Accelerated Approval Program
30 Years On: Insights and Experiences

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Meeting Transcript

Welcome & Opening Remarks

Susan Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Good afternoon, everyone.

Welcome to our virtual public meeting to talk about the accelerated approval program at the Food and Drug Administration.

My name is Susan Winkler, and I serve as the chief executive officer at the Reagan noodle foundation for the FDA and we are so pleased to host today's event.

I'm going to go through a couple of housekeeping announcements, just to take us through the next few hours.

I'll note that, because of the meeting size attendee cameras and microphones will remain off throughout the meeting.

Also note that the workshop is being recorded and that provides us the available the ability, rather, to have the slide deck.

The recording and the transcript available on the Reagan udall foundation website on Monday that is Reagan you'd all.org.

Also, then let's talk a little bit about our agenda, we have the next three hours packed for you.

And so, a quick overview and highlight, we are going to start with an presentations from FDA to look back at the last 30 years since the accelerated approval pathway was created by Congress.

Ben we're going to turn to learn about the real world implications of accelerated approval from patients, as well as in a discussion with providers payers and regulated industry.

Now, as we jump into this discussion, I want to walk you through a bit of a visual to ground us all in what it is that we're going to talk about in the accelerated approval pathway so today's discussion we go to the next slide.

is about, there are many we know there are many different ways to expedite the review of drugs and biologics and and other regulated products at FDA.

But today we're focusing on specifically the accelerated approval pathway.

Now this here is something that we call an infographic at the foundation, but we recognize that it's an infographic for those who are deep in.

The understanding of various FDA processes, but it's structured here to help us compare the traditional pathway for approval and then to see how that might compare timing wise in process wise with the accelerated path.

So this is just a visual way to think through what we'll be talking about in the next three sessions.

One note and you'll hear this again and again, but to remind us that accelerated approval uses an identifiable surrogate endpoint.

That's considered a reasonably likely to predict clinical benefit so, for example, and oncology the surrogate endpoint maybe tumor shrinkage which is reasonably likely to predict increased survival.

So this will be posting this infographic and kind of walking through things to better understand how one moves through the process, but you move from left to right.

In having the application come through the Agency and then you'll see well, you have confirmatory trials that are required FDA review and then.

Have those confirmatory trials and then either a stay on the market and convert to a conditional approval brother to a full approval or to be withdrawn from the market or have the indication removed from the labeling So this is the rough high level non-FDA visual to show what it is that the agency walks through so for all of our visual learners that you have a bit of a sense of how to walk through each of those processes.

With that I'm going to step out of the way to turn to the official discussion and presentation, where we will hear specifically from three experts at the Agency to talk about the accelerated approval process origin to now here 2020 to 30 years later, so our first presentation will be from Dr Jacqueline Corrigan cry, who is the principal deputy Center director at the Center for drug evaluation and research at FDA.

Dr Corrigan cry would you come on camera and unmute so that we can hear from you and introduce us to this first part of our programming.

Accelerated Approval 1992–2022

Accelerated Approval 30 Years On: Lessons and Next Steps

Jacqueline Corrigan-Curay, JD, MD, Principal Deputy Center Director, Center for Drug Evaluation and Research, FDA

Failure or Success, Results are Essential

Kevin Fain, JD, MPH, DrPH, Senior Policy Advisor, Office of New Drug Policy, Center for Drug Evaluation and Research, FDA

Accelerated Approval in Oncology: 1992-2022

Gautam Mehta, MD, Clinical Reviewer and Medical Officer, Office of New Drugs, Center for Drug Evaluation and Research, FDA

Jacqueline Corrigan-Curay, FDA

Great Thank you and welcome everyone I’m trying to take control and I’ll start my slides, I just want to thank everyone for for coming and joining us for this review.

of accelerated approval and where we've been and i've also wanted to thank our panelists for coming and sharing their time and expertise and especially to our patient panelists who really has agreed to come here and share some more personal experiences.

And they Thank you Susan and everyone at the Reagan udall foundation we've made this possible.

I am the as Susan said, the principal deputy Center director for the Center for drug evaluation and research, but as I go through my slides.

What you'll see is really applicable not only to the Center for drugs, but also to our Center for biologics so let me sorry and.

Sometimes the technology gets ahead of me okay so let's jump in here what i'd like to do is just spend a couple of times a minute, making sure you understand just the drug approval standard and sort of endpoint.

As for all of our approvals and then we'll jump in a little bit more deeper dive on accelerated approval, which is what we're here to do so.

To approve a drug FDA needs to find that first there's substantial evidence of effectiveness.

And the statutory definition of substantial evidence is that we have adequate and well controlled investigations, including clinical investigation.

That on the basis of which is fairly and responsibly be concluded by such experts that the drugs.

will have the effective reports or is represented to have under the conditions of use prescribed recommended or suggested and subsequent court cases have confirmed that the experts who make that decision on substantial evidence is the FDA.

that's not the only thing we need, we then need to go and make sure that we're approving a drug, whereby the benefits of that drug outweigh the risk so it's a two part standard what will be really focusing on is that first part and that Evan.

So let me go to my next slide.

So the most straightforward, of course, when we approve a drug we're looking at is that drugs affecting

And that may be a very straightforward assessment on something that we can all agree, improve survival.

or reduced occurrence of some events that we think will will decrease survival, you know multiple hospitalizations organ failure.

or and a little bit more challenging can we really have a measurement of how the patient feels or functions and often.

For some diseases that are chronic and have progressive it means we have to develop a detailed step by data driven approach to ensure that whatever endpoint is measuring aspects of the beach or to patients.

are sensitive to change with the interventions and provides an accurate and reliable assess cross population.

So we developed those clinical endpoints so when you look at different diseases, sometimes trying to get the evidence and better drug will.

make an impact on some of these endpoints can take a while, but it's important.

Nonetheless, for certain serious and life threatening diseases, without adequate therapies, we know that there's an urgency to get effective and safe therapeutics to patients.

And, in certain cases, if we have sufficient understanding of the disease, we can identify a surrogate endpoint or an intermediate clinical endpoint.

That occurs earlier in the course of that disease and it's not a clinically clinical outcome per se, but it is predictive of that clinical outcome.

And what that does is it creates an opportunity for a more streamlined development program by enabling trials that can be shorter and, in certain cases, smaller and then what we can get is, we can get greater access to the drugs as we confirm benefit.

So let's talk about surrogate endpoint when we're using surrogate endpoint we're usually talking about a lab measure, a radio graphic image a physical sign or other measures.

The end of itself, as I said, is not a direct measure of clinical benefit, but is predictive and the data that supports that conclusion that linkage.

It can be epidemiologic therapeutic passive physiologic or other scientific evidence and often it's more than one and the way that we use a surrogate endpoint in approving a drug really depends upon the left, the strength of the evidence.

So, in certain cases, we have what we call validated surrogate we have sufficient evidence that we know that that marker is going to predict clinical benefits so, for example, we know that if we keep your blood pressure at a.

Good you know 120 over 80 or less we're going to reduce your risk of stroke, we don't have to run a

And look for stroke, we can look at blood pressure, we know that forced excretory volume and certain pulmonary diseases is going to predict clinical benefits.

In other cases where we have some evidence it's robust evidence, but it's not quite certain evidence is what we call reasonably likely and in those cases.

It is what we call it is a surrogate as we might use an accelerated approval for like total kidney volume and polycystic kidney disease or clearance and amyloid plaque in old timers which we recently used.

So what we have is two pathways that we can use, we can use what we call traditional approval and that's where we're going to rely on a clinical endpoint or validated surrogate if one's available.

But if we have a reasonably likely surrogate or an intermediate clinical endpoints we can go down the

To find out a little bit more.

So this is what Congress told us they told us that and repetitive what i've said that for those series and life threatening diseases.

If you have a surrogate is reasonably likely to predict clinical benefit or clinical endpoints its measured early than irreversible morbidity and mortality.

You can make this approval under accelerated approval, taking into account the rarity to be already prevalence of the conditions and the availability, or lack of alternative treatment, so this is not used in every case.

Congress also put some limitations on the use, it said the approval of products under this subsection may be subject to one or both of the following requirements.

One is that the sponsor conduct appropriate post approval studies to verify the describe and describe

And to that the sponsors to make copies of promotional materials related to the product i'm not going to read everything during the pre approval review period and following approval for such period.

FDA routinely requires us post approval studies we know we need to verify that benefit, and we do do special review promotional materials.

So the framework we operated on allows us to approve a drug for serious and life threatening disease for which there are not adequate therapy.

Based on adequate and well controlled clinical trials or clinical investigation, so the same ones, we would do for traditional approval that demonstrate, now that the drug has a significant effect on either the surrogate endpoint reasonably likely or this intermediate clinical and.

What does that mean that means that there is going to be uncertainty regarding whether the drug will actually impact a clinical outcome at the time of approval.

Such uncertainty is resolved with a post approval study that was conducted and uncertainty, by definition, means that not every study will confirm benefit.

So failure to confirm benefit can result in withdrawal the drug now, you may ask why would we subject those with the most serious life threatening diseases to uncertainty.

You must remember that accelerated approval is only going to be used when there's an assessment that there's not an adequate available therapy for these diseases and so when we look back at 30 years of accelerated approval we might want to look and remind ourselves how we got here.

So this was the beginning right, this was the AIDS epidemic when you know we really didn't have treatments and in 1992 after the first approval of an HIV drugs.

We issued accelerated approval regulations and then approved under accelerated approval, the first drug downside of being for HIV and now in December 21 he has 307 accelerator approvals across descending for drugs and the Center for biologic.

And let's make this a little bit personal this was actually recently published in the New York Times by Dr Greg and solace I hope i'm pronouncing his name correctly.

He wrote an opinion piece about the danger declaring the pandemic over too soon.

But you wrote about the early 90s, and being in many ways the most terrible their first years of the AIDS epidemic.

and research on the diseases in high gear, but drug after drug fail to stop HIV funerals for friends and families and their 20s 30s 40s and 50s continued unabated.

And many of us at risk for getting sick have given up hope with normal life, my friends and i'm most of us were a few years out of college living in the moment because we weren't sure how much time we have left.

He told of his cousin Carl dying of AIDS in 19 lymphoma and in 1995 and he himself finding out who is HIV positive and wondering what his fate would be.

