleeding within the
15 moderate range, and then even within the mild
16 range, some continued improvement in risk for joint
17 bleeding, until we get out to around 12 to 15
18 percent.
19 But we need to be careful of how much we're
20 extrapolating from this graph. These are all
21 hemophilia patients, all of whom have a mutation,
22 and particularly if we're going to make judgments

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1 about what's happening in this range of the curve,
2 we need to understand that everything we know about
3 this part of the curve comes from patients who have
4 mutant factor VIII molecules, not replacement
5 therapy.
6 So what do we know about some insights on
7 mild and moderate hemophilia? Well, if we look at
8 a number of mutations that have been described for
9 mild, so basically non-severe hemophilia, we can
10 see that these often are not just affecting the
11 expression and secretion of the protein, and more
12 often these patients have circulating abnormal
13 functioning factor VIII. These are defects in
14 factor VIIIa stability, thrombin activation, their
15 inability to bind to and interact with von
16 Willebrand factor, phospholipid binding, and even
17 defects in factor IX interaction.
18 Particularly within mild hemophilia, about
19 20 to 40 percent of our patients exhibit 1-stage
20 2-stage assay discrepancy, and it can be in both
21 directions, either one stage higher or two stage
22 higher. If we look at those where the factor VIII

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1 activity is higher by the 1-stage assay than the
2 chromogenic, these genetic defects tend to cluster
3 in the factor VIII domain interfaces between the
4 a1, a2, and the a3. And these have been shown to
5 cause reduced stability of the VIIIa heterotrimer
6 and lead to increased a2 dissociation.
7 Alternatively, when the factor VIII
8 activity is higher by the chromogenic assay than
9 the 1-stage assay, these genetic defects tend to be
10 clustered around thrombin cleavage sites and the
11 factor IXa binding sites. So these are thought to
12 cause impaired factor VIII activation by thrombin
13 or an impaired binding of factor VIII to
14 factor IXa.
15 If we think about these altered functions
16 of these mutant molecules, it would be hard to
17 suggest that these are only relevant in in vitro
18 assays and couldn't also be contributing to the
19 clinical phenotype expression of these patients'
20 diseases. So extrapolating from mild and moderate
21 hemophilia on the clinical characteristics, their
22 bleeding rates, et cetera, purely based on a

<p style="text-align: right;">Page 213</p> <p>1 factor VIII assay, without taking into account this 2 aspect of the function of the molecule, I think is 3 a potential mistake. 4 So now, let's shift to the other main 5 arena, which is in clinical management of 6 hemophilia A. This was demonstrated years ago as 7 the principle for modern prophylactic therapy. It 8 was a suggestion that we've talked about the peaks 9 and troughs today of traditional factor VIII 10 replacement therapy, but it seems that the time 11 spent with factor VIII trough levels below 12 1 percent is directly correlated with bleeding 13 risk. And the more hours per week you spend at 14 those low levels, the reduced likelihood that you 15 will remain bleed free. 16 But this is not an absolute threshold. 17 This continuum exists whether you said time spent 18 below 1 percent, time spent below 3 percent, or 19 perhaps even time spent below even 30 percent. 20 There is still some degree of correlation here with 21 increased risk of bleeding. 22 If you look at the typical prophylactic</p>	<p style="text-align: right;">Page 215</p> <p>1 the same interval with the standard half-life, in 2 which case re-dosing is occurring before patients 3 get anywhere near these critical thresholds, and 4 for individual patients, this has been important to 5 gain real good control of their bleeds. 6 This was from a secondary analysis from a 7 study in which all patients had their prophylaxis 8 optimize. So they were all dosing at a fixed 9 interval of every 3 days, and all of their 10 individual pharmacokinetics was known so that the 11 optimal dose could be given at a 3-day interval, 12 such that their factor levels would never drop 13 below 1 percent before their next dose. 14 So because we knew the factor level at any 15 given time of the day, we could correlate that with 16 the timing of their bleeds and make some assessment 17 of what were some critical thresholds for 18 breakthrough bleeding. 19 What this is showing is the continuum as 20 far as predicted maximum factor VIII activity level 21 at the time of bleed and the proportion of those 22 who were without any spontaneous joint bleeding.</p>
<p style="text-align: right;">Page 214</p> <p>1 pattern of replacement therapy, this is 2 demonstrating the peak and what we call the trough, 3 and then with the next dose, you achieve the next 4 peak. 5 Where you assign that critical level for 6 what you consider optimal prophylaxis in a patient 7 has a lot of interindividual variability. And 8 we've learned years ago that programmatic 9 prophylaxis may be able to deal with the majority 10 of patients, but there's going to be outliers who 11 need higher trough levels to maintain a good bleed 12 control. 13 The advent of the extended half-life models 14 does change characteristics of the curve overall, 15 but we still have the principle of peaks and 16 troughs. And although we can extend the area onto 17 the curve if we really push the limits of the 18 interval between dosing, patients can spend 19 inordinate amounts of time with quite low factor 20 levels towards the trough. 21 To counteract that, what has been used in 22 the era of extended half-life is to even maintain</p>	<p style="text-align: right;">Page 216</p> <p>1 Some of the targets that could be identified is a 2 target of 5 percent factor VIII trough level would 3 have led to about 71 percent of patients achieving 4 zero spontaneous joint bleeds. But approximately 5 15 percent of the patients would have required a 6 factor VIII level well above 15 percent to have no 7 spontaneous joint bleeds. 8 So again, even within this cohort, 9 optimizing for their individual pharmacokinetics, 10 we still see interindividual variability on the 11 risk of them having breakthrough bleeding. 12 Assay discrepancies in clinical monitoring 13 can also depend on the factor replacement product. 14 Elaine has presented to us nicely here about issues 15 reduction standardizing the products that we 16 actually infuse into the patients, but even after 17 infusion, there remain issues. 18 Discrepancies between 1 stage and 19 chromogenic assays have been reported. 20 Discrepancies may be exacerbated by B-domain 21 deletion and sometimes maybe even the length of the 22 B-domain linker. And some high discrepancies have</p>

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1 been reported with some pegylated B-domain-deleted
2 recombinant factor VIII, and some of this may also
3 be influenced by the reagents that are chosen for
4 assaying that particular product. Nicely, these
5 discrepancies can be overcome by using product-
6 specific standards as Elaine has shown us.

7 One emphasis I would like to make is we
8 have been dealing with assay discrepancy for a very
9 long time. If we think about some of the
10 challenges in the recombinant era, just the
11 biochemical characterization of these products have
12 shown that they may have altered post-translational
13 modifications by glycosylation, phosphorylation,
14 sulfation.

15 There may be presence of dysfunctional
16 proteins that either have reduced through absent
17 activity, reduced through absent binding to protein
18 partners, the assay discrepancies that have been
19 mentioned, and even discrepancies in the vial
20 content versus the labeled potency.

21 On the clinical side, we've had to deal
22 with altered pharmacokinetic parameters. Some

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1 products have shown reduced recovery, shorter half-
2 life, changes in the volume of distribution,
3 dealing with clinical reports of reduced efficacy.

4 When a patient has been on a particular product for
5 their whole life, and they start on a new product,
6 then they come back to the clinician and say, "I
7 just don't feel that this is working the same as my
8 previous product," even though the factor assays
9 would give no insight as to why that would be the
10 case.

11 Reports of increased inhibitor risk; this
12 has been demonstrated from retrospective studies
13 all the way through randomized controlled trials
14 and some sense that there may be reduced efficacy
15 in some immune tolerance induction applications.

16 But it only gets worse. That was with the
17 so-called facsimile recombinant products, where we
18 are trying to mimic the endogenous proteins, but
19 this is the bioengineering strategies for enhanced
20 biologics that are now being applied for modern-day
21 replacement therapy. So as we make more and more
22 bioengineering changes in these molecules, we're

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1 apartment to see even more differential between
2 these products.

3 This is emphasizing the same principles
4 that Elaine's already shown you, but if you're
5 using a particular EHL recombinant factor VIII, you
6 increase the accuracy by 1-stage clotting assay
7 when a product-specific standard is used. Here you
8 can see that drift that Elaine showed us, as well
9 as the wide spread across a range of
10 concentrations, but this all collapses down with a
11 product-specific standard. This can also be seen
12 with the same product against a chromogenic assay,
13 again, with this drift and the widespread in the
14 assays, but then collapses down with a product-
15 specific standard.

16 We shouldn't take from this that one
17 particular assay is more accurate or reliable than
18 the other because if you look at the variability in
19 these assays, even when labs are using both the
20 1-stage and the chromogenic assay, we see really
21 that we're seeing the similar types of variability
22 within these assays, even if you were using a

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1 product-specific standard. So we still have the
2 same issues with both of these assays.

3 Now, if we look across the eras of
4 treatment for hemophilia, we've been having to
5 increasingly deal with these bio-engineered
6 molecules, both in standard half-life and extended
7 half-life products. But it's not going to end there
8 because now when we move on to gene therapy, we are
9 also having to deal with bio-engineered molecules.

10 We've talked about the point mutation of
11 the factor IX Padua. B-domain-deleted factor VIII
12 is the primary construct in gene therapy, but it's
13 not the same, which I will show you in a minute.

14 We've added codon optimization to these transgenes,
15 and there's probably more targeted mutagenesis to
16 come in subsequent upcoming gene therapy protocols.

17 So what's at issue with codon optimization?
18 So in codon optimization, we're replacing rare
19 codons. Because of the redundancy of the human
20 genetic code, you can replace rare codons with
21 frequently used ones to attempt to increase the
22 protein expression. Because of the redundancy,

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1 you're not changing the amino acid sequence of the
2 molecule.
3 This has already been used for at least one
4 commercial extended half-life recombinant factor IX
5 in their production cell line, but it's a main stay
6 now of factor VIII and factor IX transgenes for
7 gene therapy. Adding codon optimization to
8 factor VIIIb domain deletion substantially
9 increases protein expression and allows you to
10 either reduce the vector dosage or achieve higher
11 plasma levels.
12 But there may be some unanticipated effects
13 of codon optimization; altered protein confirmation
14 and stability, altered post-translational
15 modifications, and perhaps even altered protein
16 function in a number of different areas.
17 The proposed mechanism is that codon usage
18 determines the translation rhythm, so causing
19 ribosomes to slow down or pause at specific sites.
20 This can modulate the sequential folding events
21 that occur co-translationally.
22 The thought actually is that codon usage

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1 acts as a secondary code, so not just the codon
2 determining the protein structure itself, but this
3 secondary code because of these ribosomal
4 regulations, these pauses, can actually guide
5 in vivo protein folding.
6 How do we know that this really happens?
7 Well, we can gain some insight from some work that
8 was done by scientists here at the FDA, looking at
9 a single synonymous mutation in factor IX that
10 disrupts protein properties.
11 So here, this patient has a single
12 nucleotide change, which does not change the coated
13 amino acid for factor IX. Yet, because of this
14 alteration, and this leads to altered messenger
15 RNA, secondary structure, and codon usage. It
16 alters the kinetics of translation, alters the
17 protein confirmation and post-processing, can lead
18 to enhanced protein degradation, and results in
19 reduced protein expression and expression. This is
20 the root cause of mild hemophilia in this
21 particular case patient.
22 So we're talking about codon optimization

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1 of factor VIII. The preclinical studies had
2 actually predicted this. Codon optimizing
3 B-domain-deleted factor VIII exhibited 7-fold
4 higher expression from CHO cells, but there were
5 some observed differences in post-translational
6 modifications and in O-linked glycosylation, the
7 degree of tyrosine 1680 sulfation.
8 Curiously, the specific activity was 1 and
9 a half-fold higher by 1-stage clotting assay
10 compared to chromogenic. This was not predicted
11 from what we knew about B-domain-deleted factor
12 VIII and other settings. As Elaine had introduced,
13 this came to show up in the clinical gene therapy
14 with these codon-optimized B-domain-deleted factor
15 VIII as well, where we see about a 1.6 ratio
16 comparing the 1-stage to the chromogenic.
17 Is this going to be an issue for factor IX?
18 Well, actually, we're learning that it is. This
19 was just presented at the ASH meeting from one of
20 the factor IX trials. This is showing across the
21 bottom here is chromogenic factor IX, then these 4
22 reagents that are chosen here represent about

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1 90 percent of the testing that would be done in
2 clinical laboratories across the U.S.
3 These are individual patients in the
4 colored lines, but you can see that they're all
5 showing this same degree of variability depending
6 on what reagent is used. So depending on what the
7 central lab is using, you're going to see very
8 different results from the local lab and as
9 compared to the chromogenic.
10 If you look at spiking the Padua variance
11 specifically into a factor IX-deficient plasma,
12 again, we see variability across these assays and
13 clearly different from the chromogenic. This also
14 exists for BeneFIX, but it doesn't show the exact
15 same pattern as we're seeing with the Padua
16 variant.
17 So assay selection is going to influence
18 the readout of factor IX activity in these gene
19 therapy clinical trials. We are lacking clinical
20 correlates with the factor IX chromogenic activity.
21 Elaine mentioned that we don't have an approved
22 chromogenic factor IX in the U.S., which means none

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1 of our clinicians have established any sort of
2 correlation clinically with a chromogenic readout
3 from a factor IX assay.
4 Endogenous expression of the transgene
5 product also introduces potential for
6 interindividual variation. If you're talking about
7 standardizing a product, where you're controlling
8 the cell line and the transgene that goes into
9 that, you can get a fairly uniform product. But we
10 are taking these transgenes, and we're putting them
11 in individual livers, if you like, individual
12 manufacturing facilities.
13 What kind of standardization can we do when
14 every transgene that's expressed is coming from a
15 separate patient?
16 In summary, measuring factor VIII levels is
17 absolutely necessary for accurate diagnosis and
18 phenotyping of hemophilia A as well as monitoring
19 during treatment, but both 1-stage and chromogenic
20 assays should be used for diagnosis and
21 phenotyping.
22 Product-specific standards can overcome the

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1 discrepancies we see in clinical monitoring, but
2 correlation of factor levels with clinical outcomes
3 is really context specific. Caution should really
4 be exercised when extrapolating from one clinical
5 context to another.
6 Mild hemophilia is not equal to replacement
7 therapy and replacement therapy may not be equal to
8 gene therapy. We have already highlighted here the
9 issue of comparing patients who have mutant
10 factor VIII molecules to those that are getting
11 native molecules, and also the peaks and troughs of
12 replacement therapy may be difficult to compare to
13 the steady-state levels that are being achieved
14 with gene therapy.
15 So hopefully, this will stimulate some
16 conversation for our panel coming up. Thank you.
17 (Applause.)
18 Panel Discussion
19 DR. OVANESOV: Thank you very much,
20 Dr. Pipe, for your presentation.
21 Now, I would like to direct your attention
22 to our panelists, who will help us discuss the role