And then he said about getting lucky, then in 1996 a new generation of treatments called protease inhibitors emerge and were able to control HIV.

and doctors talks about the Lazarus effect washing their patients go from your desk to help.

The protease inhibitors that were approved under accelerated approval in 1990, and this was when you know access was done earlier until we validated the surrogate endpoint for HIV that we're using at that time viral load, this is not all the drugs approved under accelerated approval and the timeframe, there was others from other classes for these purposes slide I just didn't see the previous.

So our requirements are originally likely surrogates which requires that robust data set to use port that it provides a clean clinical benefits of postmarketing confirmatory trial to verify the anticipated clinical benefits we also require that the indication statement and the labeling disclose that approval is based

We have special review of promotional materials and ultimately approval may be withdrawn and trials fail to verify clinical benefit So where are we.

So this is a snapshot of FDA is accelerated approval and, as you can see, back in the 90s, you can see, this non oncology or in grey in which represents a lot of the drugs for HIV and then sort of an explosion in the accelerated approval for ecology from about 2012 onward and also the mythology.

And when you think about why is that well the key driver was a scientific advancement in ecology.

and understand kinetic molecular and in the tomato Tory drivers in the 90s and 2000s, and my colleague from oncology can speak more to that.

We discovery a molecular mechanisms targeted therapeutic biomarkers for decision making and the establishment of surrogate endpoint that could be used to support approved.

Decisions and many of these drugs are transformative and i've just listed a couple of them, there are many more, but what I wanted to list, as illustrated is what it means for years of access prior to what

So accelerated approval, of course, is not without challenges, everything has challenges I think one challenges, there are many diseases, where we have on the needs that are very serious and life threatening and yet there's sometimes just limited pathogenesis of what's leading to the disease complications and progressions and the data to support.

A relationship between a surrogate endpoint if we can identify one and clinical benefits of women is limited, as well as information and critical to establishing a biomarker.

And, well, we may have animal models that are not fully recapitulated key aspects of it disease or not translational.

They are not mayhem for us in finding the surrogate endpoint that we use so one challenges we may not be able to use it in the diseases, where we know we might like to use it.

second challenge is once a drug is on the market it's a confirmatory trials are not ongoing at the time of approval they're really can be challenges.

To conducting those trials that are needed to confirm clinical benefit because again we're entering this drug in a field where there's on me.

And the framework is built upon around greater access with more uncertainty and there, for we can expect that there will be some failures.

But for diseases, with few or no alternative therapies many patients may feel they are personally benefiting either, and when we have well designed trials, demonstrating know clinical benefit, and there can be toxicity.

And then withdraw procedure which is described and statutes follows the secretary withdraw approval for product approved under accelerated approval using expediting procedures.

as prescribed by the Secretary regulations which shall, including the opportunity for informal hearing as you'll hear from my colleague Dr thing in practice it's really not that it's potatoes and the hearings are not informal per se.

Nonetheless, despite these challenges, I think, overall we're doing good well.

So this is a snapshot of cedar accelerate approvals from 92 to 2021 in the darker blue you see those that are what we call converted, so we have the confirmatory study.

In the light green those are the not yet converted, and you see a sort of focus of like green on the right and the more recent approvals, and then the Turquoise or the withdrawn.

And if we want to look back and say well you know let's look at our older ones have they all been converted.

are not yet converted, I would mention that not everything withdrawn means that it was a failure, some of these, for example, there's a handful in here that are anti biotics that were approved for in relational anthrax and.

There was never a confirmatory study in that setting, which is probably a good thing.

fever i'm sorry.

I just wanted to show some of the statistics are and having trouble with this computer with fever fever, has it has not used to that as much as.

fever, but again, you see a similar sort of pattern the not yet converted or the more recent ones to 18 to 21 and when you look back 10 years 80% converted 7% which is really just one is withdrawn and 7% one it's not yet completed.

So in some I would say accelerated approval continues to be an important pathway serious life threatening diseases with inadequate therapeutic options.

When we've identified an appropriate surrogate that are reasonably likely and as we've seen in oncology and certain other diseases, but it remains a challenge in many diseases with on that needs because of.

The underlying pathology is not well understood and the model to identify surrogates are lacking, we know that was greater uncertainty comes greater risk of failure therapies and where did that line be drawn in terms of reasonably likely.

And we also know that, in the face of on that medical need removing any therapy is challenging.

Finally, a failed study can occur, for reasons that do not negate that the surrogate is reasonably likely, making it even more complex.

But, finally, I think, providing access and completing confirmatory trials expeditiously is how we best serve patient.

I'd like to thank my colleagues for their contribution, and I will turn it back to Susan Thank you.

Winckler

Dr Cork and for I thanks so much for that overview, if I could capture as you were presenting I was thinking through and perhaps one way to think about this is that the accelerated approval pathway presents us with a structure to have deliberate uncertainty is that a way to think about it, that we we know.

we've got uncertainty, but we want to do something, but let's be deliberate about that uncertainty is that way to think about it, I think that is one way of thinking about it, we have some uncertainty, it has to be.

We have some uncertainty with regular approvals, we know that when we go out, we may find safety signals, but we have a little bit more uncertainty.

Here in the relationship between that surrogate and the clinical benefit, and we are taking the deliberate step of going, the next step with a new trial to.

To reduce or eliminate that uncertainty great Thank you so much for that overview and so let's talk about.

Moving past that or how we how we learn more or resolve that uncertainty, and that is through the.

confirmatory trials, and so I have here that we're going to hear now from Dr Kevin Fein who's a senior policy advisor in FDA office a new drug policy in cedar so Dr Fein would you help us a bit with this.

With resolving we have our deliberate uncertainty, then we want to do some work to help us get to.

more certainty, would you pick up the microphone and tell us about confirmatory trial, thank you.

Kevin Fain, FDA

Absolutely happy to do that and i've just put on the screen and outline to help you all see where we're headed in this presentation and I want to echo.

Important, for I said we really appreciate everyone's interest in this topic it's very important, as well as our other panelists, particularly the patient panelists.

But I do want to dig a little bit more into that confirmatory trial step.

And you see here an outline just going to touch on very briefly the regulatory framework which Dr kogan cry nicely walk through but i'll highlight the points that are relevant for the confirmatory trial phase.

And then the second part of the presentation will be thinking about the plan of the consumer to trial, and especially the progress of that trial.

From the point of the approval of the drug through the various timeframes, I will talk a little bit about the reporting of the status of the confirmatory trials to FDA and then reasons for delays.

because those are very important to understand and the third and final part will be looking at regulatory options thinking about those results of the confirmatory trials.

What our options that FDA has, in certain circumstances for involuntary withdrawal or volunteer or withdrawal and we'll talk more about that.

So the regulatory framework i'll just cover this very briefly so just please keep in mind that our overarching level requirements for drugs in section 505 or the.

drone cosmetic act those still apply for accelerated approvals and so it's important to understand that substantial evidence, based on adequate and well controlled clinical investigations of the drugs of fact that's necessary.

For approval, as well as the benefits of the drug outweighing the risks, this is an important part of the capital.

But it's Dr Korean garage try explain, for accelerated approval the effect can be shown on the surrogate endpoint or an intermediate endpoint reasonably likely but.

not known for say to predict benefit and those outcomes that we care about help patients feel function or survive.

And our regulation itself actually notes that there's some uncertainty as to that relationship between the surrogate endpoint and the clinical benefit.

So the confirmatory trials are designed to address this uncertainty and we can require these trials under the statutory framework.

That was mentioned earlier, and our regulations or regulations, interestingly note that sub trials will usually be studies already underway, but that's not always the case, there are exceptions to that.

And the fact that the trials must be adequate and well controlled and by assessing the drugs clinical benefit.

Really, the goal has documented or said, is the goal of the consumer to our trials to address that remaining certainly between the surrogate endpoint the clinical benefit.

And there is an expectation that some of these clinical trials, you know adequately designed and conducted will not confirm clinical benefit of the drive so that's important to keep in mind.

And the completion of the confirmatory trials and the submission of those results it's critical for FDA to understand ultimately that Association and the benefit of the drug.

So let's talk a little bit about that, and the second part for confirmatory trials so taking a step back and thinking about the point of approval of that drug under the accelerated approval pathway.

So that the confirmatory trial is established in that approval.

and specific milestones are laid out so i've listed some here in the sub bullet about initiating the trial enrollment targets completion, and even that final report submission to FDA and i've just given a snapshot here.

Have a sample excerpt from an approval letter, this is all publicly available on drugs that FDA so you and the public can can search for examples.

That you care about but you'll see in this language, the emphasis on due diligence of the conduct of the trial.

As well as the fact that if there's failure to verify political benefit, we do have this option to withdraw what i'll call involuntary withdrawal and i'll talk a little bit more about that.

So just digging a little bit deeper in the approval.

phase, this is the same approval letter but It just shows more details about that confirmatory trial, and this is all again publicly available information, but you see a description of the confirmatory trial, the enrollment criteria.

As well as the endpoint the primary endpoint what's trying to get at that clinical benefit.

And then you see a timeline in place here for the interim report submission and the completion of the trial and that final report submission so that's all laid out in the approval letter and that.

Is track like the the the progress of the trial is tracked.

Through the annual report, so the regulations for accelerated approval fire sponsors to every year in the annual report provide information about the status of the confirmatory trial.

And i've just given you some examples here at the bottom of the slide of that information, the approval rate now, the number of subjects enrolled up to the time of reporting.

The status of the study i'll talk a little bit more about the statuses on the next slide but the completion date.

The final study report submission day that that's a clickable and revised schedule, if the schedule has changed, all of this is being recorded on an annual basis, the FDA for all of these confirmatory trials for tracking purposes.

In terms of the status categories, you see them here it's pretty straightforward it's defined a regulation.

The only nuance is the pending status, that means the study has not been initiated, yet so enrollment has not been done.

But that's still on the timeline for the milestones so it's not considered the late ongoing status means what it says the trial is meeting those milestones and that might even be ahead of schedule.

delayed we'll talk about that more in a moment and terminated as the study was ended before completion and the final study reporting is not yet been submitted to FDA.

The final category of submitted is the study has been completed or terminated and that report has been submitted to FDA.

So what does this mean, so I wanted you to understand in terms of tracking information is available, of

Which is a search engine where you can select accelerated approval for these posts marketing requirements and commitments, there are other options as well if you're interested.