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1 of factor activity as discrepancies in clinical
2 trials.
3 We have several new people on the panel who
4 were not introduced yet, and I'm going to go ahead
5 and let you introduce yourself if you don't mind.
6 DR. FRIEDMAN: Good afternoon. My name is
7 Ken Friedman. I'm the director of the Hemostasis
8 Reference Laboratory at Blood Center of Wisconsin,
9 which is now part of a group of blood centers
10 called Versiti. I direct that lab, and I also am
11 involved in hemophilia care of mostly adult
12 patients, but also some pediatric patients. I've
13 been involved in some of the monitoring of the
14 clinical trials.
15 DR. DODT: Good afternoon. My name is
16 Johannes Dodt. I'm from the Paul-Ehrlich-Institut
17 in Germany, and we are a national authority for
18 licensing blood products. I am involved in the
19 quality aspects of these products, and we are also
20 doing the licensing of the recombinant analogs.
21 Thank you.
22 DR. MARLAR: I'm Richard Marlar, professor

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1 at the University of New Mexico. I'm also the
2 director of the Coagulation Laboratories at
3 TriCore, which is a reference lab for about 16
4 hospitals in the state of New Mexico, as well as
5 doing the special coag for the hemophilia program.
6 DR. OVANESOV: Thank you very much.
7 Let me introduce an overview of a very
8 packed agenda for the discussion today. The
9 discussion will be facilitated by three groups of
10 questions; the first group about the clinical lab
11 practice, the second one is factor assay
12 discrepancies, and the third one, surrogate
13 endpoints.
14 Now, without further ado, I will let our
15 panelists respond to the first question. Is it
16 practical for clinical laboratories to carry
17 different factor activity assays for hemophilia
18 patients on different therapies?
19 DR. MARLAR: From my perspective, I think
20 that we need to look at laboratories in different
21 ways. There are different types of laboratories.
22 There's the large reference laboratories that see

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1 many samples. They don't know what's in the
2 sample. They get in and get a request to do a
3 factor VIII or a factor IX. There are hospital-
4 based laboratories that may or may not work with an
5 HTC. And then finally, there are smaller the HTC-
6 specific laboratories.

7 So I think, from that perspective, we have
8 different ideas of what's needed. I don't think,
9 in the majority of laboratories in the U.S., that
10 we can handle more than 2 factor VIII or 2
11 factor IX assays at a time on that. And I think it
12 really depends on how technological and innovative
13 the director and the technical staff is to be able
14 to set those assays up in there.

15 DR. FRIEDMAN: I'm going to also chime in
16 on this question about using different reagents.
17 Most laboratories actually have automation that
18 they have validated, and that automation is
19 actually sold in conjunction with specific
20 reagents; that is, by the same automation
21 manufacturer.

22 As a result, if you ask a laboratory can

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1 you put on a different reagent set, then you're
2 actually not mirroring the reagent set to the
3 manufacturer. And in most cases, that would mean
4 that you're ending up asking the laboratory to make
5 a laboratory-developed assay because it's not
6 necessarily what will be validated in the licensure
7 of that payer.

8 For this situation, what ends up happening
9 is that you have to then validate this assay with
10 all the things that are expected of validation,
11 including accuracy precision, lower limit of
12 detection, et cetera, and that becomes quite an
13 issue. That's in part why many clinical
14 laboratories stay with one manufacturer, which may
15 be contracted by their institution such that they
16 don't even have the flexibility to choose which
17 reagents they're necessarily going to use.

18 Then finally, the last point which I'll say
19 is that if the reason to have that is in order to
20 be able to accommodate different factor products
21 that the patient's on, then you need excellent
22 communication between the clinicians taking care of

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1 the patient and the laboratory so that they can
2 choose the right assay. Then the laboratory has to
3 report the right assay the right way, and then it
4 needs to go into the hospital electronic medical
5 record in such a way that it's traceable.

6 All those connections, which are somewhat
7 outside the laboratory but communicating between
8 the laboratory and the clinicians and the patients,
9 are all problematic connections.

10 DR. PIPE: I would also say that, at our
11 laboratory, the precedent has already been set in
12 other therapeutic areas, particularly in
13 anticoagulants, where we have a product-specific
14 anti-Xa assay for essentially every one of the
15 anticoagulants that are used.

16 We had to set up all of those product-
17 specific standards, and we demand, when those
18 samples come to the laboratory, that the clinicians
19 identify the product that the patient is on, and if
20 it's not apparent on the order, our lab staff
21 actually do the next step to make that
22 determination.

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1 There was motivation to have those
2 internally and to be able to accurately report that
3 out, and we were able to accommodate that. And we
4 do way more anti-Xa testing than we would do for
5 hemophilia applications. So as far as the
6 practicality's concerned, I'm not sure that's the
7 limitation. I think it's the internal motivation
8 and the ability of clinicians to influence their
9 individual labs to make this happen.

10 DR. MARLAR: I can understand that, and we
11 have the same thing for the Doax [ph] as well, but
12 it's the absolute communication because we will
13 report out a wrong answer. If we don't get that,
14 we have to spend time, which is money in our
15 laboratory, to look into the medical record to find
16 out what's going on. And if it's somebody outside
17 of our hospital system, we have no idea, and that
18 could possibly be the same way.

19 DR. OVANESOV: So one way to go around the
20 need to introduce a brand new assay is to use a
21 product-specific standard to pre-qualify or
22 calibrate routinely used assays. Is it practical

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1 for the labs in the United States to use product-
2 specific reference standards similar to previously
3 available ReFacto standard?
4 DR. DODT: Thank you. Before we start the
5 discussion on the product-specific standards, I'd
6 like to mention an important point. All products
7 have been licensed based on an assay, which was the
8 best assay for that product at the time of
9 licensing. It is well described in the licensing
10 dossier, and it is up to the companies to provide
11 the users with information, which are the tests to
12 be used and which are not suitable for that
13 product.
14 So thinking about the comment from Kenneth,
15 it is the interaction between the medical doctor
16 and the lab to choose a test, and that, as I said,
17 is a problem. So how can a product-specific
18 reference standard be better communicated to a lab
19 than the best method? What is your opinion on
20 that?
21 DR. FRIEDMAN: Well, I guess my opinion on
22 that is that when there were very few products, it

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1 was a little bit easier to do. The laboratory that
2 I direct, and probably other laboratories also, set
3 up the ReFacto standard. And when we set up the
4 ReFacto standard, we actually had the order set
5 such that people were ordering a ReFacto
6 factor VIII. And since the order was specific,
7 then we knew what to do.
8 However, when I look at product-specific
9 standards, theoretically, it sounds wonderful. The
10 problem with product-specific standards are
11 multiple; one, if you have a product-specific
12 standard, you still have to validate the assay, and
13 it's now, by almost definition, a laboratory-
14 developed assay for that specific product standard.
15 In addition, you need to have materials to
16 actually perform tests of accuracy. So you need,
17 actually, materials that are provided by the
18 manufacturer or by buying the actual products in
19 order to calibrate your assay. You also need to
20 participate in external quality assessments, and
21 are there samples to actually do with a product-
22 specific external quality assessment sample; so

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1 there's that issue as well.
2 So you can see how the number of issues
3 that come up with product-specific standards
4 multiplies as the number of materials that come out
5 there multiply. So I think, ideally, it sounds
6 wonderful.
7 The last thing, which I'll say, is that if
8 you have one patient who's on product X, but all
9 the rest of the patients are on product Y, then you
10 set up your assay for product Y. And then when the
11 patient comes in on product X, that becomes a very
12 expensive assay to run as a onesie for that one
13 particular patient. So there are many logistic
14 complications, is what I would say.
15 DR. MARLAR: One other point is that when
16 you have patients on multiple products, which we've
17 already had on two occasions, how do I measure that
18 on two separate products, especially if they don't
19 look like plasma or factor VIII? So that's another
20 issue.
21 DR. PIPE: Richard, you brought up a point,
22 because what we didn't really talk about in the

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1 formal presentations is, for the first time, we are
2 mixing therapeutic agents, both of which affect
3 clinical assays. And if we talk about emicizumab
4 being used for the routine prophylaxis, and then on
5 top of that, they come in for acute surgery or need
6 breakthrough bleeding management, if the clinician
7 wants to monitor that patient, this adds a whole
8 new complexity that wasn't anticipated.
9 DR. OVANESOV: I think that brings us
10 nicely to our third question. What do hemophilia-
11 treating clinicians want to achieve with factor
12 activity testing? There are different scenarios,
13 obviously.
14 DR. PIPE: I guess I tried to highlight a
15 few of these. I think in prophylaxis, you
16 certainly can get away without having to do routine
17 monitoring. Some patients sort of find their sweet
18 spot of dosing and interval based on the clinical
19 feedback. But maybe getting back to Marilyn's
20 point at the very beginning, you would hate to have
21 to use the trial-and-error approach early on in
22 life with a young pediatric patient, and have to

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1 have bleeds be the readout for whether you've
2 optimized their prophylaxis.
3 So I think the utility of having access to
4 monitoring and then maybe application of population
5 PK models seems to be a popular management issue.
6 But definitely being able to understand why a
7 patient is having a breakthrough bleed and
8 monitoring for surgery, these have all been proven
9 to be critical areas where, if you tell the
10 clinician that they will not have access to those
11 monitoring tools, they become quite anxious,
12 actually.
13 DR. OVANESOV: Thank you.
14 DR. FRIEDMAN: Can I just go back to
15 one -- I feel like I've been the naysayer about
16 everything, and I'm sorry to do that, but I
17 actually want to also make one potential suggestion
18 related to the last question, which is that the
19 labs that participate in the field studies get an
20 idea of how their particular reagent responds to a
21 particular engineered product. And the
22 availability of testing those things going forward

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1 after something is licensed is something
2 that -- when you talk about postmarketing-type
3 things, I don't know if FDA would consider that
4 postmarketing issue.
5 DR. OVANESOV: We did consider that in some
6 situations. It's obviously risk based. In some
7 cases, we've worked with the company, and the
8 company proposed to maintain a hotline that
9 clinical labs can call, and they will be guided
10 through the difficulties within assay
11 standardization and calibration, and in some cases,
12 the company might provide the material that is
13 representative of the product.
14 This is not something that is done
15 consistently, meaning that we don't require every
16 company to have that, but some companies opted to
17 have that in place.
18 But to put things into perspective, we have
19 18 licensed BLAs for factor VIII products and
20 9 factor IX BLAs. Not every product would require
21 product-specific standards, but if you add a couple
22 of gene therapy products to the creation, it's

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1 going to be very challenging to have.
2 DR. MARLAR: Yes, I agree with you on that,
3 that it is going to be challenging. And I also
4 think that the laboratory community needs to have
5 some information that's out there for every
6 laboratory to assess, to know that, well, this
7 product, you need to do this with, and this
8 product, you need to do that with, that's available
9 for everybody, rather than having to go through
10 every product insert and through the original data
11 to get that out. I mean, a summary of what's there
12 is something that should be used or available.
13 DR. OVANESOV: Thank you.
14 DR. GRAY: I think that is important to
15 remember that when we talk about a product-specific
16 standard, the usage can still be discussed because
17 you don't have to -- your lab, if you want to have
18 a look to see exactly how your own assays behave,
19 that's where the product-specific standard would be
20 useful.
21 At the moment, the way I see it being used
22 in the clinical lab is, really, for the clinical

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1 labs to understand how their reagent behaves, and I
2 think that's important. So you don't have to use
3 it in every single assay. I think it's
4 understanding the characteristic that's important.
5 But I think with the product-specific
6 standard, it's also important from a manufacturing
7 point of view because if we have something that's
8 stable, we know that it's there. It pins down the
9 unitage that's related to that product.
10 As someone who makes an international
11 standard, when I replace a standard, I worried
12 because those standards, the products right now are
13 so intrinsically linked to the international
14 standards that have been calibrated against using a
15 specific set of reagents. If I decided not to make
16 SynthASil anymore, what would happen?
17 So I think we have to think about it from
18 several different angles about the usage of a
19 product-specific standard.
20 DR. OVANESOV: Thank you. I think it's
21 time for us to move closer to the surrogate
22 endpoints, and I will read these two questions.

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1 What would you consider a clinically
2 meaningful assay discrepancy, and what are the
3 safety risks that can arise from factor assay
4 discrepancies to patients on replacements or gene
5 therapies?
6 DR. PIPE: I think right before this, you
7 had what degree of variability do we have even
8 within even the individual assay; is that correct?
9 DR. OVANESOV: That's right.
10 DR. PIPE: I think they're both related.
11 We're already starting with a variability that
12 could be as high as, certainly, 5 to 10 percent,
13 but maybe also pushing above 10 percent for some
14 assays for variability. And then now you're laying
15 on top of that a discrepancy, where there could
16 actually -- you're overlapping with those
17 interassay variabilities.
18 So as far as what's clinically meaningful,
19 I don't actually believe that that's been sorted
20 out even with the original discrepancies that I
21 pointed out. We do not know -- even from the mild
22 hemophilia patients with the 1-stage/2-stage

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1 discrepancies, it's not clear that you could define
2 one assay for those patients and say that is the
3 truth. It's just an observation that illuminates a
4 molecular mechanism that's a problem in that
5 particular molecule.
6 I think you could say the same thing with
7 the 1-stage/2-stage discrepancies with the clinical
8 management with replacement therapy. We identified
9 this problem in our laboratories, but we haven't
10 done sufficient work to be able to say that one
11 particular readout of those assays is truth as far
12 as representing a clinical outcome. And I don't
13 think we're any further ahead today than we were
14 probably 25 years ago, when this first became an
15 issue in replacement therapy.
16 So to answer your question, I would say I
17 don't know how we could know that information at
18 this point.
19 DR. OVANESOV: Thank you. It makes a lot
20 of sense to me, but we need to get closer to gene
21 therapies. So if a discrepancy is found, how do we
22 pick the assay and threshold to measure factor

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1 activity as a surrogate marker? And remember, we
2 use a surrogate marker for the accelerated approval
3 pathway, but are going to approve a product,
4 hypothetical product, on the basis of the presence
5 of a certain level of factor activity in blood of
6 gene therapy patients.
7 Is it even valid to use this approach,
8 given all the issues with assay discrepancies, with
9 clinical lab issues, and what just Steve said, that
10 we don't know what we're measuring, basically.
11 Well, we know what we measure; we measure factor
12 activity, but how does it relate to normal
13 activity? That we don't know for sure.
14 DR. PIPE: I guess what I would say is, the
15 continuum is always going to remain true. More
16 factor activity is always apt to be better than
17 less. So I don't think we can discount that the
18 factor activity is absolutely useful and has proven
19 to be a valid surrogate marker for decades, from
20 diagnostics to replacement therapy, and now will
21 also prove true in the gene therapy era.
22 Where we're maybe running into issues is

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1 when those assays are straddling key decision
2 treatment triggers. So if you're doing prophylaxis
3 and you're running someone close to the wire with a
4 trough of 1 percent, you're really putting a lot of
5 stock in the ability for your lab to actually
6 measure that 1 percent and to be making laboratory
7 adjustments accordingly.
8 If your gene therapy outcome, on one assay,
9 your median is, say, 7 percent, but on the
10 chromogenic, those patients' median is down around
11 3 or 4 percent, that's putting clinicians at an
12 awkward interface because they would make maybe
13 clinical assessments of outcome differently based
14 on where that straddle occurs.
15 But the further we move up the continuum,
16 these discrepancies become less and less relevant
17 to us clinically. It's hard to imagine, from
18 anything that Marilyn showed us today, that we
19 would really be making a different clinical
20 decision for a patient who sits at 40 percent
21 versus a patient who sits at 27 percent. I just
22 can't imagine how I would manage that patient much

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1 differently with that kind of a differential.
2 So is it clinically meaningful at that
3 level? I would say no. But at the low end, it
4 definitely could be. So related to these gene
5 therapy trials as a surrogate marker, I guess it
6 really does depend on where they are on that
7 continuum.
8 DR. OVANESOV: I think I can refer back to
9 the discussion we've had on the instruments on
10 whether we have evidence to say that the difference
11 that was measured by a particular, say,
12 quality-of-life measure is meaningful.
13 We actually have the same problem here. I
14 understand that a 20 percent increase or an
15 increase in 20 percent of factor activity may seem
16 meaningful, but where is the evidence that supports
17 this statement?
18 Maybe there is evidence, and that's
19 actually the question that is represented here, and
20 we described that in our guidance for gene therapy
21 and hemophilia. But the issue is the kind of
22 evidence that is available to us to say that this

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1 is enough.
2 I think Steve already responded to this
3 question; does factor activity level post-gene
4 therapy have equivalent meaning to prior levels
5 achieved with exogenous factors? Probably, not
6 always.
7 So considering the discrepancies between
8 assays and reagents, can we predict the correlation
9 of factor activity and bleeding in a particular
10 case? In general, yes, we can agree more factor is
11 better, but when we are presented with a particular
12 gene therapy, how do we predict that correlation?
13 What kind of evidence would we need from the
14 company?
15 Maybe the companies can respond if they
16 want.
17 DR. PIPE: I guess I'm somewhat fixated on
18 the fact that we have had traditional clinical
19 decision-making triggers that are benchmarked
20 against certain thresholds of factor activity. But
21 once we get anything above 10, 15 percent, we're on
22 very shaky ground as far as being able to

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1 distinguish clinically meaningful differences
2 across patients.
3 So when you say, can we predict the
4 correlation of factor activity bleed, I think
5 there's plenty of evidence that after you cross a
6 certain threshold, spontaneous joint bleeding
7 stops, traumatic bleeding becomes much, much less
8 frequent, and at some point, clinicians will
9 probably even choose not to recommend additional
10 hemostatic replacement therapy or even coverage for
11 surgery based on a particular factor level.
12 So as long as critical thresholds are
13 surpassed, it may not be important to be able to
14 make a clear predictor between these. So your
15 20 percent example is sort of an interesting one
16 because I think anybody looking after hemophilia
17 would say you would not expect spontaneous bleeding
18 at that level. Almost all traumatic bleeds would
19 probably be prevented for the most part. And
20 you're probably talking limited to need for
21 replacement therapy with certain types of major
22 surgery.

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1 So I would be hard-pressed to demand that
2 there be a clinical correlate with that 20 percent
3 activity. As a secondary outcome, almost
4 certainly, it would be obtained in the course of
5 the trial, but there would be no reason to doubt
6 the utility of that 20 percent in that patient.
7 DR. OVANESOV: Thank you very much.
8 DR. MARLAR: Steve, I have just a question
9 to follow up on that. Do you think that the
10 products are going to have a different 20 percent
11 level when you start working with that?
12 DR. PIPE: If there's an alteration of the
13 biology of the molecule, codon optimization, which
14 is a hypothesis at this point, of course, or Padua,
15 where actually there's clearly an alteration of the
16 biology, there may be not reagent issues that are
17 at the root of that, but actually, the biology of
18 how the molecule gets activated and how it
19 initiates in early components, for instance, in a
20 1-stage assay.
21 So what you're going to be challenged by
22 there is that may not only be an in vitro

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1 manifestation of the biology of that molecule.
2 That benefit, if you like, that altered activity
3 advantage of that molecule could also be relevant
4 in vivo.
5 So 20 percent at a non-bioengineered VIII
6 versus bioengineered, the activity is still the
7 activity. And if it's an alteration beneficially,
8 if you want to call it that, for the molecule, you
9 would think that that would probably be represented
10 clinically. And I don't know how you would tease
11 that out in the levels that we're talking about
12 here.
13 When we were down at, say, 1 to 5 percent,
14 these would have been absolutely critical ideas to
15 try to wrap our minds around, but as soon as we get
16 across some critical threshold levels, I think this
17 becomes kind of noise.
18 DR. GRAY: But then the problem becomes
19 that your assay discrepancy, say within 2 APTT
20 reagent, could be 40-fold difference, so --
21 DR. PIPE: Did you say 40?
22 DR. GRAY: -- yes, which happens with one

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1 of the, say, pegylated factor VIII molecules.
2 So if you really chose -- well, I don't
3 know what is right and what is wrong, but it tells
4 me that the reagent that gave lower activity,
5 obviously, is not quite right in some way.
6 So I think it goes back to the point that
7 it's very important that the information for these
8 products, about how these products are potency
9 labeled, the assay that's being used should be
10 information that should be accessible because in
11 those types of situations, you really don't want
12 people to use a certain reagent and then think the
13 company should come straight out and say you
14 shouldn't be using those reagents.
15 DR. PIPE: To that exact point, I think
16 from Mikhail's example in gene therapy, knowing
17 what the distribution of those factor VIII levels
18 or IX levels are across a variety of different
19 reagents should be a critical part of the learning
20 from these trials because, then, that information
21 is available to the clinicians.
22 It won't be 40-fold for any of the gene

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1 therapy of course, but it could be 1.5-fold
2 differential, maybe even up to 2-fold differential
3 if you want to talk chromogenic and certain
4 specific 1-stage. But I think, as long as the
5 clinicians know that and they know what that
6 differential is, I think we would all be
7 comfortable in the day-to-day management of these
8 patients.
9 DR. GRAY: I think that it may also help
10 for the gene therapy product if the in vitro
11 produced expressed protein. If you do a
12 characterization of that with a different reagent
13 and follow up looking at patient sample from that
14 gene therapy to see whether they follow the same
15 pattern or not in terms of the reagent
16 characteristic, I think that would be helpful to
17 help us understand a little bit more whether you
18 can predict what reagent you should be avoiding.
19 DR. OVANESOV: Thank you very much for this
20 excellent discussion. We ran over our time, and I
21 want to thank our panelists for their time they
22 spent with us today. Thank you.

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1 (Applause.)
2 DR. LOZIER: Let's go ahead and take our
3 recess.
4 (Whereupon, at 2:38 p.m., a recess was
5 taken.)
6 Session 5
7 Moderator - Jay Lozier
8 DR. LOZIER: I am a medical officer in the
9 Center for Biologics and Review, among other
10 things, gene therapy and various factor
11 concentrates.
12 In this session, we're going to talk about
13 clinical trial design, and we'll be talking about a
14 couple of things that are of particular importance
15 to us, one of which is when do we move from adults
16 to kids, however carefully, and we'll have a couple
17 of presentations addressing that. And then we need
18 to address some of the issues about long-term
19 surveillance and focus on a particular risk that's
20 been identified in the preclinical animal models.
21 The first question up here for your Slido
22 polling is at what age is the human liver

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1 essentially an "adult" organ? And your options are
2 13 to 14 years, 15 to 16, 17 to 18, and 10 to 12.
3 I notice about 30, 35 people have been responding
4 to the morning session, so I hope you won't slack
5 off and we'll get a good response on this. And
6 there's no right answer, I don't think.
7 (Audience responds.)
8 DR. LOZIER: Why don't we go ahead and
9 close this down? It looks like there's a sliding
10 scale here around 13 to 14 years.
11 Let's go to our second thought-provoking
12 question. How long should factor VIII or factor IX
13 levels be demonstrated to be stable in adults
14 before treating adolescents with gene therapy; that
15 is, what sort of a track record do you want to see
16 with adults before you move to children, whether
17 they're older adolescents? Let's just assume that
18 and not young children.
19 This one gets a little more activity a
20 little quicker.
21 (Audience responds.)
22 DR. LOZIER: We'll give that a pause. It

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1 looks like quite a few people are wanting at least
2 1 year and some are wanting 5 years. Let's put the
3 questions down now, and I'll go ahead and introduce
4 our first speaker.
5 Amy Shapiro is the founding member and the
6 medical director and CEO of the Indiana Hemophilia
7 and Thrombosis Center in Indianapolis and has been
8 a leader in hemophilia treatment for many years.
9 She's also an adjunct professor of pediatrics at
10 Michigan, where she, I think, administers a
11 coagulation fellowship with Steve Pipe. She is
12 going to talk to us today about the duration of the
13 gene therapy response.
14 Amy?
15 Presentation - Amy Shapiro
16 DR. SHAPIRO: Thank you very much for
17 inviting me today. Dr. Lozier asked me some very
18 difficult questions. Here are my disclosures. The
19 questions that Jay posed to me include this set of
20 4 basic questions: how long data would be required
21 in adults for duration of response before trials in
22 children could be initiated; the duration of the

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1 vector-sustained expression in children, would it
2 be different in children compared to adults, what
3 would we want to achieve; and can we define the
4 target factor level in children based upon the age
5 treated to achieve a reasonable level as an adult,
6 so what would be the end target level and what
7 would you be starting with based upon the age that
8 the child received that therapy; and how do we
9 proceed in children? Do we consider age cohorts?
10 In order to approach those questions, I
11 broke this down into a few areas, the data on the
12 duration of response that we have so far; specific
13 pediatric concerns, including the age of the
14 patient, pulling out what I might call special
15 populations, where the risk-benefit ratio for
16 specific therapies could be considered slightly
17 different than the general pediatric population;
18 and then those unknown issues, the things that we
19 don't really have enough information about at this
20 time, and do we need further information as we
21 approach pediatrics; and then looking at the
22 overall risk versus the current burden of therapy

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1 based upon what do we have available at this point
2 in time to treat patients.
3 In terms of duration of response, the most
4 information we have at this point in time is
5 regarding factor IX gene therapy. The St. Jude
6 Children's Research Hospital and University of
7 College of London project was originally published
8 approximately 8 years ago and stills shows
9 continued sustained factor IX activity in the 3 to
10 5 percent range. It was present in a dose-
11 dependent manner with no long-term safety issues
12 for the duration of follow-up at this time.
13 Subsequent trials by Spark and other
14 companies have used factor IX Padua and have
15 achieved higher factor IX levels of approximately
16 30 percent with lower vector doses, with a
17 follow-up that's shorter since that is a newer
18 innovation, lasting approximately 2 to 3 years.
19 Then newer trials, including one recently
20 discussed at ASH by Dr. Nathawani, looking at a
21 different vector achieving levels of approximately
22 90 percent with a Padua variant, and then other

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1 modalities where we don't even have clinical data
2 as yet; for example including gene insertion in the
3 safe albumin harbor of the albumin gene from
4 Sangamo, and here we don't even have any data on
5 the levels achieved or the response duration.
6 So we have quite a big range in terms of
7 what we have available and how gene therapy is
8 moving forward.
9 For factor VIII, the most mature data we
10 have is from BioMarin. This used, in the original
11 study, 2 dose cohorts. There was not a linear dose
12 response. The higher dose cohort, which consisted
13 of 7 patients, achieved levels that varied between
14 19 percent to 164 percent.
15 Interestingly, in this study, there didn't
16 appear to be a clear connection between the
17 elevated ALTs and the anti-capsid T-cell response,
18 and then the steroid use in factor VIII activity to
19 ameliorate the elevated liver enzymes. Four of the
20 7 patients with steroids did not halt the increase
21 in ALT, and the question is then raised, is this an
22 immune response versus actual hepatotoxicity? Is

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1 there a difference?
2 This is the data that was published from
3 the BioMarin trial looking at the high-dose cohort
4 with 7 patients. For the first 52 weeks, there is
5 further data that is now available, but not yet
6 published in a manuscript. The lines show the
7 median levels, the little areas -- these are the
8 mean levels, and this is between the 25th and 75th
9 percentile. But you can see that the majority of
10 these patients are within the normal range,
11 although as I said before, there was quite a bit of
12 variability in the levels that were achieved within
13 the same dose cohort.
14 We have quite a bit of information in terms
15 of development of this technology, including the
16 AAV as a vector capsid and lots of different things
17 that have been performed over the years in order to
18 try to achieve where we are today and the success
19 that we have achieved. As you can see, we have a
20 lot more data with factor IX gene therapy as we do
21 with factor VIII at this point in time.
22 What are our concerns in pediatrics? Well,

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1 age is an important concern. If we have an
2 episomal vector, it's going to be diluted as time
3 goes on with liver growth, so what level you
4 initially require to achieve is going to have to be
5 targeted at a different level to achieve an adult
6 liver size and as the vector dilutes over time.
7 So we have to think about what we want to
8 achieve as an adult and then work backwards in
9 terms of what we need to achieve based upon the age
10 of the child that we treat.
11 The answer may be different for factor IX
12 deficiency as compared to factor VIII. Consistent
13 levels of factor IX of about 30 percent are likely
14 better than anything right now that we can achieve
15 with current available therapy, and consistent
16 factor VIII levels of 40 percent are likely better
17 than anything we are likely to achieve right now
18 with current therapies with factor VIII, including
19 novel therapies.
20 In terms of durability of response, it's
21 clear that as you transfect to youngest patients,
22 we're going to want the longest durability of

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1 response. So if you treat someone who's 50 years
2 old, they have a shorter life expectancy in terms
3 of what you want to achieve in terms of durability
4 response as compared to treating someone who is
5 10 years old, where you want a much longer
6 durability of response.
7 Pediatric patients represent a vulnerable
8 population in terms of participation in clinical
9 trials and consent, so we have to be very careful
10 as we approach this population because the parents
11 are essentially consenting for these young
12 patients.
13 Safety data and long-term durability are
14 required if other reasonable therapies are
15 available, so we really have to think about what's
16 the burden of disease and what is reasonable to
17 treat our patients with, when we take risks with
18 young patients.
19 We also have to think about data about
20 overcoming development of neutralizing antibodies,
21 If a second vector infusion is required later in
22 life, if durability of response is not what we want