And when you do this and you use this mechanism, you can see more details about these confirmatory trials and i'm sorry I advanced a little too soon.

And what I wanted to do in terms of details, is the way so for some of these trials, the status will be delayed and it's important to understand the hospital reasons for this, and i've listed some here in terms of trial completion, but i'm going to go back.

I apologize so i'm going to focus on trial completion and final reports and mission So these are very important to understand So you see an example in the first bullet.

If that completion milestone was miss because there have been fewer progression free survival events, for example, something that may not have been expected in terms of the planning of that confirmatory trial and it turned out to be the case, as the trial is progressing.

That there were just an inadequate number of events to meet that completion milestone some other examples here the middle bullet.

If the patient's haven't reached the response yet sufficient number of patients in order to make that a meaningful comparison analysis and the final bullet is the same type of theme.

or overall survival, has not yet been reach So these are examples of reasons that were not expected not anticipated that we're causes of the blind.

And, here are some reasons also.

For protocol and enrollment so just thinking about that earlier things, so the protocol example it might be that the initiation of that child is dependent on results from another study and those results have not been transmitted in analyzed yet.

It could be that the company's incorporating feedback from FDA that's another example, and again, all of these are on that search engine in terms of the status of these trials.

enrollment there could be difficulties or challenges not anticipated that will be reported to FDA and, in some cases, the trial could be behind schedule, but it is underway, and in this case, all the patients have been enrolled.

Okay So what about regulatory options so i've walked you through status of confirmatory trials and

What our options for FDA when those results are included and submitted to FDA, especially when we're thinking about results that fail to confirm clinical.

So I apologize these slides are are out of order.

This slide is talking about informal hearing, which is very important point but i'm gonna go back so just bear with me.

and see this slide Thank you so this is a very important point I want you all to understand, so if a confirmatory trial fails to verify clinical benefit.

it's important to consider the reasons for this, and it could be that there are reasons unrelated to the drugs true effect and i've listed some of these here and FDA has faced this and real examples where perhaps the selection of the primary endpoint.

That something about the trial design inability to select the patients, most likely to have a response.

or it could be certain statistical issues i've given some examples here like power calculation.

Those can be driving the results that we see in this stuff inventory trials, but it's not being driven by the drugs through effect.

And so it's important to understand if there are clear reasons why the trial may not have achieved that primary endpoint.

And there's no evidence that that surrogate marker is not reasonably likely to predict medical benefits of our understanding of that association is not change.

And there's still that unmet medical needs for patients with that disease fema work with a sponsor to identify possible additional trial and additional from our trial.

That we think could be adequately designed to address those issues that could then go forward and truly measure, the effect of the drug so that's just something I want you to understand if it's a very important point.

apologize again having some computer issues i'm going to advance this.

Okay, so the first option, I want to talk about is the informal hearing option, so the results that failed in front of the benefit, you cannot see legitimate reasons.

outside of the drugs to affect one of the options to pursue is this withdraw through an informal hearing now it's important to understand.

There are procedures in place for this and there's spelled out in the regulation i've listed that here, in part, 15 of the regulation gives the structure.

For a lot of the steps that are involved for the informal hearing and it's due to contort and nature that's important to understand there's a presiding officer.

But there's also an advisory committee that's convenient to give assistance and console for that hearing officer on the science of addition to.

Some of the features i've listed here that are really important are the starting point.

So the relevant Center could be cedar or seaver they issue a notice of opportunity for hearing the call this no age to get the process started it's the proposed withdraw.

The sponsor at that point in the specifically request to hearing and i'm assuming all the information.

In supportive that request, so the scientific information that they think supports clinical benefit, for

And at that point, there are many steps that FDA goes through, for that hearing and i've mentioned some of them here things like document production.

required submissions advisor many planning and there's other types of procedural issues so it's it's a duplicate tori in nature, and so that involves many steps.

Another option is the voluntary recall, so this would be based on the confirmatory travis results, again, but it could be a situation with the trial is not completed.

So it couldn't be both of those of those situations and if FT determines that their grounds for withdrawal, the agency may ask the applicant to request withdrawal of approval under this regulation that i've shown here, and some people aren't aware of this option it's in pre.

And we do have sponsors, in some cases voluntarily withdrawing approval and there's a process for that.

And it goes through the Federal Register notice so i've just given sample here.

This was an example with a company failed to complete the confirmatory trial for various visibility reasons, all of this is publicly available, you can see other examples of these voluntary withdrawals, let me just giving you one here.

So it's an important mechanism to understand, but it depends on the agreement of the sponsor do that.

Another aspect I wanted to point out for you is that there is publicly available information about these steps so for the advanced and withdrawal and that's on the left hand side, this was a breast cancer indication that there was a proposed withdrawal.

cedar and went through this hearing process that I just described and because of the numerous steps involved.

In the time is confirmatory trial results were submitted it took about two years to the time the FDA, Commissioner, it should the order of.

draw all of the steps are publicly available and what we call the public docket so its own regulations that God, and you can see.

All the submissions from the Center the submissions from the company, the sponsor and then the public has opportunity to go away and as well and submit their.

Scientific and patient foods so it's very important resource to understand for that involuntary withdrawal approach.

The other point I wanted to make is on the right hand side, these proposals to withdraw a drug involuntary withdrawal procedure.

In this case, we can have publication so McCain others a proposal from the Center for drug evaluation and research.

to withdraw that fraud and there's a perspective piece in the New England Journal of medicine from cedar staffers walking through the scientific reason for that proposal, so I just want you to understand there are options for seeing these procedures.

A little bit more information sorry the slides got out of order, this is just an example of the voluntary withdrawal, so that Federal Register notice I mentioned it specifically walks through.

The reasons for the withdrawal and, in this case, it was because the study could not be completed and you see here i've just highlighted the important points about the correspondence that went in with request and ultimately at the bottom, the approval is with john so that's legally effective.

So the final slide I just want to to wrap up so you can see these options to try to put together what I just walked you through.

Thinking about confirmatory trial results and thinking about the regulatory pathways so on the left side, the Left box, where we have the confirmatory trial results in some cases, many cases and see on the far left.

They verified described clinical benefit and so no further action is needed at that point in terms of the confirmatory trial.

But there are situations, you see, on the right side of failing to verify and describe clinical benefit, and the decision point is to think about if another study might be valid.

In that situation and I explained to you some of the reasons why that might be the case if the reasons unrelated to the drugs to effect for why that study they'll do.

Anything but if not, you see, on the right side that what's Raul option and I mentioned the voluntary pathway and involuntary apple.

But I also want you to understand on the right side, what if the confirmatory trial fails to be completed, so we talked a little bit about this, but a decision point there, you see, in the middle box, you have to consider the alternative study design may allow.

needed evidence generation, if there were legitimate reasons scientific reasons why that study cannot be completed and that case another study might be appropriate, but if not withdrawal is also an option in that situation, it could be voluntary.

or involuntary so I really appreciate your time, I hope that was helpful just appreciate your attention to it, thank you.

Winckler

Kevin that was excellent, and I want, I want to kind of take our story Arc here right so.

Jacqueline helped us with the structure and that you know, this is an area where we have deliberate uncertainty, so we set a.

We, we need to make some advancements here but let's have it, but there's uncertainty so let's be deliberate about it, and then I heard you explain.

The disciplined or predefined communication, so we don't just kind of stop at the deliberate uncertainty and the accelerated approval, but we say you need to communicate and continue to do this work and so.

Even though FDA you know monitors all approved drugs in the accelerated approval space you've got this pre defined discipline, communication and action is that is that a fair interpretation.

Fain

Yes, that's right I think that's important with those updates that are coming in, about status so FDA can think ahead.

Especially if things are getting delayed and so that's very important, I know, Dr Mehta is going to talk a little bit more from the oncology perspective on that, but that's an important thing, yes.

Winckler

And then we've got you know so you've got that predefined communication have to be continuing to do the work and then this slide pizza very nicely.

Right like what happens with those confirmatory trial so so when we're working through that process of trying to resolve the uncertainty, you could you know, have the blue.

Excellent right, and then the orange here where maybe it didn't quite work but it might the route might be a withdraw or the route might be to do another study.

And then Similarly, if you just you know for for as the reasons you teed up the trial might not be completed, then you can say all right, maybe we need to revisit that and again collect continue this.

You know collaborative exploration to get us through that valley of uncertainty

Fain

Exactly I like that summary and it's important to stress and I didn't stress this about.

Each approval has unique issues scientific clinical so it's very important to put yourself in the shoes of these decision points of people if they trying to understand the reasons for drug feeling.

benefit and what what could be done and what are the options yeah

Winckler

yeah great.

Kevin Thank you so much for that presentation and, as you teed up quite well we're now going to talk about the oncology experience if folks remember in DR Corrigan crisis.

overview, there was a lot of experience here in oncology and so i'm pleased to welcome.

Dr Gautam Mehta to the the stage and Dr Mehta your your day job is clinical reviewer and medical officer within the office of new drugs at theater would you pick up the microphone and tell us more about the oncology experience with accelerated approval.

Gautam Mehta

Thank you Susan i'm really excited today to discuss how accelerated approval program has been applied in oncology over the past three decades.

And this experience with accelerator approvals specifically and oncology is critical to understanding this regulatory pathway as a majority of these expedite approvals to be granted for cancer indications and I have no disclosures in will not discuss me off label use of products.

See just trying to advance the slides

Winckler

do lower left hand corner in the arrow

Mehta

perfect Thank you.

So today i'll review how the accelerated approval program has been applied to oncology indications i'll go over some of the endpoints that are used to support approval in this pathway.

As well as what happens after accelerated approval is granted.

And then finally i'll introduce an oncology Center of excellence project we launched in the fall on accelerated approval called project confirm, whose goal is to increase public awareness and the transparency of the accelerator approval program for oncology indications.

So Cancer is the second leading cause of death in the US and not surprisingly, then, given the enormity of this problem and the vast majority of accelerated approvals to date have been granted in oncology.

Including over 85% of the approvals and past 10 years this has been made.

Possible in part by the availability of endpoints and oncology that are able to support the requirements of this program which we'll discuss later in the talk.

for providing a path to expedited approval this program balances the benefits of providing patients with cancer early access to potentially life saving products with that calculated level of uncertainty that our other speakers had described before.