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1 for a lifetime, how are we going to overcome that,
2 and we need to think about that and plan for that
3 as we approach children.
4 We might pull out what I would call a
5 special population of children. I'm using this as
6 an example and not saying that this would represent
7 the special population of children, but patients
8 with inhibitors are clearly more vulnerable
9 patients, as we've heard before. Gene therapy
10 could provide the ability to tolerize these
11 patients without costly, burdensome infusion
12 therapy, and they may represent, therefore, younger
13 candidates for gene therapy due to the burden of
14 care and the sequelae experience.
15 With the advent of emicizumab to at least
16 control bleeding in factor VIII inhibitor patients,
17 it does not tolerize them, but at least we get
18 better bleed control. This is not available at
19 this point in time for factor IX inhibitor
20 patients, which are far more difficult to tolerize
21 and difficult to treat. So you might even
22 categorize a factor IX inhibitor patient different

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1 than you would categorize a factor VIII inhibitor
2 patient in terms of risk and risk-benefit ratio.
3 Then there are a whole group of what we
4 would consider to be those unknown issues. Does
5 the cell line for vector manufacturer result in
6 different pathophysiology of the elevated liver
7 enzymes that we see in patients post-infusion?
8 Some of these cell vectors are produced in
9 mammalian cell lines and some in insect cell lines.
10 And does, perhaps, one create a cellular immune
11 response versus the other actual hepatotoxicity?
12 The seroprevalence of immunity to AAV
13 serotype is likely based on age, so that if you got
14 a younger patient population, you might have
15 eligible a larger number of patients for this
16 therapy, so you have to try to figure out what's
17 your optimal age to reach the most eligible
18 patients while considering and balancing the risks
19 at that point in time.
20 Then you have to consider about overcoming
21 immunity to AAV serotype positivity, whether it
22 exists in the patient before due to some natural

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1 exposure or whether the individual has been exposed
2 to that vector in the past and would require
3 retreatment later in life.
4 Longer-term outcomes and unanticipated
5 events need to be thought about. Apoptosis of
6 transduced cells due to protein overload and loss
7 of efficacy over time can occur, so some degree of
8 prolonged observation with some of these particular
9 technologies should be considered; a potential for
10 malignant transformation later in life; for
11 example, hepatocellular carcinoma. This may depend
12 upon the age at which the patient was treated. It
13 may depend upon their prior viral exposure. It may
14 depend upon their stage of liver development or
15 insertion of the vector, even if it's episomal off
16 site or off target.
17 We need to think about this and know how to
18 monitor our patients who undergo this therapy: how
19 often do we see them and what's the optimal tool
20 for monitoring them for long-term sequelae related
21 to unanticipated events?
22 If you think about patients from birth to

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1 adulthood, we think about their growth of their
2 liver over a certain period of time, at which point
3 we can consider their liver to be near mature in
4 size. We think about the prevalence of the vector
5 serotype, which can be perhaps very low at birth
6 and then increase with increasing age. And then we
7 think about, for example, special populations,
8 including inhibitor populations.
9 So when do we pick the best opportunity to
10 increase eligible patients in terms of
11 seroprevalence of a vector; in terms of the optimal
12 level when the adult liver size can be near
13 achieved and you don't worry about dilution of the
14 vector; and when we call out specific patient
15 populations that we think the risk-benefit ratio
16 would warrant perhaps earlier therapy; and then we
17 need to create a stepwise approach to including
18 pediatric patients as we move forward into gene
19 therapy for children.
20 So we need a balanced approach to pediatric
21 patients. The benefits for gene therapy obviously
22 are consistent levels, bleed protection, decreased

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1 burden of care, improved quality of life, and
2 tolerance even for some patients with inhibitors.
3 The risks include perhaps a waning level over time,
4 a need for reinjection in the presence of positive
5 antibodies, consideration for hepatotoxicity, and
6 some late effects, including malignancy, and then
7 their very long life expectancy; how do we monitor
8 these patients? What are our care plans for
9 follow-up of these patients? What are the best
10 modalities for following them?
11 Against that, we have to balance new agents
12 that have come to market, including novel agents
13 such as emicizumab and those in clinical study, for
14 example anti-TFPI inhibitors; and then also
15 extended half-life products. And I've highlighted
16 factor IX here because, clearly, what we've been
17 able to achieve with extension of half-life for
18 factor IX has been much better than as compared to
19 factor VIII, although at ASH we heard about a new
20 factor VIII engineering that extended the half-life
21 at a higher dose of up to 7 days. So there are
22 some nice things that are coming along the pipeway

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1 as well.
2 We need a balanced approach and a stepwise
3 population approach to pediatric patients. We need
4 to determine the durability of the response,
5 especially for the less mature trials; determine
6 the optimal level required based upon the age of
7 administration; and we need probably a better idea
8 of a dose-response curve as we're treating these
9 patients so that we know exactly what we're going
10 to get when we expose a patient to gene therapy;
11 determine the need for further data based upon the
12 deficiency itself in the vector; evaluate the risk
13 in children based upon the current therapies and
14 the current burden of care in populations that
15 could represent increased need such as inhibitors.
16 So going back to Dr. Lozier's questions,
17 how long is data required before we proceed in
18 children -- and I didn't mean this in a facetious
19 standpoint -- really, the longer the better for
20 response duration in safety, especially as you
21 approach children.
22 The duration of vectors sustained expressed

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1 in children; is it different in adults? Yes.
2 Their life expectancy is longer. We need a longer
3 duration to assure that what we're doing is safe
4 and beneficial and really exposes them to a risk.
5 What's our risk-benefit ratio in terms of
6 the burden of care, and can we define the target
7 level in children based upon the age treated to
8 achieve a reasonable level as an adult?
9 Well, we'd have to work backwards. These
10 are just guesses, but if we got a level of
11 30 percent or above for factor IX, and if we got a
12 level of above 30 to 40 percent for factor VIII,
13 that's likely better than what we're achieving with
14 current therapies, including novel agents. That
15 would consider perhaps a different weighing of risk
16 versus benefit and burden of care for patients.
17 How do we proceed in children, and do we
18 consider age cohorts? I think, yes, we would have
19 to work backwards unless we found a population that
20 was of extraordinary need in a particular pediatric
21 group, where current therapies are clearly not as
22 good and the patients are suffering more sequelae.

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1 And I would say that perhaps factor IX-deficient
2 inhibitor patients represent one of those groups,
3 although very small. I think that's it.
4 (Applause.)
5 DR. LOZIER: Thank you, Amy.
6 We'll be holding the questions until after
7 our speakers have finished their presentations.
8 Dr. Stacey Huppert is an associate
9 professor of gastroenterology, hepatology,
10 nutrition at Cincinnati Children's Hospital Medical
11 Center and at the University of Cincinnati College
12 of Medicine. Her research specifically focuses on
13 hepatic cell plasticity commitment and therapeutic
14 potential of differentiating hepatocytes. She also
15 works on the molecular regulation of hepatocyte
16 differentiation via transcriptional networks in the
17 epigenetic landscapes.
18 I thought she would be very well positioned
19 to give us a talk on the development of the
20 adolescent liver. Stacey?
21 Presentation - Stacey Huppert
22 DR. HUPPERT: Good afternoon. So this is

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1 definitely a different type of meeting than I
2 normally go to, but it's been very enlightening.
3 Jay had given me three areas to talk about
4 considerations for hemophilia gene therapy
5 treatment. They're listed here, basically talking
6 about hepatocyte, differential gene expression, and
7 physiological function that evolved from a neonatal
8 period to adolescent stages.
9 I added in models for molecular regulation
10 and hepatocyte differentiation, where the field is
11 at this point in time, what we know about it, and
12 then finally liver growth, which has come up a lot
13 so far. This is my funding.
14 As Jay said, really, the bread and butter
15 of my group is really looking at molecular factors
16 involved in regulating cell identity and commitment
17 in the liver. For this group, really, the
18 important things are in the orange box down below.
19 As we all know, the liver is alone in solid organs
20 and its ability to regenerate mass, so we need to
21 think about that all the way through life. And
22 mouse studies in the last couple years have really

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1 shown us in cell fate tracing studies, that there's
2 no evidence of a contribution of a reserved stem
3 cell population.
4 I've diagrammed that in the right side.
5 You can see that hepatocytes and cholangiocytes,
6 which make up the bile duct epithelium in the
7 liver, are really in states of transition when you
8 are replacing mass of either this population or
9 this population. So you need to think about, in
10 states of liver disease, that cells are continually
11 in flux, and this makes a difference when you're
12 trying to find vectors that hit a specific cell
13 identity.
14 Just to set you up about hepatic
15 architecture, I think when we're talking in this
16 group about trying to target hepatocytes to express
17 different factors, we need to think about all
18 hepatocytes are not the same.
19 I'm just showing you this diagram here
20 where the hepatocytes in zone 1 do very different
21 functions from hepatocytes in zone 3. They produce
22 substances and metabolites that are secreted into

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1 this canalicular membrane and go into the bile
2 duct. Then in this structure here, you can see are
3 then exported out of the liver. Hepatocytes also
4 dump on their basal lateral side substances into
5 the blood that is carried out of the liver.
6 A liver-centric view is really that
7 hepatocytes perform a very specialized function,
8 yet they remain very plastic in adults and in
9 children. The other issue is that the absence or
10 low expression of many hepatocyte-produced enzymes
11 at birth is thought to be responsible for the
12 differences in pharmacokinetics and toxicity
13 between pediatric and adult populations.
14 Here, two extreme examples are glutamine
15 synthetase. The hepatocytes that do a lot of this
16 function are in zone 3, and cholesterol synthesis,
17 the hepatocytes that do that function, are mostly
18 in zone 1. So there are very diverse populations
19 of hepatocytes in the liver.
20 These are images from an experiment that
21 Abby [ph] in the lab performed just to show you
22 visually the changes of hepatocytes and some of

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1 their functional enzymes where they're expressed.
2 On the left-hand side is in a mouse
3 embryonic liver at 14 and TBX3 is a transcription
4 factor. You can see red in the nucleus. Glutamine
5 synthetase that I told you in adults is in zone 3
6 hepatocytes. You can see that all hepatocytes
7 expressed both of these markers early postnatally,
8 so 3 days after birth in a mouse, you can see the
9 glutamine synthetase is mostly located in zone 3,
10 whereas TBX3, the red, is still diverse in its
11 expression pattern, but it's starting to resolve.
12 At 4 months of age, you can see glutamine
13 synthetase is tightly correlated with a central
14 vein area of zone 3, and now TBX3 is localized
15 there. These are just background because we have
16 to amplify to see that signal. So there's really a
17 chance in the expression pattern across the liver.
18 The other thing that we want to think of
19 and, especially bringing up hepatocellular
20 carcinoma or liver cancer, are these factors at the
21 top. I'm showing you 3 factors, delta like 1,
22 alpha-fetoprotein, and glucagon 3, that are

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1 expressed highly in early postnatal liver and also
2 in hepatoblast or embryonic liver. But as the
3 mouse ages from 15 days, 21 days, 28 days, that
4 gene gets shut down, and these are all factors that
5 get re-expressed in hepatocellular carcinoma.
6 Here on the bottom art, I'm showing you
7 just a few markers, which are known to be involved
8 in the canalicular membrane or forming that
9 secretion level. So as hepatocytes start to
10 mature, they start to up-regulate expression of
11 these genes and functional genes within the liver.
12 I think the clearest example of the changes
13 that happened; here, I'm showing you our
14 cytochrome P450, which was the example earlier,
15 that are really phase 1 enzymes that are involved
16 in metabolizing many different chemical compounds
17 in the liver. You can see here that in mouse doing
18 RNA sequencing and of all the genes expressed in
19 the liver, that there are two surges. There's one
20 that happens a few days before birth, and then a
21 few days after birth, you can see the surge of a
22 few P450 genes.

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1 Then there's another surge that happens
2 between 10 and 20 days, and that's really still
3 core to this peak and liver volume or growth in
4 mouse liver, and also at the time when weaning and
5 changing of food diet happens in the liver.
6 At the bottom, I'm not going to go through
7 it, but you can see that these P450 genes can
8 really be classified into 4 different groups, ones
9 that are very early in the neonatal liver that
10 reach peak and then decrease, and then adult. Over
11 here, you can see that they don't become expressed
12 until about mid-gestation out a few days, and then
13 they level off and peak out here.
14 In this slide, I wanted to show you that
15 this is just a visual representation of specific
16 cytochrome P450s. These labels are all incorrect
17 here.
18 This is at day 10 and this is at day 20.
19 This CYP2D1 is not expressed if this pie graph
20 would have showed up here at neonatal times, and
21 then starts to increase, whereas a few other
22 cytochrome P450s are not expressed at all in

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1 neonatal and then start to be expressed in adults.
2 So there's a big switch.
3 This is also observed in humans when you're
4 looking at proteomic profiling of P450s, that you
5 can see that some of these cytochrome P450s are
6 expressed at a low level no matter what age, then
7 up here is late first trimester, all the way up to
8 adult. Some are expressed at fairly high levels no
9 matter what age, the hepatocytes are. Then there
10 are some that are very low expressed in the early
11 liver and hepatocytes, but then become upregulated.
12 So you can see there's definitely a transition of
13 the liver and the hepatocytes as they mature.
14 What's the molecular regulation of this?
15 There really have been found 6 key master
16 regulators or liver-enriched transcription factors
17 that are expressed in the liver, both at embryonic
18 and adult times. One of the areas that we're
19 really interested in is how do these master
20 regulators, which are expressed at both these
21 times, really coordinate the transcriptional
22 changes that happen and are necessary for organ

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1 maturation and also to mature hepatocyte
2 physiology.
3 There are two different models that are
4 thought about. One is progressive assembly of
5 transcription factors, that you may just have a
6 couple on gene X, but in adult hepatocytes, you
7 have 4, 5, or 6 of these master regulators that are
8 sitting on the promoter.
9 This, you can see in mouse, looking at
10 embryonic day 14 to postnatal day 45. If you focus
11 in on Hnf4, which is this center circle right here,
12 you can see that the number of arrows pointing in
13 on Hnf4 increases with age, meaning that many more
14 of these liver-enriched transcription factors are
15 sitting on the promoter.
16 In human, chip sequencing has been done on
17 the genome, and many genes you can see have
18 2 regulators, 4 regulators, and 6 regulators, so
19 there's this reinforcement and progressive assembly
20 on the promoters.
21 The second model is really differentiation-
22 dependent enhancer switching, and this is from

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1 Pamela Hoodless' group, where she's shown, if we're
2 focusing on gene X in a neonatal stage, you can see
3 that it's bound by these couple transcription
4 factors, but if you look in adult hepatocytes, it's
5 no longer bound. But if we look at gene Y in
6 neonatal hepatocytes or hepatoblast, gene Y has no
7 transcription factors, only enhancers, but in adult
8 hepatocytes, now you see occupation. So there's
9 this switch of what's regulating hepatocytes.

10 The other thing we need to think about is
11 also epigenetic regulation. If you take public
12 data from in ENCODE and look at H3K4
13 monomethylation, you can see that there's
14 differences in changes in the pattern of where the
15 peaks are, and the binding of these different
16 histomodifications receive bimodal distribution in
17 adults where you have enhancers bound inside a
18 promoter, and monomodal if you don't have binding.

19 I also had one of the bioinformaticists in
20 our division to look at the ENCODE database to see
21 DNA sequencing if you look at hepatocytes at birth
22 and hepatocytes in the adult. And this is just a

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1 region where we knew there were adult-expressed
2 cytochrome P450s but were zoomed quite a bit out.
3 You can see that whole region of the chromosome is
4 regulated so that, at birth, it's completely closed
5 down, and in adults, it's opened up for expression.

6 There are really dynamic and epigenetic
7 changes that occur in the postnatal liver as it's
8 maturing, and these hepatic master regulators
9 obviously play a very important role.

10 I just pulled out a few genes that would
11 interest this audience, and it's not an in-depth
12 bioinformatics that were done, but just to look at
13 RNA sequencing, you can see that, some of those,
14 yellow means higher expressed postnatally at 28
15 versus day 7. Some of them get up-regulated. Some
16 of them get down regulated.

17 If we look at the promoters of factor VII
18 and factor IX, which are expressed in hepatocytes,
19 you can see that they're all bound by Hnf4, one of
20 these master regulators, but all the work has been
21 done in a very minimal promoter situation. So we
22 don't know anything about epigenetic regulation.

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1 My last topic is liver growth. In a mouse,
2 the peak of liver growth and proliferation is
3 around postnatal day 10 and 20, and reminder that
4 this is when cytochrome P450 transcripts are really
5 having that high surge that they're changing into
6 postnatal differentiation.

7 This correlates with humans in body growth.
8 The liver is really tied to the metabolic
9 requirement of the organism. This is showing you
10 liver growth. This is a group at Cincinnati
11 Children's that has really looked at bone mineral
12 content with size and height growth of normal
13 children, both African-American and non-African-
14 American. The girls are these solid lines here,
15 that peak in their linear body growth around
16 age 11, and boys here are peaking around 13. This
17 really matches the CDC stature for age and weight
18 growth.

19 When we look at liver volume by micro-CT,
20 really, the conclusion, just to cut the story
21 short, is that there is significant change in liver
22 volume in these ages when you look at a couple

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1 months of age down to 18 years of age.
2 When you get here to age 13 to 18, there's
3 not a significant difference, but that's with no
4 liver disease going on in these kids. There also
5 is a decrease, when you look at liver to body
6 weight, from a couple months old into 18 years. So
7 there's really a rapid increase in infants, there's
8 gradual increase in liver volume in school
9 children, and there's not so much in adolescents in
10 normal kids with no disease.

11 This is just one study for your reference
12 that went through all of the micro-CT studies at
13 the time to look at combining all the different
14 reference sets from different ethnicities. It
15 basically comes down to the same conclusion, that
16 the liver is about 4 percent of the body weight in
17 infants compared to adults, where it's around 2 to
18 3 percent. Really, the best correspondence is body
19 surface area to liver volume versus looking at
20 weight and height.

21 This is one of the more recent studies,
22 which was done in 2011, which really was trying to

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1 get at very neonatal early liver size, and it
2 predicts a little bit better than some of the early
3 studies that were done. What they show is that
4 there is this difference once a child hits
5 20 kilograms in the slope of the curve. and the
6 other magic point is 110 centimeters in growth
7 height.
8 Just to finish up, as far as hepatocyte
9 differential gene expression and physiological
10 function from neonatal to adults, there is this
11 spatial and temporal changes that happen with age
12 and that hepatocytes remain plastic even as cells
13 with specialized function. That's very important
14 as you're targeting in a non-diseased versus
15 disease state, if there's any underlying liver
16 disease that the vectors may be targeting different
17 cells.
18 Also, models for molecular regulation of
19 hepatocyte differentiation really begins to
20 basically lay out what the impact might be if
21 targeting specific cells and the impact of choice
22 of promoter for gene therapy, and also, really,

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1 what's open epigenetically if we start discussing
2 integration of some of these vectors.
3 Finally, liver growth, it increases
4 basically with human linear body growth. and liver
5 volume seems to subside around 11 to 15 years of
6 age, and this may impact the timing of vector
7 delivery. That's it. Thank you.
8 (Applause.)
9 DR. LOZIER: Thank you very much, Stacey.
10 Our next speaker is Dr. Mark Sands, who is
11 an NIH-funded investigator in genetics at the
12 Washington University of St. Louis and studies
13 various lysosomal storage diseases. In the course
14 of his experiments with AAV gene transfer, he made
15 some very critical observations about the incidence
16 of hepatocellular carcinoma in mouse models, so we
17 thought he would be a very good speaker to tell us
18 about what some of the preclinical animal data are
19 for this risk factor.
20 We're also grateful that you broke away
21 from a site visit for child health and development
22 to come here.

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1 Presentation - Mark Sands
2 DR. SANDS: Thank you, Jay. Actually, I
3 appreciate you tearing me away from a site visit.
4 This is better.
5 What I'm going to do this afternoon is tell
6 you about a rather troubling finding that we had a
7 number of years ago, and this association of
8 AAV-mediated gene therapy and hepatocellular
9 carcinoma in our mouse models. I have no conflicts
10 of interest to disclose at this point.
11 back in the mid- to late 1990s, we did a
12 number of experiments using AAV-mediated gene
13 therapy to try to treat our mouse models of
14 lysosomal storage disease. Since these diseases
15 are progressive, the question we were asking is if
16 we deliver this vector during the neonatal period,
17 when they're pre-symptomatic, can we prevent the
18 onset of the disease?
19 To summarize 10 or 15 years' worth of work,
20 the answer is, yes. If we deliver these vectors
21 very early on, they have a much better impact. But
22 as part of those studies, we did several lifespan

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1 studies. And what we discovered is that animals
2 that lived a very long time -- and when I say very
3 long time, a year or more, what we discovered is
4 that there was really quite a high frequency, about
5 40 percent, of our AAV-treated animals that
6 developed hepatocellular carcinoma. Now, again, we
7 didn't see it very often before 1 year of age, but
8 again, between 1 year and 18 months of age, there's
9 relatively high frequency of hepatocellular
10 carcinoma.
11 In fact, the average age that we saw this
12 was about 16 months. And one thing that was very
13 puzzling was when we were analyzing these animals
14 to try to determine if AAV might be the causative
15 factor, we hypothesized that if it was, we should
16 see about 1 AAV vector genome per cell in the tumor
17 tissue. Interestingly, what we saw was very much
18 less than 0.1 vector genomes per cell.
19 So this actually suggested to us that it
20 might not be AAV. But we had been studying this
21 particular mouse model for the last 10 or 15 years,
22 and what was very troubling to us was simply the

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1 presence of hepatocellular carcinoma. We had never
2 observed that before in any of the studies we had
3 done, and we developed other therapies that would
4 make these mice live a long time.

5 So this raised a number of questions to us.
6 The first question, and what we actually had hoped
7 for, was that perhaps there was some contaminant,
8 either infectious agent or a chemical agent, in the
9 AAV prep that would ultimately lead to
10 hepatocellular carcinoma.

11 Also, another question, is the
12 hepatocellular carcinoma disease specific? So is
13 it a feature of mucopolysaccharidosis type 7? Is
14 it mouse-strain specific? Is it transgene
15 specific, dose dependent, age dependent? Is it
16 AAV-serotype specific? And again, this question
17 that really bugged me for a long time was why do we
18 have very much less than 1 vector genome per cell
19 in the tumor tissue?

20 So the first thing that we needed to do was
21 to try to replicate this finding. Again, this
22 potentially could have been a one-off observation,

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1 never seen again, so we tried to replicate it. And
2 to make a long story short, we were able to
3 replicate it. And over here, on the lower right,
4 that shows a typical liver from an aged animal
5 treated with AAV. And what you see is a little bit
6 of normal-looking liver tissue and then usually
7 multiple tumors within that liver.

8 So we did the exact same experiment we did
9 the first time. The mice received an intravenous
10 injection of an AAV-2 vector the day they were
11 born, during the neonatal period.

12 In this particular experiment, exactly half
13 of the animals treated with AAV developed
14 hepatocellular carcinoma. Now, what we did
15 determine here was that it was not disease specific
16 because the MPS 7 animals, half of those had
17 hepatocellular carcinoma and half of the wild-type
18 animals. And these were littermates, so there's no
19 differences in the genetics here.

20 Same thing; we saw a rather protracted
21 phenotype. The hepatocellular carcinoma showed up
22 between 54 and 72 weeks. We also asked the

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1 question, is it an infectious agent, and the most
2 likely culprit would be Helicobacter hepaticus,
3 which is known to infect mice, and ultimately
4 result in hepatocellular carcinoma. All of our
5 mouse colleagues are Helicobacter hepaticus
6 negative.

7 Also, the strain of mouse that we use; all
8 of our disease models are on the C57 black 6
9 background. And if you go to the Jackson lab
10 website and you look, part of their website is a
11 table of tumor susceptibility in various strains,
12 and C57 black 6 are relatively resistant to
13 hepatocellular carcinoma.

14 I'm not going to go through this in detail,
15 but this is a table showing the breakdown on the
16 various animals. This was the original
17 observation, which we replicated, and you can see
18 about half of those animals developed
19 hepatocellular carcinoma.

20 Importantly, the wild-type animals, you see
21 the same proportion, but we answered a couple of
22 other questions here as well. These MPS-7 animals;

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1 if we treat them with bone marrow transplant, which
2 extends their lifespan, or if we treat them with
3 radiation to try to bring out this phenotype if
4 it's a function of the disease, very few of those
5 animals developed hepatocellular carcinoma.

6 There is some low frequency of
7 hepatocellular carcinoma in the untreated wild-type
8 animals, but it's less than 10 percent. And this
9 is an important group right here as well. These
10 are untreated transgenic animals. So we have a
11 transgenic animal that harbors the same transgene
12 as our AAV vector, and this animal produces about
13 20-fold higher than normal levels of beta
14 glucuronidase, and you can see no hepatocellular
15 carcinoma.

16 Now, the truly striking finding, though,
17 from this replication experiment was when we tried
18 to pull out junction fragments -- in other words,
19 insertion sites from the AAV vectors -- we were
20 able to isolate 4 junction fragments from 4
21 individual mice, and these junction fragments are
22 represented here, here, here, and here. And again,

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1 the really striking finding is, all 4 of these
2 landed in essentially the same spot. It's within a
3 6,000 base-pair region of what's referred to as the
4 Rian locus, which is on the distal end of mouse
5 chromosome 12.
6 So all of these fell right into this little
7 bitty area here, and when we analyzed the
8 transcription of downstream genes and micro-RNAs,
9 all of these were dysregulated.
10 So we answered a couple questions with this
11 replication experiment. First of all, we had no
12 Helicobacter hepaticus in our mouse colonies. This
13 doesn't completely eliminate an infectious agent,
14 but this is the most likely candidate here.
15 Wild-type animals had the same frequency of
16 HCC as the MPS-7 mice did. All of our mice are on
17 a C57 black 6 background, which are relatively
18 resistant. Is this transgene specific? Well,
19 probably not; at least our transgenic animal would
20 suggest that the presence of that transgene and
21 dramatic overexpression is not a problem.
22 Is this dose dependent? We don't know yet.

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1 Age dependent? Don't know yet. Why is there less
2 than 1 vector genome per cell? When we originally
3 did our analysis on the first observed
4 hepatocellular carcinoma, we were trying to
5 quantify the vector genomes by using primers within
6 the transgene, and all of those insertion sites are
7 rearranged AAV vectors, and the transgene is gone.
8 And that's typical for what people are finding when
9 these things integrate. So that explains why we
10 had this strange number initially.
11 Then quite a bit of time went by, and no
12 one else had ever replicated this finding until, in
13 2013, a group in Pennsylvania was working with gene
14 therapy for ornithine transcarbamylase deficiency,
15 and they had earlier published a paper where they
16 had injected AAV vectors in the neonatal period,
17 and they discovered a high frequency of liver
18 tumors.
19 Their initial conclusion was that it was
20 caused by something else and not AAV. But once we
21 published our data and then they went back
22 retrospectively and reanalyzed those tumors, they

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1 actually did find a number of tumors with AAV
2 integrations within the Rian locus, very much like
3 what we saw. In fact, on that chromosome, it was
4 very near where our integration sites were as well.
5 Then in 2015, there were two papers that
6 came out almost simultaneously. One was from a
7 group in Canada that was studying Sandhoff disease,
8 which is another lysosomal storage disease. They
9 did the same thing; IV injection at birth to try to
10 prevent the onset of the disease. Their mice were
11 also on C57 black 6 background. They saw
12 80 percent of their AAV-injected animals develop
13 hepatocellular carcinoma. Again, it's a rather
14 protracted phenotype. They also saw high frequency
15 of AAV integration in the Rian locus.
16 At the same time, Chuck Venditti's group,
17 who's at the NIH, who studies methylmalonic
18 acidemia, again, did the same experiment; IV
19 injection, newborn animals, and about 50 percent of
20 his animals also developed hepatocellular
21 carcinoma. He used several different serotypes,
22 same thing; high frequency of AAV integration

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1 within the Rian locus, and also just like we saw,
2 dysregulation of downstream genes.
3 I'm not going to go through this whole
4 table because it would take me too long, but this
5 highlighted region, Chuck was able to answer
6 several other burning questions that we had. These
7 two groups here, this AAV vector had a very strong
8 promoter, the CBA promoter. But they were injected
9 with a relatively low dose of virus, 10 to the 10th
10 vector genomes, and you can see the frequency of
11 hepatocellular carcinoma is quite low.
12 In contrast, all these groups here in
13 green, same promoter with one exception,
14 serotype 8, but they were injected with a dose
15 vector 10-fold higher, so 10 to the 11th vector
16 genomes per mouse. This is where you see all the
17 hepatocellular carcinoma.
18 He had two more groups, same serotype, same
19 dose, 10 to the 11th vector genomes per mouse, but
20 in this case, he had a much weaker promoter. This
21 is the human alpha 1 antitrypsin promoter, which is
22 much weaker than either the TBG or the CBA