And again, as described in the other talks this generally includes initial trials, demonstrating, safety and efficacy of the product for a specific indication, which leads to the accelerated approval.

That are then followed by post approval confirmatory trials to verify a benefit suggested by those initial trials and then, once this is accomplished traditional approval is granted.

So accelerated approval is really an important regulatory pathway in oncology and has been utilized frequently in fact over the past two years, over one third of all oncology approvals were accelerator approvals.

In oncology as the other speakers alluded to many of the studies to support accelerated approval have relied on a response on response rate as a primary clinical trial endpoint.

And this is a measure of how much tumors shrink with the treatment given this endpoint allows for the use of single arm trials with fewer patients and the ability to measure effects earlier than with more direct measures of clinical benefits such as overall survival.

less frequently and in specific cases other endpoints such as progression free survival and disease or recurrence free survival have been used to support accelerated approval as well.

it's it's really important to understand the context of this add that traditional approval in oncology may also rely on response rate and points, particularly with rare cancers cancers with long survivorship cases where the response, or the tumor shrinkage itself.

Is the clinical benefit, such as we've seen with this motive for basal cell carcinoma fetal cell carcinoma in cases where a randomized studies lack ECHO points because, if an inferior existing control are.

Like accelerated approvals these traditional approvals have sometimes also been based on progression free disease free or recurrence free survival.

mean important distinction here is that many traditional approvals and oncology are also or have been based on overall survival, as a direct measure of clinical benefit.

So leveraging these accelerator approval regulations this expedited approval pathway has been applied to 167 oncology indications over the past three decades and during this time, the cancer landscape has expanded significantly.

As Dr Oregon pariah described, including breakthroughs in immunotherapy and precision oncology.

And this has led to really exponential increase in the application of accelerated approval to oncology indications was only 18 approvals or 18 accelerator approvals in the first decade and 112 accelerate

The impact of this really cannot be overstated, as these accelerator approvals have included transformative drugs like leaving that ushered in the era of targeted therapy drugs like Derek.

Mad and velcade the change the field of multiple myeloma and targeted therapies, such as elective and also learned that have revolutionized lung cancer treatment.

And these impactful drugs were approved years earlier than they would have been otherwise, if we use time to verification of benefit based on those confirmatory trials as a measure of when these drugs would have been approved, through a traditional pathway.

For example, this included the approval of gleevec for gastric cancer nearly seven years before traditional approval was eventually granted.

The approval of the immunotherapy drug new volume APP for melanoma over four years before traditional approval is granted.

And the targeted therapy preservative for our positive lung cancers over two years before traditional approval is granted.

And this is really important, because, as not all patients are able to enroll in a clinical trial these accelerator approvals are critical to promoting equitable access early access to these potentially life saving drugs.

As Dr Fain reviewed in.

detail after an accelerator approval is granted it must be followed up by post approval studies to verify that clinical benefit that was predicted by the initial study.

And i'll review this In brief, in the context of oncology in oncology this verification of benefit has often been achieved through randomized trials with survival and points.

or with alternative design designs, depending on the situation, such as additional response rate or duration of response data.

Because it may be difficult to enroll patients in a randomized trial for the exact same indication that the accelerated approval is granted in.

oftentimes accelerated approval is initially granted in a later line or factory line of therapy and confirmatory trials to verify benefit enroll patients in earlier lines of therapy.

This avoids overlap and has the added potential benefit of expanding the indication after the confirmatory trial has been completed.

Once benefit is verified a traditional approval is granted and in oncology this process has taken a median of 3.1 years.

To encourage this timely completion of confirmatory trials.

and building on what Dr fain describe the oncology Center of excellence, has a comprehensive program that monitors confirmatory trial progress if there's time points.

we've also conducted multiple advisory committee meetings on products for accelerated approval to further examine confirmatory data and and or the status of these trials.

And then finally our program includes efforts for tracking and outreach with oncology drug development stakeholders, including patients, as well as educational outreach on accelerated approval which i'll describe a little later on.

Because accelerated approval balances some degree of uncertainty which we talked about earlier, it is expected that this process will not always lead to a verification of benefit.

In fact, if 100% of accelerator approvals were successful than the program would not serve a purpose and regular approval should have been granted in the first place.

In some cases, because of for variety of factors such as enrollment challenges confirmatory trials may not be started or completed in a timely fashion in other cases, these confirmatory trials may simply not been demonstrated clinical benefit.

And in these cases the indication may be withdrawn either voluntarily by the sponsor or by FDA after a public hearing.

And this ladder scenario is time and resource intensive and has taken over two years to complete as Dr pain described in the case of avastin for metastatic breast cancer.

So, so now putting this, all together, we can look at the current status of accelerated approvals in oncology of the hundred and 67 accelerated approvals that have been granted to date 67 of these still have ongoing confirmatory trials or pending verification of that benefit.

100 oncology accelerated approvals, are no longer ongoing and, however, have a final disposition of these confirmatory trials have been completed and verified clinical benefit for 83.

and traditional approval has been since granted for these indications again in oncology this has occurred immediate a 3.1 years after the accelerated approval is granted.

And then finally in 17 cases either the confirmatory trials were not completed with due diligence or did not verify benefit, and these indications were withdrawn.

This last process to withdraw an indication is not automatic and the onus rests on FDA to initiate this withdrawal Program.

The term dangling accelerated approval was coined to describe indications for which confirmatory trials have been completed and fail to verify clinical benefit, but which have yet to been withdrawn.

And so i'll talk a little bit more about this now.

This term has been recently applied to a number of immunotherapy indications for immune checkpoint inhibitors and oncology, and this was a subject.

Three day advisory committee meeting in April of 2021 i'll note, however, that this category of dangling approvals.

Accelerated approval is not limited to immune checkpoint inhibitors and other products have fallen into this category recently we plan to take a similar approach in such cases, including regular public hearings to discuss the status of confirmatory trials.

The immunotherapy indications that were classified as dangling were part of a class of drugs that targeted immune checkpoint PD one and it's like end or target PD l one.

it's important to recognize first that these drugs have been transformative in oncology and have led to 91 approvals overall.

Among these, there have been 38 accelerated approvals 10 of those accelerated approvals, which covered the for drugs listed here were considered dangling with failed confirmatory trials.

In many of these cases relatively low response rates are initially used to support accelerated approval did not translate to survival advantage.

See.

think the slides might be a little out of order that's that's right.

So for these indications were removed by the company voluntarily without further FDA action.

And then the advisory committee meeting I mentioned earlier, was called over three days to discuss the remaining indications after this three additional indications, which are highlighted here were removed.

After the advisory committee meeting one indication pemberley is mad for patients with cisplatin ineligible your affiliate cancer was modified to include a narrower population of patients ineligible for platinum chemotherapy as a whole.

Finally, the last two indications a diesel is mad for patients with cisplatin ineligible your affiliate cancer.

And pemberley map for patients with had a cellular carcinoma that has been previously treated with terrapin it remain under discussion with an ultra with alternate confirmatory trials ongoing, and this is that right sided graph that Kevin is shown earlier.

Overall, this experience has been critical to understanding how accelerated approval should be applied in this novel class of drugs for initial response rates did not consistently predict long term outcomes.

So, in summary, perhaps note therapeutic area has demonstrated the worth of accelerated approval program as well as oncology with the large majority of FDA expedited approval is granted for cancer indications.

Cancer is a significant problem worldwide, and the second leading cause of death in the US.

The use of accelerated approval oncology over the past three decades has been a driving force to maximizing early access to transformative and potentially life saving therapies for patients living with this disease.

This has been supported by endpoints such as response rate their unique toxicology and have facilitated our implementation of this program.

Finally, well, the majority of confirmatory trials after accelerated approval eventually verify clinical benefit and lead to traditional approval.

or proportion will fail to verify benefit, and we need to withdraw the indication it's important to emphasize that this is an expected outcome of the Program.

And as a cancer treatment landscape is constantly evolving in cases such as what we experienced with the dangling approvals and immunotherapy.

provided an opportunity to better understand how accelerated approval should be best utilized in these emerging therapeutic areas, this will help us provide continue to provide early access to important drugs, while minimizing risk.

And then, finally, before I finish, I just wanted to introduce the oncology Center of excellence.

initiative called project confirm this project was launched publicly in October 2021 to increase transparency around accelerate approvals for oncology indications.

The centerpiece of this effort is a curated database of oncology accelerated approvals, which is public searchable and updated in real time.

We also provide general education on accelerated approval program it's outcomes, including answers to some frequently asked questions and a description of the processes.

For verification of benefit and withdrawal that we talked about today.

And this web site is available on the oncology Center of excellence homepage and you can contact us about the project at the email list here, we hope that this will complement programs and meetings such as this one, today, by providing important and reliable information to relevant stakeholders.

And I just like to thank the following individuals for their help for this talk and thank you again to the Reagan-Udall foundation for the option to speak about this important topic.

Winckler

Dr Mehta Thank you, I want to take us so So if I think about how you've taken us on the art, we talked about the structure and the deliberate uncertainty then talk through the disciplined and pre determined communications to work through that that all of which are part of that accelerated approval process and then you've helped us see that practical application.

So a couple questions, based on that it, it looks like as we might expect when you're dealing with uncertainty and then kind of doing the work to work through that uncertainty.

Sometimes you get the answer you expected and sometimes you don't get the answer you expected, but FDA works with both of those situations and and and navigates forward, but is it fair that in both of those situations.

The Agency is learning industry is learning and we're kind of advancing the field overall is is that a way to think about what's happening.

As we have that discipline, communication and the confirmatory trials and continuing to do the work to net to resolve the uncertainty

Mehta

That's absolutely right Susan and I think the dangling immunotherapy indications were really a learning point.

kind of for accelerated approval, overall, and both for FDA and industry, and this was a new field, so there was there's so much to learn, not only from a scientific standpoint but also from a regulatory standpoint and so so it's been.

it's been a great opportunity to provide access to these important drugs early, but at the same point to learn from you know how how these regulatory tools can be applied to to providing that access.

Winckler

So we in order to use accelerated approval, we have to know enough to kind of put the box around the uncertainty is that.

A way to think about

Mehta

I think we, we do have to, we do have to learn from our experience and to continue to use it.