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1 promoter. And you can see down over here, no
2 hepatocellular carcinoma.
3 The other thing that Chuck did, which is
4 really helpful for this analysis, he pulled out the
5 sequences for a portion of the Rian locus from
6 multiple species; mouse, rat, importantly human.
7 He got elephant DNA, too. I'm not quite sure where
8 he got that, but he directly compared these
9 sequences. And what he discovered is that there's
10 about a 65 base-pair region in the rodent genome
11 that is unique to the mouse and rat. It's not
12 present in any of these other species, and
13 importantly, it's not present in human.
14 Then what he did is he superimposed all of
15 these integration sites that were identified by
16 multiple groups; Chuck's group, our group, another
17 group. And you can see that a number of these
18 integration sites fall right within this unique
19 region.
20 Now, I will caution you at this point.
21 This is a little bit misleading in that these
22 integration sites, this only represents about

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1 60 percent of AAV integration sites. About
2 40 percent of the integration sites that people
3 have pulled out are outside of this unique region,
4 so in regions where there's nearly perfect homology
5 between the mouse and human.
6 So what about this issue of newborn versus
7 adult? There are two studies here, both groups
8 studying hemophilia. This is Kathy High's group
9 here. This is a group from Japan working with a
10 Padua mutation. They injected young adult animals
11 with high doses of AAV, and then asked the
12 question, do they develop tumors?
13 What you can see is when you postpone the
14 injection to young adults, you see the frequency of
15 hepatocellular carcinoma decreases dramatically.
16 It doesn't drop to zero if you look. If you read
17 the entire paper, it does look like there's still
18 some propensity towards hepatocellular carcinoma,
19 but it's dramatically reduced.
20 Finally, for the data slides, this was
21 published just recently, in 2017. This is a study
22 where a group did in utero IV injection into fetal

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1 macaques. So it's a primate model, IV injections
2 in a fetus, what would be closest modeling to a
3 newborn mouse, I guess.
4 What you can see is there are two animals
5 here at least that have an enormous number of
6 unique integration sites within the genome. Keep
7 in mind this is from a needle aspirate, so it's not
8 a big chunk of tissue. And again, many, many
9 thousands of unique integration sites, which is
10 troubling. In fact, if you read this paper,
11 they're troubled by this as well.
12 But what I will say, this is a 6-year
13 follow-up from these animals, so it was 6 years ago
14 that these animals were injected intravenously in
15 utero, and so far, there have been no adverse
16 events noted from any of these animals, so it's not
17 clear it's a problem.
18 So at this point, what do we know? We know
19 that AAV integration in and disruption of the
20 murine Rian locus can cause hepatocellular
21 carcinoma. It seems to be independent of disease
22 model. There have been lysosomal storage diseases

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1 and methylmalonic academia and ornithine
2 transcarbamylase. They all develop hepatocellular
3 carcinoma.
4 It seems to be independent of serotype. It
5 is age dependent, and newborn animals seem to be
6 much more susceptible to hepatocellular carcinoma
7 development than do young adult animals. It seems
8 to be promoter dependent. Strong promoters have a
9 greater propensity for developing hepatocellular
10 carcinoma than we weak promoters.
11 There's a high frequency of AAV
12 integrations in a rodent-specific region of Rian.
13 And again, there's a large number of unique AAV
14 integration sites throughout the genome,
15 independent of Rian, in this primate study. But
16 again, I'll point out, so far, there's been no
17 hepatocellular carcinoma or any other adverse
18 events noted in those animals.
19 Finally, what don't we know? Well, this is
20 a really short list. There's a lot we don't know
21 about this yet. But first and foremost, what we
22 don't know is AAV-mediated hepatocellular carcinoma

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1 problematic for human gene therapy? And we really
2 don't know at this point, and it's extremely
3 difficult to accurately model.
4 Are other tissues also susceptible to
5 malignant transformation? There hasn't been a lot
6 of reports. There is one report where other types
7 of tumors have arisen, but it's not widely known at
8 this point.
9 Are there other consequences, either acute
10 or chronic, of AAV-mediated gene therapy? And
11 again, importantly, can the AAV vectors be
12 redesigned to be safer? Chuck Venditti's data
13 would suggest that that may be possible, but what
14 you may be doing is trading efficacy for safety,
15 and trying to find some balance there.
16 With that, I'll stop, and I guess you're
17 holding questions until later. Thank you.
18 (Applause.)
19 DR. LOZIER: Thanks, Mark.
20 Our next speaker is Theo Heller, who is the
21 chief of translational hepatology in the liver
22 diseases branch, in the NIDDK institute at NIH.

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1 His work includes studying factors that cause
2 progression of liver disease and rare liver
3 diseases. They've got liver access in the
4 microbiome, and we thought he would wrap things up
5 and tell us what are we going to do with these
6 safety signals. Theo?
7 Presentation - Theo Heller
8 DR. HELLER: Thank you, Jay.
9 Thank you, everyone. I thank you all for
10 being at the end of a long day. I'm impressed that
11 so many people have stayed, and that's why I'm
12 particularly grateful to Jay for telling me I have
13 2 hours to review the literature, including the
14 molecular aspects of hepatocellular carcinoma. I
15 refused. I said, "I'm not going to do it. I'm
16 going to stick to five minutes."
17 So I'm going to do a very conceptual talk.
18 I'm going to try and fill in thoughts as we go
19 through concepts, and I'm going to tell you how I
20 think about these things and how I approach things.
21 The first thing we should talk about is
22 just some definitions. Screening is when you look

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1 once. All the baby boomers are now recommended to
2 have hepatitis C testing 1 time. Surveillance is
3 where you look repeatedly. Someone is at risk for
4 carcinoma of the cervix, pap smears are done
5 repeatedly. You wouldn't just accept one. An
6 objective for both is to reduce disease-specific
7 mortality.
8 There's a paper that I would recommend from
9 the American Journal of Pediatrics Hematology and
10 Oncology in 1992 because I think it's really a good
11 approach to surveillance and how we should think
12 about surveillance. There are a couple of points
13 that I'll make, and I'll fill in as we go.
14 First of all, you have to have a common
15 disease with morbidity and mortality, so if we
16 think about hepatitis B and liver disease, once
17 patients developed cirrhosis, the risk of cancer is
18 3 to 8 percent per year. That's significant
19 morbidity and mortality, and it's relatively common
20 in that population.
21 Easily identifiable target population; yes,
22 hepatitis B, hepatitis C, Wilson's disease

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1 hemochromatosis, these are diseases you can
2 identify, diagnose, and follow. As a subtext in
3 that category, surveyors have to agree -- in other
4 words, the physicians or the mid-level providers
5 whose job it is to survey the patients have to
6 agree that this is something we should do. And the
7 target population, the patients, have to agree that
8 we want this sort of screening.
9 The test has to have low morbidity -- in
10 other words, we're not going to take off your right
11 leg to see if you have a clot inside it -- high
12 sensitivity, and specificity. There is to be a
13 standardized recall. In other words, what do you
14 do if you do an alpha-fetoprotein and it comes back
15 high?
16 We have to have a standardized approach to
17 follow through on that. It can't be that some
18 people say, "Let me re-check in 3 months," some
19 people say, "You're probably flaring; let me check
20 the ALT," and other people do further imaging.
21 There has to be a test acceptable to target
22 population. If we recommended colonoscopy every

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1 3 months, I don't think we'd get everyone agreeing.
2 The fact that we suggest it every 10 years as
3 gastroenterologists makes it palatable. I think
4 gastroenterologists would like to do it more.
5 There has to be an acceptable and effective
6 therapy. So for hepatocellular carcinoma, in the
7 early stages, now we have very effect therapies.
8 Resection and transplant has dramatically changed
9 the landscape. Once tumors are advanced, the
10 standard of care is palliative. That's an
11 important thing, advanced disease, palliative care;
12 early disease, possibly curative; even 60, 70
13 percent range.
14 This is not in that paper, but this is
15 something I added. There's an important concept of
16 competing mortality. We'll come back to that in
17 the guidelines, but someone with metastatic lung
18 cancer doesn't need to have a colonoscopy to check
19 if they have polyps. So we need to bear in mind
20 what the patient looks like, who the patient is.
21 We can't just stay this is the test you should
22 have, this is the guidelines. We need to think

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1 about who we're dealing with.
2 This is something that I get asked a lot
3 and comes up a lot, surveillance versus diagnosis.
4 Once you have an abnormality, you're no longer
5 surveying. And if we stick to the theme of
6 hepatocellular carcinoma, if the alpha-fetoprotein
7 is high, we don't do an ultrasound to follow up on
8 it. Ultrasound is a screening test.
9 If you have an elevated alpha-fetoprotein,
10 you would go to an MRI, or if you have an
11 ultrasound that shows a nodule, you wouldn't then
12 do an alpha-fetoprotein, you would go to an MRI or
13 a CT scan. This concept of repeating another
14 screening test is something we run into all the
15 time and delays care.
16 Biology break. In general, hepatocellular
17 carcinoma requires risk factors, and the most
18 significant is cirrhosis. Eighty percent of
19 hepatocellular carcinomas will occur in cirrhosis.
20 That makes it easy, again, to define the population
21 that should be screened.
22 These are general concepts. This is not

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1 unique to hepatocellular carcinoma. This is by the
2 economics people, the CMS-type people, and the
3 people who sit in front of computer screens. Their
4 outcome desired is that we should increase survival
5 by more than 100 days, and the second is that it
6 should be cost effective.
7 There's the concept of QoLies [ph] or year-
8 of-life gained, and the cost should be less than
9 50,000 per year. That's for the whole population
10 screened, not for the individual patient where you
11 find something, and that takes in work, hours lost,
12 and all sorts of things.
13 These are the guidelines. From this year,
14 update is from this year, the American Association
15 for the Study of Liver Disease puts out regular
16 guidelines, and the recent most up-to-date
17 guidelines say that in adults with cirrhosis, we
18 improve survival by screening. That's without
19 question.
20 What's recommended is an ultrasound with or
21 without an alpha-fetoprotein. I'll get back to
22 alpha-fetoprotein and why that says with or

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1 without. And it's recommended to do it every
2 6 months.
3 That every 6 months is not a convenient
4 time frame. It's based on biology. Given the
5 doubling time of hepatocellular carcinoma, the
6 optimal time for most patients would be 4 to
7 8 months. So if you screen every 6 months, you're
8 less likely to miss tumors of significance. You're
9 still likely to find small tumors.
10 Do not screen Child C. Child
11 classification is how we think of cirrhotics. A is
12 good. C is very bad. C is close to death,
13 decompensated yellow with ascites. And the
14 mortality there is so high once they reach Child C,
15 that there's no point in screening for
16 hepatocellular carcinoma because even if you find
17 it, they're likely to die of the liver disease
18 first.
19 Novel biomarkers; everyone is very excited.
20 There are 186 gene profiles that have been looked
21 at. There are all sorts of novel panels looking at
22 different genes. They require further evaluation.

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1 There are other biomarkers. There's
2 AFP-L3 percent. There's DCP. You might have heard
3 of all of these.
4 Some of these are FDA approved for risk
5 stratification. Once you have something, but not
6 approved for screening, the jury's still out. And
7 if you look, CT or MRI is not recommended. That's
8 because of cost, because of radiation, because of
9 convenience. We're talking about ultrasound, a few
10 hundred dollars, CT, MRI, a few thousand dollars.
11 It really changes the equation.
12 There are exceptions. Patients who are
13 very obese are very difficult to do an ultrasound
14 that's high quality. Patients who can't go into a
15 CT scan are allergic to contrast, you might come
16 back to an ultrasound. Again, it's a matter of
17 looking at the patient and not being fixated on
18 guidelines.
19 What about gene therapy in our situation?
20 It's not quite surveillance because we don't really
21 know that adult humans getting gene therapy are at
22 risk for hepatocellular carcinoma in this setting.

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1 So it would be different. The risk is unknown.
2 And surveillance is really defined in the context
3 of prevalence. We have no idea what the prevalence
4 is, so we can't talk about surveillance.
5 There are thousands, tens of thousands of
6 patients who went into studies from which the
7 guidelines were derived. We don't have any
8 patients here.
9 There are other needs, the competing needs.
10 As scientists, as an approval agency, as physicians
11 taking care of the patients, and as patients, we
12 want to know if cancer really occurs. How risky is
13 the therapy? What is the percentage? And we want
14 to know this with some rigor. We want as small a
15 margin of error as possible. So how badly do you
16 really want to know? Because if you want to know
17 really badly, you would not screen with alpha-
18 fetoprotein and ultrasound.
19 What are our options? The first option is
20 to do nothing. The second is blood tests. Third
21 is imaging. The liver biopsy always comes up. I
22 spent the morning doing liver biopsies. I love

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1 them, and the patients don't always; different
2 story.
3 Symptoms are no longer surveillance. So
4 once the patients have symptoms, we're no longer
5 talking about surveillance. So the first option,
6 do nothing. I don't think that's an option. The
7 second, blood test.
8 These are best studied in regular
9 cirrhosis. An alpha-fetoprotein, more than 20, is
10 considered the cutoff. Normal range in my hospital
11 at the NIH is 6.6, so 20 is more than 3 times that.
12 Results vary at different labs. You were speaking
13 about that earlier.
14 Sensitivity of 60 percent; that's not
15 great. Specificity of 90 percent, and if
16 hepatocellular carcinoma is 5 percent, it's a
17 25 percent positive predictive value. There are
18 variances already mentioned the AFP-L3 percent, the
19 DCP, for risk stratification.
20 What about novel tests? Well, there's even
21 less known, and even less known in this setting.
22 What about imaging? Ultrasound is the best

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1 studied. Cost-wise, it's the most effective. It's
2 very available. It is somewhat operator dependent,
3 but I think that's less and less of an issue with
4 higher-quality machines in academic centers.
5 Efficacy, it's pretty good, and we can go
6 to MRI and I'll put that into context. MRI is a
7 lower false-positive, 3 versus 5.6 percent. It is
8 a greater sensitivity and specificity, 80 to
9 90 percent and 91 to 98 percent. And I use the
10 recent reference, Kim in JAMA Oncology from last
11 year, but there are many other references which
12 show similar things.
13 The MRI has to be dynamic. That means they
14 have to get contrast. It's about 45 minutes to an
15 hour, and it requires a center that's comfortable
16 and familiar with doing liver MRIs. We see a lot
17 of MRIs from smaller community hospitals; they're
18 not adequate.
19 CTs have to be 3-phase, again, with
20 contrast, and that's a significant amount of
21 radiation. So as hepatologists, we are doing less
22 and less CTs because we don't like the abdominal

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1 radiation. We're moving more and more towards
2 MRIs, but again, that requires greater facility
3 with it and also cost is greater. But CTs are
4 easier to reproduce and are more generally
5 available.
6 CT and MRI are very helpful. Actually,
7 it's considered diagnostic in most instances. And
8 in the liver, we find lots of other things, which
9 is why I like being a hepatologist. We find focal
10 nodular hypoplasia, we find hemangiomas, we find
11 all sorts of things, and ultrasound can't
12 distinguish that very accurately, but MRI and CT
13 are very good. So that makes it easier and less
14 likely that you'll go down a rabbit hole.
15 What about biopsy? I apologize for the
16 small print, but I really wanted to include these
17 concepts. It's invasive. There's risk. It's
18 150,000th of the liver, so to do a blind biopsy in
19 someone with hepatitis C where the whole liver is
20 affected, if you have an adequate biopsy, your risk
21 of sampling error is less than 2 percent and
22 98 percent good; same for hepatitis B; same for

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1 autoimmune hepatitis. But if you're looking for
2 random hepatocellular carcinoma, is 1 in 50,000
3 adequate? No. And as I said, although it's good
4 for me, going through it for the patient is not
5 always pleasant.
6 This is from the guidelines. Biopsy may be
7 required in selected cases, and this is for
8 diagnosis, not screening. But its routine use is
9 not suggested. Biopsy has the potential to
10 establish a timely diagnosis -- and, again,
11 diagnosis -- in cases in which a diagnosis is
12 required to affect therapeutic decision making.
13 However, biopsy has a risk of
14 bleeding -- it's a good thing there's no risk of
15 bleeding in this patient population -- and tumor
16 seeding -- in fact, some transplant centers won't
17 do liver transplants in patients who have
18 hepatocellular carcinoma and have had liver
19 biopsies because of that risk -- and the
20 possibility that a negative biopsy is attributed to
21 the failure to obtain tissue representative of the
22 nodule rather than a truly benign nodule.