Patient Perspective Panel

Moderated by Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Alberto Rubio, MBA, patient with HIV

Navdeep Singh, PhD, patient with beta-thalassemia

Teonna Woolford, patient with sickle cell disease

Katherine Couvillon, patient with metastatic breast cancer

Winckler

Great Thank you Dr Mehta and in all of our three of our speakers from FDA for taking us through.

That deep understood you know deep education on what it takes what the accelerated approval of 40 is how that structured and what it is that we.

are working with when we talk about the accelerated approval pathway and then also the experience to see how it's been working in the oncology Center of excellence.

That means it's time to move to our second panel, and this is a panel we're going to move from the technical overall structure to the why.

So we talked about the what and now we're going to talk about the why and Why are there situations where we would want to have.

That deliberate you know we've gotten to a place where we have the deliberate uncertainty and we would want to follow this type of path, and so we are going to hear from.

Patients for individuals have graciously agreed to join us and talk about their experience with products made available via the accelerated.

approval process each of them has direct experience and from a different vantage point, and this is one place where i'll say it's it's really.

A benefit of these virtual meetings that we have the opportunity to connect with folks who are all over the country and hear their voices.

without putting kind of the the the requirement for travel and all that that involves and so i'm particularly pleased to move to this next section where.

We are going to turn to these patients to hear directly about their experience.

So we're going to open and I am going to rather than put my voice over any of our individual patients i'm going to ask our patients to.

Introduce themselves as they step up to to tell their story and we're going to start with Alberto rubio Mr. Rubio, you are joining us from Texas, and want to share your experience in thinking through kind of the the patient with HIV so.

I see you on screen and unmuted.

Alberto.

Alberto Rubio

Thank you everyone, and thank you for the gracious introduction to thank the FDA and the Reagan you know foundation know.

Pharmaceutical REPS and other researchers in the audience and from the bottom of my heart, thank you for the dedication and devotion to God meant, not just for HIV, but for so many other diseases your sacrifices have not gone unnoticed, thank you for that.

i'm never was a respiratory therapist in in in early 1980s in Dallas Texas that at baylor medical Center, though.

Probably the ninth largest hospital in the nation at the time I was the icu supervisor and I showed up in ship to get report from the first shift supervisor.

And he said Alberto i've got the damn this case he said this guy came in this morning and gave him a breathing treatment between nine and 10 in the morning.

And he's now in the intensive care unit on a ventilator on on on dialysis he was a nice day suppressors he was on pretty much every machine that we could have in intensive care room and he was 29.

He looked like a strapping model, he was a new yorker who came into the visit a friend for the weekend and he was going to die, we had no idea what was going on.

We had no one, you were there was a virus so was he contaminated with some chemical.

What was it a bacterium and identified know when you anything, and so we put him in isolation, under the strictest isolation and we made some very hard choices about how to treat a deadly unknown.

And that uncertainty is what we referenced today happened with.

It has is that the unknown and how do we call it, how do we make the uncertainty smaller, how can we diminish it so that we know that we are advancing.

And that took sacrifice and my people the gay and lesbian community of data sets that are actually of the nation would not go gentle into that good night.

We were told in the 1980s, that there was nothing that could be done for us and we refuse to believe that.

There were only a certain number of centers in the nation, a few of them think three or four I can't really remember now i'm old but.

We were asking, we were told, we would have to fly to these centers if we were if we were going to be patients involved in clinical studies.

We would have to be taken to the centers we had T cell constantly in a true hundreds, we couldn't go out and crowds we've died from getting a disease just from somebody sitting next to his coffee on the plane.

Worse than that you guys were trying to develop studies with maybe 20 or 30 people and your studies were six to nine months long and half of your study patients would die halfway through it.

limited access to patients, limited access to drugs and we had all these wonderful centers southworth Medical School and parkland in Dallas we had.

San Francisco Chicago there was absolutely no reason to follow the old protocol, the do protocol did not yield easily.

We had that we had die-ins we had to sit on the side lay on the sidewalk chalk lines drawn around us, we had the panels, that the the age panels, where people who had died would make one and add it to to the blankets that were spread out in Washington DC.

But I understand that, in the 1980s, it was a different mindset. HIV was considered by pastors to be a condemnation of a lifestyle. Politicians did not go anywhere near us because there was nothing politically to be gained. I understand that is harsh, but I was there.

And we knew that the population that was that being affected gay men sex workers IV drug abusers are the marginalized minorities who was going to stand up for us.

So we decided to stand up for ourselves, and we made the unspeakable declaration that patients should be involved in the development of clinical research, we insisted upon have.

a seat at the table and when the clinicians rightfully said the researchers this afternoon have told us how difficult it is to design a trial so many things could go wrong with it.

And if we were going to multiply these research centers what we need biotech decisions we've made nurses, we need trained researchers and we would need the space in the hospitals to house them that meant money, so we had to pressure.

The legislators who kept telling us know but we'll have to take money away from cancer.

Research if we're going to do an HIV and our response was why does the pie have to stay the same size, make a bigger pie get more money out there.

And all the time, my brothers and sisters I watched my friends die I watched my friends take that same position as that first man that I treated back in the early 80s and in that patient bed, I saw myself.

I saw myself.

But thanks to the research that came about thanks to people who devoted themselves to.

tweaking AZT to thanks to the incredible biologist who figured out how HIV infected the cell and showed us the different stages that.

individually be targeted with different drugs, we got protease inhibitors and truly I saw last moments I saw the Masters effect.

So, today I want to thank everyone who participated in which made it possible for me to be 68 years old, something that I was told back in 1987 was probably not gonna happen.

i'm Alberto Rubio, I'm a person living with AIDS, thank you for listening.

Winckler

Alberto, thank you for sharing and you illuminated a couple of things for us so let's let's talk about those right you you underscored that participating in clinical trials, is something that particularly that and but still exists today is not necessarily available to all patients right.

Rubio

that's right, it is population centric it's got to be a metropolitan area, you have to have an ability for the patient to get to the Center which means some kind of driving service.

And then someone to pick them up someone could care for the patient that thing that he is if he's if he or she's debilitated yes, there are lots of different steps to getting that patient into the Center.

Winckler

And so, when we talked about you know you heard the discussions about the you know that we tried to go here with deliberate uncertainty.

Part of that accelerated approval is to then make the product more available, while we work through that So how do you think about the you know the impact of.

Knowing that you're using something where there's you know it's it's there's uncertainty with all drugs, but here we know.

We know that it's uncertain, but then you've got the broader access give us a bit of the patient perspective, and particularly in the HIV Community how you thought about that.

Using being able to use something recognizing that it you, you were still learning a lot about certain

Rubio

Certainly and from our perspective in a closed the gay and lesbian community we all knew one another.

I can remember, being in a room of 50 political activists, it was 1969 with stonewall so 19 8010 years later, we have all these brilliant and leaders.

In the leading the fight for gay and lesbian civil rights and then in the 80s, they were dead.

So we had a choice, either we participate in these clinical studies and try to gather.

to live long enough to find that drug that will do it or to die, with a life or death that had meaning at least I tried, I participated in any number of drug studies at parkland.

I injected medication sick to my stomach I ride in the middle of the end of my bed at two in the morning, but I had to do it because.

As I said, beginning I was not going to go gentle into that good night, I was not going to go without a fight that wasn't going to happen, I said goodbye, my friends, who did give up.

Who did give up, they couldn't take side effects, but there were many of us have said for the better betterment of all.

We need to participate and that's what we did yeah

Winckler

which then reminds us, you know part of when we heard about the structure and the the.

The technicalities of the law right a critical eye on you know unmet need in a serious than life threatening illness which you, you have here and then.

i'll note also you spoke to the activism of, we also need to know enough right there's that when you think about that deliberate uncertainty you do still know enough.

To be uncertain, which is more than, then the not knowing enough so you you write the the we had to have the research to yield.

The the product that you know could could get to the point where they could be used in an accelerated approval process so you're pointing out there's there's active, you know you know there's work that has to be done before that, and then making it.

available in this space

Rubio

we had to educate the public, there were some among my community who distress in the medical community why wouldn't want to help us.

You know, there was talk of the pharmaceutical companies throwing anything out there to make a buck.

This was not the case, but that's what some people thought we had to educate our Community, in fact, that the very beginning, we had to educate the entire population of the country.

First, it was a misunderstanding that it was a gay disease, I gave white man's disease and then was a couple of years later and 83 or 84.

The sex workers in San Francisco women were identified so slowly the spectrum of potential infected patients went from people like me to everybody in the world, and that was the how to prepare the audience for a better understanding we're all in this together that took time.

Winckler

Absolutely well Alberto i'm going to thank you for what you've done and for sharing your story today, you know i'm going to come back to you at the end of this segment so don't go away, but you can step away for now and we'll turn to to our next patient but Alberto Thank you, thank you.

So we We said we have we're going to hear from for patients, and so the second patient from whom we

Would you, you are joining us from Michigan I see you on camera Thank you so much for taking the time to join us today why don't you tell us you know we heard Alberto has the the powerful early advocate you know now decades of experience with products under accelerated approval.

let's hear from you, you have a very different experience, please, please tell us your story doctor says.

Navdeep Singh, PhD

hi everyone yeah.

That was very powerful elbert, I just wanted to was very, very powerful and I, you know, I was very interested to hear that, because my experience was actually very.

Different I was born with beta-thalassemia I was diagnosed at about nine months old So when I was born my parents, you know they're always very happy bouncing you know eight pounds 10 ounces boys.

You know, doing really well but about nine months, as you know, with beta thoughts email you start to go off.

The fetal hemoglobin and you start to produce your own so they started noticing, you know he's getting really sick he doesn't look good.

They took me in and ran a slew of tests and they found out that I was united beta fallacy, you know.

So my treatment plan ever since I was a child, was to get chronic blood transfusions so I have been receiving.

Blood transfusions for as long as I can remember, I believe my dad even says that you know I used to.

When you were a baby where you add your first transfusion and you know I would move the IV Pole and holds you because you would cry you know when I was a young child so.

So blood transfusions old have been just my my kind of it's my booster shot I just find it as a way of keeping me going and.

just making sure that I am suppressing the bone marrow and keeping my hemoglobin at adequate level and for a long time I don't remember.

getting any kind of treatment and then, when when, as I was getting older than there was a new thing that came out called desk for all and so desk for all was a way of.

helping with the iron relation, so, as you know what the blood transfusions you start to get all that iron overload so you start to you know damage deliver it can go into your heart and you start getting just some.

iron overload your face can start to look, you know, a darker color and you know all these things so.