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1 Then I included something else from work
2 from the NIH. We looked at our last 3 and a half
3 thousand liver biopsies, and we looked at risk of
4 complications, and we published this last year.
5 Compared to viral hepatitis, biopsies performed of
6 certain diagnoses had significantly higher odds of
7 major complications: NRH, drug-induced liver
8 injury, GBHD. And look at the odds ratio for
9 hepatocellular carcinoma, 34, greater risk of
10 complications compared to viral hepatitis.
11 So that's one of the reasons we don't like
12 to biopsy hepatocellular carcinoma and one of the
13 reasons we rely on CT and MRI criteria. And we do
14 biopsy if we have to, but it's not just to be
15 certain and because we're curious.
16 Furthermore, by multivariate backward
17 logistic regression -- don't ask me any questions
18 about that; I don't understand what that
19 means -- platelets less than 100 and APTT greater
20 than 35 were independent risk factors of
21 post-biopsy bleeding. So I think we can put biopsy
22 to rest.

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1 Where does that leave us? So we have to
2 make peace with the silver standard. Imaging is
3 the core, and I don't mean core biopsy. I mean
4 core. That's what we rely on as hepatologists. We
5 don't rely on the FP for the reasons that I
6 explained. We rely on ultrasound to screen. If
7 you really have a high-risk population and you want
8 to know with absolute certainty, for example, a
9 transplant population where people are going to
10 liver transplant and you cannot afford to miss an
11 HCC, we would rather use an MRI.
12 The age is important. We heard discussion
13 from Dr. Sands about what time people are exposed
14 to risks. And it's true, in human disease, too,
15 the earlier you are exposed to hepatitis B, the
16 earlier you develop cirrhosis, the more time you
17 have to develop cancer.
18 How long people have had the disease, so
19 even if you were affected as an adult, your risk
20 factor started at adult. It's not the same when
21 you're 30 as when you're 60. And when to stop
22 screening or when to stop surveying; 10 years after

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1 gene therapy, 20 years after gene therapy, 5 years
2 when the factor levels drop? I don't know the
3 answers.
4 I would say that, for me, thinking about
5 this patient population, this is not the same as
6 surveying a patient's group with hepatitis B. I'd
7 want to know with certainty. I would not be
8 comfortable with a 60 percent sensitivity. I'd
9 want to go to something a little bit more certain.
10 Biology is great. We can never have
11 100 percent certainty, but as close as we can get.
12 Thank you all for putting up with me and listening
13 to the last talk on what looked like a fantastic
14 day.
15 (Applause.)
16 Panel Discussion
17 DR. LOZIER: So at this point, we'll open
18 things up for some discussion and questions with
19 the panelists. Stacey had to catch a plane, so
20 she's not with us. Don't take it personally.
21 I had a question, I guess, first for Amy.
22 And I would say people should be ready to ask

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1 questions here at the microphone. I want to get
2 some things into our panel specifically. But go
3 ahead and come to the microphone, and we'll also
4 look at Slido questions if they're pertinent to
5 this session.
6 So you talked about special population,
7 pediatric populations that might be, say,
8 attractive targets for gene therapy, in particular
9 inhibitor patients. Would you worry about either
10 exacerbating a factor IX inhibitor titer, and then
11 have continuing production of factor IX in those
12 patients which could lead to complement-mediated
13 disease?
14 For instance, if you get factor IX and have
15 anaphylaxis, you don't do it. But once you give
16 the gene therapy, you can't go back.
17 DR. SHAPIRO: Yes. That's a very good
18 point. There was some very good work presented at
19 ASH, looking at platelet-derived gene therapy with
20 factor IX in a mouse model where, actually, the
21 mice do get anaphylaxis when they're exposed, and
22 they were tolerized using that method.

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1 So there might be specific modalities that
2 you could consider. But yes, if you were just
3 using standard therapy and that patient had an
4 anaphylactoid phenotype, you'd be very concerned
5 about avoiding that or developing -- even if you
6 were able to desensitize them, you'd be concerned
7 about the longer-term effects of, say, nephrosis in
8 those patients.
9 DR. LOZIER: Was there any evidence for
10 complement-mediated problems with that, that you
11 know of?
12 DR. SHAPIRO: It was just a 10-minute
13 abstract, but it was Dr. Montgomery's group, who I
14 think is gone now. But no, there wasn't anything
15 that was presented.
16 DR. LOZIER: I guess a similar question
17 would be, for factor VIII inhibitors, we think that
18 continued exposure to factor VIII is usually okay
19 because it's a non-complement fixing IgG4 antibody
20 most of the time. But would you worry about
21 something about gene therapy could change the
22 subclass to one that fixes complement or causes

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1 problems?
2 DR. SHAPIRO: It hasn't seemed to be a
3 problem in those patients. Even those patients
4 undergoing standard immune therapy with very high
5 doses over very long times have not had that. So
6 it's been a rare patient who's had what we'd call
7 an infusion reaction in that category, whereas it's
8 far more common in factor IX.
9 DR. LOZIER: I did have a question for Mark
10 on the AAV story. You made the point that the
11 promoter, the alpha antitrypsin promoter, you
12 called a weak promoter. But it's a strong promoter
13 in liver, is what I thought I understood. Or is
14 that not really so?
15 DR. SANDS: I mean, everything is relative.
16 Relative to the chicken beta-actin promoter, it's a
17 weak promoter. Anybody who does this sort of work,
18 the CBA promoter, if you wanted to direct very high
19 levels of expression, that would be the promoter
20 you would choose. And very much like Chuck, we've
21 done some direct comparisons with CBA versus
22 alpha 1-AT promoter. It's 5- to 10-fold weaker

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1 than the CBA promoter.
2 DR. LOZIER: So I guess, if I was
3 summarizing your talk, it seems like you've
4 identified a signal that may be species specific,
5 has a prototypical integration in the mouse, in the
6 Rian locus, which is not found in humans or
7 non-human primates, but there can be random
8 integrations that, so far, are not associated with
9 hepatocellular carcinoma that we know of, at least
10 with 5 or so years of follow-up.
11 Is that about right?
12 DR. SANDS: Yes, that's correct. One thing
13 that is pan species, if you will, for all the
14 difference species that have been injected with
15 AAV, the people that have looked have seen unique
16 integration sites throughout the genome. The data
17 in the mouse, in the Rian locus, it's the only
18 example where there seems to be -- and I'm not even
19 sure I want to call it directed, but there's a
20 focal integration site. But if you look through
21 the mice as well, in the young adults, the genome
22 is littered with integration sites.

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1 DR. GEORGE: Bindu George, FDA. I had a
2 question for Dr. Sands. You mentioned that the
3 vector was rearranged in I think it was the mice
4 studies. Was that also observed in the non-human
5 primate studies?
6 DR. SANDS: I don't know. They didn't
7 evaluate it that carefully. They were simply
8 looking for unique integration sites, but there
9 were so many of them, they didn't do a detailed
10 analysis on what the structure of the vector is.
11 Honestly, it's one of the major questions I
12 have. I've never been able to get funding to look
13 at it. But one question I have is, when we're
14 seeing all these integration events, is it an acute
15 event; in other words, immediately after or within
16 a week or two after the injection, is that when
17 these integrations occur? Or as these stable
18 episomes sit around for 6 months, a year, 2 years,
19 5 years, is there some rate, continued rate, of
20 integration? In other words, again, acute versus
21 some continuous rate of integration as time goes
22 on?

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1 I think it's an important question. I
2 don't know the answer. Nobody's done that
3 experiment.
4 DR. GEORGE: I had a follow-up question to
5 that. In terms of detecting insertional
6 mutagenesis and using the PCR, what would be the
7 implications of this information?
8 DR. SANDS: I'm not sure I understand your
9 question.
10 DR. GEORGE: So if you're trying to look
11 for these insertional mutagenesis, you're using a
12 certain sequence, and you have a vector
13 rearrangement here. How useful would the PCR
14 probes be?
15 DR. SANDS: Well, it depends. I don't
16 think there's enough information out there to give
17 you a good, firm answer on that. In the mouse, all
18 the junction fragments we've ever pulled out have
19 been rearranged vectors, and primarily it's the
20 5-prime inverted terminal repeat that seems to get
21 integrated, along with all the CIS-acting elements
22 there.

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1 Are we going to see the same thing in the
2 dog, the primate, in humans? I don't know.
3 DR. GEORGE: Thank you.
4 DR. LOZIER: So we have a question at the
5 microphone. Could you go ahead and identify
6 yourself?
7 DR. BAFFI: Yes, Robert Baffi from BioMarin
8 Pharmaceutical. I have a question for Dr. Sands.
9 You didn't mention what production cell line system
10 you used to produce your vector. And did you have
11 a chance to evaluate if there was an impurity that
12 might have facilitated the integrations you were
13 seeing coming from the cell line that you used to
14 produce the vector?
15 DR. SANDS: Sure. It's an important
16 question. Our initial observation, again, we made
17 back in the late 1990s, and we were making our own
18 virus at that point. I don't know if you remember
19 the technology from back then, but it was a
20 transfection and then an infection with adenovirus,
21 and then this very laborious purification process,
22 which of course would increase the chance of some

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1 sort of contaminant.
2 When we first reported this, that was the
3 general consensus, that we had some sort of garbage
4 in our prep, and it very well could have been. But
5 since then, we've been having our
6 vectors -- because it's cost efficient for
7 me -- made either at the University of Florida,
8 Vector Core, or at University of North Carolina
9 Vector Core, which uses a column purification.
10 It's a mammalian system. What contaminants
11 are in there? They do SDS page at the end, and it
12 looks pretty pure. I'm sure there are things in
13 there that we don't know what are in there. It's
14 certainly not GMP-grade material. I'm not sure
15 that helps at all. I think it's good quality
16 material.
17 But the other reports that I've mentioned,
18 Chuck Venditti's report, the Sandhoff mice, the
19 ornithine transcarbamylase animals; all of those
20 vector preps were made in different facilities. So
21 if it is a contaminant, it may be a common
22 contaminant. I don't know. But whatever it is, it

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1 will come from multiple production facilities.
2 DR. BAFFI: If I could just follow up, are
3 those other preps made from mammalian cell lines as
4 well?
5 DR. SANDS: As far as I know, yes. I don't
6 know exactly, but most of them are made from
7 mammalian preps.
8 DR. LOZIER: We have a question over here.
9 MALE AUDIENCE MEMBER: I have a question to
10 Dr. Shapiro. We shortly discussed about use of
11 gene therapy in the patients with an inhibitor.
12 Since inhibitor formation is really mediated by the
13 T-cell responses, it's highly possible if in the
14 liver cell -- factor VIII is produced in the liver
15 cell. It's highly possible the T-cell really
16 recognized factor VIII-producing hepatocyte, and
17 it's a kind of undesired adverse cytotoxicity.
18 What do you think about that possibility,
19 and what is your opinion about that one?
20 DR. SHAPIRO: If I understand you, you're
21 asking, in patients with inhibitors who underwent
22 gene therapy, could they suffer hepatotoxicity

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1 because of the recognition of the T-cells against
2 the hepatocyte?
3 MALE AUDIENCE MEMBER: Right, because the
4 T-cell would recognize a factor VIII peptide, and a
5 hepatocyte makes a factor VIII molecule. And
6 through the ATC molecule, factor VIII peptide can
7 be exposed, so that kind of situation.
8 DR. SHAPIRO: I guess I don't know the
9 direct answer to that question, except that it's
10 not expressed on the surface of the cell. It's
11 secreted by the cell when you undergo gene therapy.
12 And in the dog models that have had inhibitors who
13 have undergone gene therapy, that has not been the
14 case. They've had the typical type of
15 transaminitis in the early period that's been
16 steroid responsive.
17 DR. LOZIER: Do we have other questions?
18 Yes, Dr. Pipe?
19 DR. PIPE: Steve Pipe from the University
20 of Michigan. My question is for Dr. Heller, how
21 the timeline for the evolution of a pathologic
22 event like hepatocellular carcinoma would influence

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1 the approach to surveillance.
2 If we're talking something that would be a
3 30- to 50-year timeline, something like that could
4 never inform the current therapeutics that we're
5 using today. So even if we pursued a pattern of
6 surveillance, by the time we actually got an
7 answer, we almost certainly wouldn't be using the
8 current therapeutics that we are today.
9 So is there a window of time -- and I
10 wouldn't limit this just to hepatocellular
11 carcinoma. I would just take the data on a
12 multiplicity of integration events and whatever
13 pathologies could come from that.
14 Does there have to be some sort of
15 practical timeline for which events have to happen
16 for a focused surveillance program to really
17 produce something that is really actionable?
18 DR. HELLER: I think there should be a
19 timeline. If it's 50 years, that would be great,
20 for something adverse to happen?
21 DR. PIPE: We're talking about bringing
22 regulatory programs before a regulatory review, and

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1 then also at a community level making decisions
2 about embracing gene therapy. And I guess my
3 fundamental question is, in what window of time
4 would we have to find a pathology in order for it
5 to actually inform what we're currently doing
6 today?
7 We already have gene therapy programs that
8 are 8 years out in humans. You mentioned some of
9 the dogs. I mean, as far as we know, all the dogs
10 that have undergone gene therapy have died of old
11 age or have been put down because of old age with
12 no known pathologies from integration events.
13 If we're going to impose postmarketing
14 surveillance on gene therapy programs, does there
15 have to be some window of time where these events
16 have to occur? Or else it's just not going to be
17 useful. How could it possibly change the course of
18 what we're doing if it doesn't occur within a
19 certain window of time?
20 DR. HELLER: Yes. So on my second-to-last
21 slide, I had the word "time." I agree the time to
22 develop something is important. If you don't see

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1 it within 10 years, and by then, as you mentioned,
2 technologies will be completely different -- this
3 is something we'd answer as -- I'm not on any
4 regulatory committee, and I'm not making any
5 decisions. I'm a hepatologist. I would imagine
6 that would be really important and would change
7 your approach to surveillance, and you'd be far
8 less concerned in humans if that's the pattern that
9 you saw. But until you have some data, are we
10 reluctant to say there's no concern?
11 DR. PIPE: And actually, I will get back to
12 one of your points you made in your slide. You
13 indicated that do-nothing was not an option, and I
14 guess it depends on what the do-nothing is.
15 So we have longitudinal close follow-up, at
16 least by our measures in hemophilia, through the
17 comprehensive hemophilia treatment center programs,
18 which have been in place for decades. That already
19 is a mechanism of surveillance in our population.
20 It's how we identify when new things that were
21 unexpected occur in our population of patients, and
22 then we can determine what actions are appropriate.