I started getting a Pope one arm for my you know blood transfusion and then they would actually do an IV so i'd have.

i'd lay there you know watching you know TV i'd watch garfield and I have one arm with my blood transfusion and another arm with my desk for all.

It was just it at that time and then, when I was about 10 to 1995 they said, you know now you have to do this at home, you have to do desk for all at home, and so you know, I was 10 years old and learn how to you know poke myself at home, and so I would.

I wouldn't I would do is desperado and it would last eight hours a night, it was it was like a syringe driver just slowly push the medicine in.

For for eight hours, so I would just do it before going to sleep, you know and.

I remember my mom and dad even kind of having a little teary eye, you know they're both PhDs in electrical engineering and you know they're not into.

Medical thing and they're learning how to pose but you know, for your children you do you do everything for your children, so they learned it and.

They would do it on me and then and then slowly slowly, as I became older I started doing it myself but.

Just my quality of life, you know I don't like going to sleep overs and taking this pump with me and you know this kind of thing, and you know people like what's going on and.

I would work as a nurse, and then, when I started getting older, I started working as a nurse, and you know I work night shifts and so I carry this pump around you know with me.

And then just, you know as you got getting older, your body starts to get very, very tired there's only so many sites, you can rotate you know these these shots.

And it's a big thing I went off to college and I had to get the you know you, you make the medicine yourself so.

You know, while you're studying you know everybody's out, you know studying or partying or sleep or I would go home and i'd have to make all this medicine, I remember, even when I went to Dubai.

I was stopped at the airport, because they said what is all this powder you're bringing in the suitcase you know, and I said no, this is my.

Medicine, this is this is desperately this is to you know, keep me alive and.

And then you know I would get hassled at the airports know next time you need to bring a doctor's note specifically saying what this is, and I said geez you know this was getting quite.

hard and then all of a sudden this medication came out was known as shade, a new and it was a pill or the very first thing that came out was actually xj which was like sprinkles.

And then, after that they said, you know now there's actually a pill that has come out because some patients that I would talk to said, you know we couldn't tolerate the sprinkles but now there's a book.

And it was a it was totally life changing it was absolutely life changing, and you know, I would just wake up in the morning and take.

Take three pills, and that was it, you know, and it was like a release and emotional release because there was no more needles, there was no more pokes there was no more.

You know, explaining myself, you know carrying the pump all day, no more some you know no more rotating the abdomen sites and and and it was it really just was a life changing thing and.

You know I could you know so normal fair 10 levels for an adult male you know, are under 200 and.

mindset been consistently around 500 600 with this new medication with the with the pill, and I could never ever get my favorite in.

That flow with dust, for all I was always around maybe 800 900 sometimes 1000 you know, so this pill and had a longer half life, and so I was able to.

You know, it was just like a win, win situation, because you know I thought oh i'm taking a pill i'll be sacrificing.

My my health, but it was it was a win, win situation for me so so I didn't know about that there was accelerated prove I just one day heard that it was released and.

And so, all this information that you are presented today is very you know life changing I had no idea, there was so much background work about this, but.

yeah i'm very, very thankful that it came out it's been totally life changing.

Getting kids you know when I used to go to fellas even conferences and getting kids to take you know pokes and him and kill children died at people die because they were just non compliant with this regimen.

But now I just I mean there's there's no excuse you know when I go to those conferences, now I say you know you kids Now you can just take a pill, you have no idea what.

older generations have to go through so it's it's it is totally changed the game with with our health so i'm i'm extremely thankful for everything.

Winckler

Navdeep, you've illustrated, you know another component which is you know here a lifelong illness that you, as you said, been dealing with this every well.

it's been clinically addressed, since you were nine months old, but you physically been dealing with it every every day of your life and here.

The opportunity in the product was about a a sub financial change and the ability of you to to function more normally.

So, but you still do blood transfusions right

Singh

yes and actually today I had my blood transfusion so I I raced out of the hospital to make sure I made it to this meeting, but yes it's.

every Friday every three to four every three to four weeks and it's just alternating just to keep my hemoglobin up but yeah it's it's on.

Until there's a something else besides with bone marrow transplant because I don't have any siblings and you know it's it's more risky, so this is this is just how it is for now.

Winckler

But the translation transition rather from I can still see your visual both arms up right in a in a with infusions simultaneously then being able to do one at home, but still, you know discipline of every day to now that ability to use something from an oral perspective.

that's and so for you to do you have any, you said you may not even have i've kind of known about the accelerated approval, but in all of these these interventions, what do you.

Think about, as you have the opportunity to try something new, is there ever a hesitation, as you think about that

Singh

yes, because I remember when____was released so that was you know you know it's a little sprinkles and and even with even with jaden Oh, you know I would you know some doctor said well there has been.

You know it's it's a pill, so you know you know you have to watch your kidneys and I said, well, I get blood work every month.

Anyway, so you know I am if something's going to happen we're already we're already going to take care of that.

But yeah anytime you try anything new it's it's it's you know, but I think I remember, starting in 1995 and I did desk brawl till 2016.

And you know so there's just so many spots, you can poke in your abdomen and and and after you know your body eventually says enough, and so you say okay i'm going to try this and.

But I was very, very, very, very diligent with the desk for all because my Mickey mythologise said, you only get two days off he or your birthday and Christmas and.

And for a 10 year old boy, you know that's that's you know when you hear that you know, so it was very hard, but I was really.

You know my parents told me that if you do this, you will have a normal life you won't have any liver problems, and so I was really, really.

Strict about it, but you know when this pill came out and my and my iron levels have dropped my my fair two levels have dropped and better than no pokes and you know it just was totally changing it was it was just night and day difference.

Winckler

Navdeep, you've given me another D for today, which is discipline and the the discipline that you showed, as I think about the 12 year old in my house and what you were able to do through throughout here it's just.

impressive and then, thank you for telling us sharing your story and helping us understand that the advancements in an unmet clinical need can be about some of that.

Just changing your ability to navigate having a better clinical outcome.

But also so dramatically changing the intensity of intervention

Singh

and one thing, also about the expense, I just want to let you, because with desperado it was like that was like a $50 a week kind of a copay.

And when this jaden new came out, you know, was a new drug and it was brand name, so they gave us this copay card, and I remember.

You know it paid your whole deductible when you when you when you, you know so for a patient.

To have when this new drug came out is just some little sideways sideways thing but it paid the entire deductible to to do this, and now it's generic so you know the costs are down, but.

But that was another thing that was just shocking at that time when new things come out in, and you know it was it was a pay the entire my health insurance and so.

The financial costs of the desferal you know, is extremely expensive also so.

And, as well as it was shipping and making the medicine and all the syringes and all the needles, so it was to go off from that from a pill.

machine yeah

Winckler

Navdeep, Thank you and you've teed up a good conversation for our final chat where we get some of that payer perspective because they too are trying to.

figure out this uncertainty, but now Dave, thank you for now i'm going to let you step away and we'll move to our next patient, but thank you for getting home from the hospital in time to share your story we greatly appreciate it

Singh

my pleasure.

Winckler

So we'll go to our third story and and each of these is so powerful, so thank you again to each of you for joining us i'm going to ask.

Teonna woolford to step up next tiana I know you are joining us from California you're bright faith, thank you for joining us, would you introduce yourself and then tell us.

Tell us your story, because you have a different dynamic here so i'm going to turn the microphone over to you tiana.

Teonna Woolford

Absolutely, and thank you so much i'm just so overwhelmed by these powerful stories and really honored to share in this space, so thank you for this opportunity So yes, my name is tiana wolford I am 30 years old, and I was born with sickle cell anemia.

And just a little bit of background, you know I did relatively well as a child.

I was hospitalized maybe once or twice a year and then things really started spiraling out of control by the time I hit puberty around age 14.

And so, by the time I was 15 I had both of my hips replaced, I was transfusion dependent and i've tried all of those iron key locations that were just mentioned.

I had been in liver failure because I started having transfusion reactions.

And this was all happening in high school at a time when you're trying to kind of fit in and find your place in the world, and so it was it was really challenging and.

By the time I graduated high school, I was hospitalized at least twice a month I had messed over 60% of my senior year of high school.

So that was really difficult and then you know, I was approached with having about having a bone marrow transplant, because my hematologist felt that I was exhausting all of my options and.

I was on a medication called hydroxyurea which for 29 years, that is the only FDA approved drug that the sickle cell community has had access to, and there are.

limitations to that medication, I mean it is disease modifying, but it is a low dose chemotherapy so a lot of parents are nervous to put their children on it, I mean it can cause low sperm count for ovarian reserve hair thinning from the toxicity and so.

You know I decided to go through with clinical research and I had a half match bone marrow transplant, and I was incredibly desperate at the time and.

pretty much willing to give up anything except my fertility and I knew that the chemotherapy and radiation could do that so long story short, I rejected the transplant and so now, I still have sickle cell and i'm infertile and.

You know, but a bone marrow transplant, I mean that is the only cure for sickle cell but it's not universal because everybody doesn't have a match and it's incredibly risky so.

A lot of people, you know don't want to subject themselves to way and so definitely by the time I had rejected the transplant.

It was clear that I was running out of options, and this is something that was common in the sickle cell Community because we've been left out of clinical research for so long, and then in 2019.

Within a two year time span, we had to FDA approved drugs through the process of accelerated approval and.

that's been amazing like, not just for me, but for my Community because.

The sickle cell community is very close knit and small so literally i'd be having conversations with individuals with sickle cell disease through social media.

never met them and now these people that i've been engaging with on social media, I now meeting them at conferences and going on vacations with them because.

Of these two new therapies, they are having a better quality of life and feel up to traveling, so I think that.

I know the biggest take home message for me is that accelerated approval offers so much promise, and I know a lot of people.

Consider sickle cell disease to just be a disease, a pain, but it's not like anywhere that there's blood flow, there can be complications so we're prone to things like stroke commentary embolisms.

Reproductive issues cognitive function issues, and so you know any day that a drug is being delayed is a day that a patient is living but not able to thrive and so.

I think that accelerated approval offers so much promise and it's been really exciting for the sickle cell community, and you know I know of at least 40 therapies coming down the pipeline.

And I think that accelerated approval is just so promising and we're so hopeful that we will have access to these medications through accelerator approval.

Winckler

yeah Thank you and and you might have have have shared but I think you, you mentioned in our earlier call that that in fact.

you're not benefiting from one of these today, but can you tell us about your experience with with trying

Woolford

right well.

Thank you for bringing that up, so I did try both of the medications but I had allergic reactions.

So I mean like I said, like i've done a bone marrow transplant i've been on hydroxeria and actually.

Because that has chemotherapy in it and i've been exposed to such high dose chemotherapy and radiation for the bone marrow transplant.

My bone marrow is very sensitive to toxicity and so i'm not really able to even be on a therapeutic dose of hydroxyurea because my bone marrow freaks out every time we try to increase the dose.

And so you know, being the bone marrow transplant hydroxyurea the allergic reactions to the two that were approved, so you know personally to move, knowing that there's 40 therapies coming down the pipeline.

i'm just so hopeful and you know not having accelerated approval means you know more days that I potentially don't get to live the quality of life that I deserve.

Winckler

Teonna, you've given us that you've given me another D in that idea of more days right and and that.

I think, would have more days on both side of accelerated approval right when when we reach.

That level of you know, the the deliberate uncertainty and we know enough, then perhaps we can provide days on the good side, but until we get to that and in the absence of accelerated approval we don't we don't have that.

But that's that's a powerful piece tiana and thank you for taking the time to share your story and help us understand it, and then the hope that you've seen in your Community right in in going from a decades long treatment, but still that unmet medical needs and needing to pursue something else, so thank you for giving us the voice of looking for, I think, looking for us to learn from what is available under accelerated approval, as well as what's approved.

And in that clinical research to then hopefully get to a day, where we have something that works for tiana woolford

Woolford

yes Thank you so much.

Winckler

Great Thank you to, but we will come back to you in just a bit with that i'm going to take us to our our fourth patient story as we've we've moved through this continuum.

i'm going to ask Catherine Couvillon of wood you're joining us from Virginia close to me here in the DC metro area Catherine, do you.

pick up the microphone you've i'm sorry that I put you after three incredibly powerful stories, but I know that yours fits in there, too, so, would you.

Would you share your story and and help us kind of get this better understanding of of what it is, you know, this is the reality of what drove Congress to give FDA this authority and then what it is that drives the work that's done to implement it.

Katherine Couvillon

Yes, thank you so much for having me for including me with these other wonderful panelists and they're extremely moving stories i'm especially grateful to hear.

about the early involvement and the accelerated approval process and where to start story and then just do hear from other people who are living with conditions.

similar to what i'm looking with who also are waiting on the next drug to improve their quality of life.

My story starts when I was 31 years old, when I found out that I had breast cancer.

You didn't have any family history of breast cancer.

It really just came out of the blue, the only thing I really knew about breast cancer was that October turned pink.

And that if you caught it early, that was a good thing.

So, thankfully, we did catch my breast cancer early it hadn't even spread to my lymph nodes so I was diagnosed as stage two.

But I decided that I wanted to fight it really aggressively, and so we went ahead with a double mastectomy and I did eight rounds of chemotherapy which.

I had said not want to do that I was really afraid of losing my hair I guess i'm vain but I had never even dyed my hair before so to have it all fall out that was something I just really didn't want to do, but my doctor has told me that my numbers would be statistically.

It would be very advantageous for me to do the chemo looking at my survival statistics, so I did agree to do that, and it was six months of just really, really difficult things.

But I knew with breast cancer you treated it you fought and then.

You became a survivor and that's what I had on my trip directory.

kind of like go fight win.

And so we barrel through all that.

I also agreed after that to do, five years of additional hormone blocking therapy, so that it could further reduce the chances of my guests are coming back.

I really resonated with what I was sharing about the fertility piece, because I was 31 I was dating someone we're talking about getting married.

But I really knew that if I didn't treat my cancer, I might not have a feature at all, so I was willing to potentially but my fertility in jeopardy.

By doing the chemotherapy and then doing this additional amo blocking therapy that I knew it would require me to postpone attempting to start a family.

I was, I was willing to do that.

I also said that I would never ever do chemo again it was so hard so awful.

But I just you know kind of kept pushing that out into the future i'm not going to do that again i'm not going to have to do that again i'm i'm a survivor.

I ended up after that, a few months later, I married my husband we bought a fixer Upper House I got a promotion at work.

And we even started talking about would be able to start a family, what would that look like.

But then three and a half years into this hormone blocking treatment began having back pain and just wouldn't go away, and it was kind of in a weird spot and so eventually I reached out to my oncologist.

To say something that we should check out.

And so, he did he recommended some imaging.

It was actually the day before my best friend's wedding and I went to do the scans.

And, before I even got to the rehearsal my oncologist called and said that the pain was from a fracture in one of my vertebrae and that able to like that fracture was caused by cancer eating away at my spine, and that that would mean that I was a stage four cancer patient now.

I went online, to see what the stage for mean what's the prognosis and I saw that it was terminal and the life expectancy was currently looking at about three years.

I knew that cancer treatment was chemo, and so I thought.

i'm going to have three years of chemo and then i'm going to die, this is really terrible outlook.

So I just sat in my car on the phone call just and cried and tried to summon up the words to tell my husband, that I was going to die, we only had three years together.

I thought at that time i'm not going to live to see my 40th birthday.

I had images of bald skeletal people with dark circles under their eyes and.

I just I didn't want that to be me but I knew that I would do whatever it took to have more time.

When we did get to meet with my oncologist amazingly he told me that there was another option for me, besides, you know, but there was a new drug that had actually just been approved by the FDA.

It was called firebrands and it was not chemo it was going to be a horrible drug and I was putting it three weeks on one week off, and I could take it from home.

he's talking about the side effects and they were don't think that seemed like something that can handle.

anything to not have the audible nausea.

And so I was really excited I thought for a while, finally, like there's some hope.

And such hope that this drug had actually been fast tracked to approval the results that is seen, for the time to progression for patients was almost double what patients were seeing when they took this drug with the existing treatment alone.

i'm a numbers person and those all those things really spoke to me and I decided to take every chance.

I can't even begin to explain how thankful and relieved, I was to have an option other than chemo.

And not only that, but an option that might give me more time than what I thought I would have.

So I took the IBM.

It actually or to me for five years in that time when I reached that three year life expectancy mark we throw a huge party.

Just to celebrate that I wasn't dead yet.

My best friend, maybe give it a different name, we call it living in the bonus in bonus time but I just thought i'm not dead, yet and we have to celebrate that.

I also was able to celebrate my 40th birthday, which you never really think i'm going to be so glad to turn 40.

But I really was because I thought I wasn't going to live to be 40.

But unfortunately in 2020 in addition to co bed I also got the first bad news for my stance that I had had in the five years since being on Librarians.

My cancer had spread significantly and now throughout my spine, and my ribs in my pelvis.

I was experiencing a lot more pain, so I wasn't surprised when the scans found that my cancer had spread.

But it was pretty devastating to realize I would no longer be able to be on this treatment that have been doing so well for me and what did my future look like what other treatments were there out there.

Since that time i've tried for new treatments.

Some of them didn't really work at all my cancer has additionally spread to my liver.

And the longest that any of them has worked so far has been five months.

So, five years on iran's five months on these other treatments that i've been trying.

And yet i've i've lived longer than many of my friends also living with metastatic breast cancer.

I would like to say, their names of the women that are my friends that have gone before Jackie Carol mondo Mara.

So many others.

That I wasn't personally friends with but.

All of us are just hoping that we can live long enough to see you cure or the next drug that's worthy of accelerated approval and yet still hundred and 14 of us are dying every day for metastatic breast cancer and we just don't have time to wait.

So we are so appreciative of accelerated approval need those drugs as soon as it safely possible to release them to us.

Accelerated approval, I believe, gave me five years that wouldn't have had otherwise and a wonderful quality of life during those five years i'm so thankful and i'm just looking forward for the next drug that's going to give me more time.

Winckler

Katherine and i'm pretty confident i'm not the only person who had a reaction to your story Thank you and for sharing the understanding.

Of the the promise of these therapies, that it may be giving you time and the the opportunity, and now you are are kind of navigating with.

Drug developers and regulators and others trying to say where can we get to this place where we have some more.

You know, some more candidate products that that could be used so Catherine, thank you, I want to invite let's have Navdeep, Alberto and tiana come back on camera i'd love for.

us to close this this session, I want to ask each of you, first I want to say thank you for honoring us with your presence and.

Trusting to share your story with us it's so powerful and taking us from the the the advocate and more of the the success story.

Arc and and then to where we see we're still striving and and moving for things you you've helped us better understand the gamut in in why we need to do this and kind of what drives that that uncertainty, but I want to give you the opportunity.

To you know, take a minute or so each of you, and tell us when you think about accelerated approval kind of what's that and you may.

As we talked to you may not have known about the regulatory structure, but when you think about accelerated approval, now that you know much more than you might have before what is that word or phrase that you think of what's the.

That headline or the takeaway from accelerated approval that you want to share with our audience today and Now let me give you the order tiana i'm going to let you go first.

And then we'll go to Catherine to Navi into Alberto so tiana would you give us your your headline or your sentence or your phrase

Woolford

yeah sure I think that my phrase would be life changing.

I think, like everyone up here is a testament to you know what their personal experience in their Community experience about the hope and the promise that lies within accelerated approval.

Winckler

Teonna Thank you i've got i'm i'm writing these down because you all, are going to continue to inspire me so i've got life changing.

and hope. Katherins would you go next

Couvillon

sure, I would like to piggyback off tiana's hope word I were necklace that says hope every day, just to remind me of that, but my phrase is actually more time.

I just think about having more days to spend with my family and loved ones.

Winckler

More days and more time, thank you, Catherine now have deep.

Singh

lines would be.

Freedom and shackle breaking I mean it was you know to no longer have to self inject every single day and to just take a pill.

It was a total freedom, I would just you know my my nighttime routine was to do a big big orchestra of medication making an injecting and just to pop a pill and go to sleep, it was was freedom and was it was shackle breaking life changing i'm echoing everything at once.

Winckler

You are providing your own voice Navdeep and important one in in in that power of.

The change in routine and the opportunities that that freedom provided you so in an important additional voice.