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1 I wonder if -- it's not just gene therapy,
2 but all of the new therapies we talked about today,
3 it's very difficult to impose some sort of a window
4 of postmarketing surveillance that is likely to
5 capture all potential pathologies that could come
6 from this paradigm shift.
7 It may be that it's not actually doing
8 nothing, meaning that we're not doing regular
9 ultrasounds, et cetera. But it's at least
10 something, that if these patients maintain
11 engagement through what we call surveillance
12 systems in our hemophilia treatment centers, which
13 will continue hopefully in perpetuity, that's at
14 least something and it's more than nothing.
15 DR. HELLER: I would say that that's not
16 nothing.
17 DR. PIPE: Yes.
18 DR. HELLER: I would strongly argue that
19 that's a very active process. Someone has to
20 maintain that database. It costs money.
21 DR. PIPE: Yes.
22 DR. HELLER: It takes effort. Someone's

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1 funding that, and patients are actively taking part
2 in that. That's surveillance at the highest level.
3 And if you're saying it goes on to perpetuity,
4 that's incredible. So you're very actively
5 surveying your patients in every single way; then
6 you agree with me.
7 DR. PIPE: I do to a point. It's whether
8 we're going to --
9 DR. HELLER: Do an MRI or put them in a
10 database?
11 DR. PIPE: Exactly.
12 DR. HELLER: I understand what you're
13 asking.
14 DR. PIPE: And we could cherry-pick assays,
15 which may or may not be relevant.
16 DR. HELLER: Yes. So you could argue you'd
17 come up with something that for the first 5 years,
18 we'll do ultrasounds and the first 10 years, we'll
19 do MRIs. I don't know. I was careful not to come
20 down one way or the other. You can make that
21 argument, and at a certain point stop, and then
22 just follow your database.

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1 That's reasonable. I think that in
2 hepatitis B, you start to see cancers in childhood
3 and people who were neonatally infected
4 horizontally from their parents. So I think that
5 if you have a reasonable window of time, which is a
6 separate discussion, you can then say let's put
7 them in this active surveillance in every single
8 way, which has been carefully considered and adapt
9 it to what we find, I think that's a very
10 reasonable approach.
11 DR. PIPER Thanks.
12 DR. HELLER: I wouldn't argue with that.
13 DR. LOZIER: So this is the regulatory
14 conundrum. We have products with a lifecycle, and
15 we're talking about kids or older kids. And maybe
16 if we follow the adults for 10 years, we're not
17 going to use that vector. And that's the problem.
18 I think I would be very nervous
19 about -- and this is just my own personal; this is
20 not an FDA-approved opinion. But it seems
21 reasonable not to think about AAV gene therapy for
22 young children. And you can define that as

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1 whatever you want; less than 4, less than 6. If
2 you're 17 or 18, maybe that's a different
3 discussion altogether.
4 But that's the problem we have. We do have
5 people saying let's go do gene therapy in the older
6 adolescents. And as you might guess, the number of
7 patients available for adults who are willing to
8 participate in a trial who aren't on 3 other trials
9 already; there are not very many patients. They're
10 not out there in droves, waiting to sign up for
11 things.
12 So that's our problem. That's why we have
13 these workshops, to discuss some of this.
14 I think, at this point, we can move to the
15 wrap-up. We're running over time, but we don't
16 have to spend the entire allotted time for the
17 wrap-up. Ann Farrell couldn't be here, so Lori
18 Ehrlich was going to come up and take her place.
19 Thanks to our speakers.
20 (Applause.)
21 Wrap Up
22 DR. LOZIER: I'm asked to make an

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1 announcement that you should find a video replay of
2 this conference, along with the speaker's
3 presentations, in about two weeks on the workshop
4 webpage.
5 I've been taking notes, and I have probably
6 40 or 50 slides here of things. We're not going to
7 read through them all, but I just think we could
8 sort of recapitulate some of the things that came
9 out of the different sessions.
10 Since I've been taking the notes and you're
11 filling on short notice for Ann, I can sort of lead
12 this, and you can stop me if you see something that
13 interest you.
14 I think, certainly, from Dr. Ragni's
15 overview, we saw that newly approved drugs such as
16 emicizumab offered the advantage of non-intravenous
17 injection and infrequent dosing compared to
18 standard factor treatment over conventional factor
19 treatment with or without inhibitors.
20 Fitusiran and gene therapy, which are
21 treatments in development, offer novel alternative
22 pathways to hemostasis or at least a one-time

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1 treatment in the case of gene therapy. And the
2 cost of these treatments will all be high, but the
3 cost of treating hemophilia by standard care is
4 also high to start with.
5 We have to worry, as the FDA, about
6 long-term toxicity, drug interactions, and
7 particularly about hepatotoxicity, because the
8 liver is our favorite organ, at least in
9 hemophilia.
10 For session 2, I think Dr. Montgomery's
11 talk was particularly critical because it pointed
12 out what I would call the physiology of
13 factor VIII, not just the synthesis. It's made,
14 and it has a certain length, and it interacts with
15 factor IX, but where is it stored; how is it
16 released?
17 I think it does lead a little bit into the
18 question of, the factor level associated with
19 replacement therapy or gene therapy when it's made
20 in a non-endothelial cell, is that going to have
21 equal hemostatic efficacy to somebody with mild
22 hemophilia who may have a mutation but has normal

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1 stores of factor VIII that can at least translate
2 increase under stress? I think that's an open
3 question, but one we have to think about.
4 It's convenient that factor IX is normally
5 made in hepatocyte, but we are talking about novel
6 variants such as the Padua that has about an 8- or
7 9-fold specific activity increase over the
8 wild type where we have other issues.
9 I think it's also important that there is
10 the interaction with von Willebrand factor and
11 collagen in the subendothelial matrix, where there
12 may be, if not reserves, at least a local
13 concentration of factor IX that occurs at the site
14 of vascular disruption.
15 I think Dr. Manco-Johnson's discussion and
16 presentation -- I think the analogy between the
17 CRPR of oncology is actually an interesting one.
18 What we would hope for in hemophilia is, just as
19 somebody with cancer would hope for total
20 eradication of a disease and all of its associated
21 pathologies, we would hope with gene therapy or
22 novel treatments, whether it's emicizumab, or

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1 fitusiran, or any other product developed in either
2 center, that we would not only restore a factor
3 level, but also at some point prevent any joint
4 damage.
5 I think earlier is better, but we have the
6 conundrum and we don't want to take the current
7 gene therapy approaches into young children. So
8 the charge to the hemophilia providers is to take
9 care of these kids with the best treatment you can.
10 Preserve their joints until they can sign up for a
11 trial at age 18, or 16, or whatever we decide is a
12 reasonable thing to do.
13 I was struck by recent presentations at ASH
14 talking about biomarkers relating to bone
15 destruction and collagen markers that could be
16 perhaps followed. It's speculative to say whether
17 that's a necessarily useful thing that we will be
18 asking people to do, but it's something to be
19 thought of.
20 I think the subclinical bleeding is a major
21 problem. It's interesting to see that ultrasound
22 seems to be adopted by most of the hemophilia

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1 providers much more. It was really unheard of when
2 I was at UNC during training there. But it sounds
3 like many of the providers are doing this on a very
4 regular basis.
5 Then we get into discussions of what should
6 be the trough levels, and this has obviously
7 evolved over time. When I was writing papers about
8 gene therapy, again, it was 1 percent and we've got
9 something to hold on to and something to offer.
10 Now, we would just say that's just not worth
11 discussing.
12 Over time, the debate has shifted, in part
13 facilitated by the fact that the vectors and the
14 constructs in the gene delivery systems are so much
15 better now. We're even now worrying about having
16 suprathreshold factor VIII levels, which is a
17 good place to be in.
18 But I think the problem then comes back to
19 the kinds of issues that we saw in session 4 about
20 the factor activity assays because, at the FDA,
21 eventually, we help sponsors write a package insert
22 or label -- and there won't be a package insert in

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1 a bottle, I don't think, but there will be a major
2 instruction manual that goes with these products.
3 So the question is, how much vector do you
4 get to get what target dose without getting too
5 much? And I think, an interesting question is if
6 we target 100 percent and we're getting some people
7 at 200 percent because of variations in just the
8 interpatient response to the vectors and then the
9 question of the assays, we worry, then, will we
10 have a problem where we are promoting thrombosis,
11 at least in the long run? Because people in the
12 highest deciles of factor VIII or factor IX are in
13 increased risk for thrombosis.
14 We never thought we'd have to worry about
15 that problem 15, 20 years ago, but that's of
16 concern. And that's part of the issue with the
17 factor assay discrepancy question that we have to
18 think about, is if they're within 20, 30 percent,
19 we really shouldn't bump up against any ceiling. I
20 think, as Dr. Pipe says, it's much more important,
21 what these troughs are, because troughs are what
22 kill you.

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1 I guess maybe a question I didn't want to
2 pose at the time of the factor sessions, or the
3 assay sessions was could we contemplate instead of
4 looking at factor levels with 10 different
5 standards and three different methods that all have
6 to be cross-validated, just something to consider
7 is whether some global assay for hemostasis like
8 thrombin generation or old-timey things like
9 thromboelastography could be considered.

10 I know that everybody says, "Not TEGs.
11 Those are terrible," but thrombin generation might
12 be something useful to think about. But we still
13 have to work on getting these assays to the point
14 where we think we know which is the right value,
15 and particularly at these low levels.

16 I think, in the PRO session, I was
17 particularly struck by the skepticism of many of
18 the patients who fill out these PRO rating
19 instruments about, well you know, maybe it's a bad
20 day and I need to get out of here, or there's not
21 enough time, or the question is not pertinent to my
22 particular situation, or I have a joint and there's

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1 not going to be any point in talking about pain in
2 the replaced joint, that sort of thing.

3 Clearly, those instruments may need some
4 work to make them more relevant to the hemophilia
5 community. I think that's actually an interesting
6 set of observations we had from our patients.

7 Regarding our last session, session 5 on
8 the two main topics, when do we go to kids, kids
9 being maybe older adolescents, and the question of
10 what should we do about the theoretical risk for
11 hepatocellular carcinoma, these are sort of our
12 hardest questions as regulators.

13 Certainly, with going into kids, we have
14 the ethical and regulatory question, but then
15 there's a practical, are the 17-year-olds,
16 16-year-olds, are they practically adults? But do
17 we know what the long-term outcome is going to be
18 with respect to long-term toxicity, particularly
19 hepatotoxicity and hepatocellular carcinoma?

20 This really is a question that makes it
21 hard to know what to do. It makes it easy if
22 you're talking about a 2-year-old, but if you're

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1 talking about a 16-year-old, it's encouraging that
2 we haven't seen hepatocellular carcinoma in any of
3 the patients that had been treated with gene
4 therapy, but I don't know that even 10 patients
5 have been treated in all the trials. Somebody
6 could look that up.

7 But we don't know what the risk is, and we
8 don't know -- if we have no events out of a small
9 denominator, it's very hard to set a risk rating,
10 but that's something we have to bear with.

11 Lori, do you have any comments on any of
12 the sessions? I'm sure you had some observations.

13 DR. EHRLICH: I think, instead of kind of
14 rehashing each session, which I think Dr. Lozier
15 did a good job of recapping all of those things, I
16 just wanted to point out that a lot of these
17 topics, we could have devoted a full day to or
18 certainly a lot more time than we were able to
19 devote to it. There were some questions, I know,
20 on Slido that we weren't able to get to.

21 We hope to use this as a starting point for
22 all of these issues, and kind of where can we go

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1 from here, and how can we improve in hemophilia
2 drug development. So we at the FDA look forward to
3 further conversations with all of the stakeholders
4 who are involved, where we can use the information
5 that we learned today, and bring that back to our
6 work, and hopefully some of your work as well, that
7 we can improve the way that we are developing novel
8 drugs in hemophilia.

9 Then lastly, I just want to thank everybody
10 that was involved in the session, certainly the
11 patients and the advocates that were able to come
12 today and share their perspectives. I think they
13 had an invaluable perspective on what we do here
14 and where we're potentially missing the mark, and
15 how we can improve things moving forward, but also
16 the clinicians, and researchers, and commercial
17 sponsors who were able to kind of come together and
18 put forth some new ideas.

19 Adjournment

20 DR. LOZIER: I think we also need to thank
21 Joan Todd and Valerie Vashio, who have been our
22 support staff and have sent out thousands of

1 e-mails, literally, to many of the participants and
2 kept the trains running on time here, and making
3 sure that everything was arranged, and the people
4 arranged travel. I also want to thank the Oncology
5 Center of Excellence for sponsoring this workshop.

6 I think at this point, we can conclude, and
7 everybody can try to catch their flights to get out
8 of here. Thank you very much.

9 (Applause.)

10 (Whereupon, at 4:30 p.m., the meeting was
11 adjourned.)

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