Alberto do you want to to give us our our phrase, or what you think of when you think about accelerated approval.

Make sure you unmute or will miss your phrase.

Rubio

Because it's so incredibly inspiring i'm remembering all of my friends who aren't here, and all of us who got into trouble good trouble.

Trying to change the system and make it more responsive and how thrilled they wouldn't know that they would be that what we we changed has benefited you and continues to benefit others, they would be thrilled that they participated in all the studies and mine my catchphrase is determination.

determination on the part of the researchers are the legislators, the directors and, yes, the patience to be determined to live.

Winckler

The four of you have phrased this all so well in in summing it up and and and and I think.

What a what a powerful picture and face on the structure that we heard about you know why why we need you know why Congress told FDA to pursue this and and also to make sure that you are.

Make sure that that you know through accelerated approval that we follow up on it and you learn more and that you.

That we continue to advance in this space, so I again thank you to the four of you for joining us and reminding us.

why we have this authority and why we pursue it Alberto for the trailblazing not deep for the shackle breaking tiana for the life changing hope and Catherine for more days and more time Thank you all so much for joining you, thank you

Rubio

thank you very much for the opportunity

Woolford

thank you.

Fireside Chat

Moderated by Susan C. Winckler, RPh, Esq., CEO, Reagan-Udall Foundation for the FDA

Provider: Julie R. Gralow, MD, FACP, FASCO, Chief Medical Officer, American Society of Clinical Oncology

Patient Advocate: Kay Holcombe, MS, Board Chair, National Organization for Rare Disorders

Industry: Michelle McMurry-Heath, MD, PhD, BIO

Payor: Michael Sherman, MD, MBA, Point 32 Health

Winckler

So I, it is time for us to move to our our third session, but I think we can all acknowledge that we have that was just powerful to help us understand as we move.

Through and talk about the accelerated approval process our next segment is going to be speaking through more of this real world.

reaction and kind of the understanding of how is it the accelerated approval we've heard the FDA perspective we've heard the direct patient care perspectives.

And now we are going to turn to a fireside chat i'll, be it without fire and well being side by side, but will be collectively together.

On the zoom call to have a collaborative discussion exploring the perspectives and experiences of the broader healthcare sector with accelerated approval, and so we have.

An opportunity this is going to be a no slide session, but we have invited our we're going to come on the on screen together, so I want to invite.

Our panelists to come on video, and I know we have three of our four and if we have the opportunity to have our fourth panelists join us.

We will, but who's going to join us on video first for the healthcare professional perspective, we have Dr Julie grillo whose chief medical officer at the American society of clinical oncology.

From the patient advocate perspective, we welcome Kay Holcombe who is board chair for the national organization for rare disorders.

For the payer voice, we have Dr Michael Sherman chief medical officer of point 32 health, which is a combination of Harvard pilgrim healthcare and tough health plan and then.

want to just confirm if she has the opportunity to join, then we will add in DR Michelle mcmurray Keith from bio if she has the opportunity to join us, but I want to see i've got my colleagues here on camera let's.

start the conversation, and I will tell you it took me.

A minute to come through those powerful stories so so Okay, as we pivot from from the those patient perspectives that were just shared.

Help us think about the patient advocate perspective and what has the accelerated program program meant to patient advocates, particularly in the rare disease space.

Kay Holcombe

Susan, thank you for asking a question, and thank you for inviting the national organization for rare diseases to be part of this conversation, it is an honor.

To speak to you on behalf of those organizations and Nord is an umbrella over many, many organizations that represent individual were diseases and i'm honored to.

give you my perspective, and hope that i'm reflecting accurately their perspective as well, one of the things that patients with rare diseases are famously known for is.

There what is so called diagnostic odyssey, and that is that they have something wrong with them, and no one knows what it is and they spend.

days and weeks and months and years going from health care provider to Internet websites to Facebook groups to everything else, trying to see if they can just figure out what's wrong with them.

But even if they exit that diagnostic odyssey with a diagnosis, they then go into this know this this next odyssey they get on the therapeutic out of the ship and then wait for that ship to land in a good place and for a long time they have and we all have been arguing that.

There are so many differences between patients who have rare diseases and patients who have non rare diseases that are well understood or better understood, at least.

And those patients with rare diseases recognized and have recognized for a long time that the traditional pathway to finding a therapy having the FDA approve of therapy is safe and effective.

It just doesn't work for them the traditional clinical endpoint does not work for them, it takes too long it's too difficult to put clinical trials together.

They just can't do the research in the same way, these are patient populations that in many cases are so small that you get.

50 of them in one place would require you to go across the entire globe, much less to get hundreds of them who are going to be able to go to clinical sites.

and participate in a clinical trial, so it was with great relief and cheers from the sidelines when FDA.

decided thanks to Alberto and his colleagues in the HIV, AIDS Community decided that maybe there could be a different pathway a pathway that recognize.

That sometimes a traditional clinical trial wasn't possible and that a clinical trial that relied on a surrogate that hadn't been yet completely validated.

could be an alternative, and how could we make that work and we from the peanut gallery were cheering them on as they figured out how could we make this work.

and obviously one of the ways is to define correctly what it is that we're thinking of doing, which is to look at a surrogate endpoint.

and make a determination, based on existing data data that's brought into the Agency by the researcher or data that have been collected elsewhere in our in the literature.

But there is a reasonable possibility.

Reasonable likelihood that this surrogate is going to predict a clinical benefit and a clinical outcome that is measurable and that is good for the patient, so we were launched on our our therapeutic odyssey ship, and it was named accelerated approval and we are.

we're concerned, right now, on behalf of advocates for patients with diseases that accelerated approval is under fire and what we hope will happen.

is not that this just gets abandoned and throws it gets thrown overboard but that people think about what are the best ways of continuing this approach, while ensuring everybody that what as patients with rare diseases want is the same thing you want.

Which is that the kinds of therapies that are available to patients are safe.

And they are effective, they actually work for the patient, we want that to we don't want a lower standard we don't want something that doesn't work just for the sake of taking a pill or an injection.

We want to know that those therapies which seem to us to be very helpful.

And may be individually helpful really are proven to be helpful and so that's why we believe that those follow up studies that are required.

Under the accelerated approval pathway are done, and they are done well, and they are done properly, and they are done timely.

So we are all in favor of making sure that we all collectively understand.

What these studies are going to be when they're supposed to be finished how they're going to be done we'd like there to be a little more transparency and who's doing what and how are they doing doing that.

Because there are ways that we as patients can be helpful, there are ways that we as advocates can be helpful and i'd like to just close I know my five minutes is probably drawing to a close.

By mentioning the fact that Nord actually within this last year has done a White Paper on accelerated approval and it's called.

If I get the name wrong they'll kill me i'll be fired FDA is accelerated approval pathway a rare disease perspective.

And you can have a look at that is by going to NORD's web page and either looking under the news tab.

Which is on the far right, I am told, and clicking there, and you will find this paper referenced right there at the top of the list, or you can click on the.

advocacy issues tab and again that will bring you to a list of important advocacy key issues of which this is the first one.

And so that paper can be opened up and read and nor does make some specific recommendations about particularly how the.

The follow up trials can be done in a way that's transparent to patient groups to patients themselves to physicians that are treating patients.

But accelerated approval has meant the difference for rare disease patients between life and death, between life and a better life, between hope and despair.

Between determination and hopelessness so every single patient who just told us their story is speaking for every single other patient who has a rare disease.

And for us the same words apply, as did for all of them, and I want to thank them for recognizing how much we all share and the determination to get this right.

And to do better every single day for patients is shared by every stakeholder patients patient advocates healthcare providers researchers in industry, researchers and academia, we all care about the same thing happening.

FDA: So let's not throw the baby out the Odyssey with the Odyssey bath and let's if there needs to be changes let's make them carefully and with determination.

thanks again for letting me share my thoughts

Winckler

Kay thank you, thank you and you I caught.

Two particular things right of importance in the rare disease that that where it appears accelerated approval has an important.

role, one is you know just small numbers and the Odyssey that you're on, and so the accelerated approval becomes.

Important in in being able to help explore some of those those endpoints and to expand.

Access sooner and then the second point, where you said you know as with with all the patients who you don't want false hope so that commitment to the confirmatory trials and continuing to learn more.

Or that there are those the two headlines I should have been

Holcombe

yeah I think so, and I think it's important also to recognize that accelerated approval is kind of a different.

different thing than if you just look at the name and then you don't know the background the wonderful background that FDA provided us today.

Accelerated approval is more, it is not just about reducing the length of time and application spends on an FDA reviewers desk.

And it's not about reducing the standards and letting something slip out under the transom instead of over the transom that's really not quite there yet.

But accelerated approval goes to the heart the therapy development matter which is reducing the length of time it takes to get in the door at the FDA in a way that makes sense, scientifically in by the data.

Winckler

Right, where you get to that.

That endpoint that surrogate endpoint where you learn enough about it, and then you can speak to the predictive clinical benefit and then go it's part of that deliberate uncertainty so say we've we've seen enough and how do we move that forward exam when invite invite Julie, Michael Michelle anyone, I want to kind of chime in on the dynamics that Kay shared and particularly this this kind of thinking about the the surrogate endpoint and and getting to that deliberate uncertainty.

Julie

Julie Gralow

yeah I think you know what we've heard was a very powerful testament to how just focusing on overall survival, adding years of life is not the only relevant and point to patients, there are very meaningful benefits that can occur short of that and getting promised I like.

The hope piece of it getting promising agents to patient sooner, is a good thing and patients can weigh the risks and benefits, you know they can accept.

The there's a risk that you might not know as much about a drug, and they deserve to be able to be in the position of weighing from their personal opinion, the risks and benefits of having access to earlier good.

Winckler

really helpful Michelle or Michael

Michael Sherman

yeah i'm just an observation so i'm you know payors are really good at evaluating.

Drugs for common conditions, high blood pressure cholesterol lowering heart disease.

they're very familiar with the endpoints but for many of the rare disease that impact on so many Americans and and my understanding is from actually from.

An order that it's about 8% of Americans so collectively they're not rare, even though they may be rare individually.

This it's hard you know pairs don't have enough experience they don't intuitively understand what's important and what isn't.

So it actually is critical that we have the groups, the patient groups and others helping inform and educate us so that we don't make the wrong decisions in terms of ensuring coverage and access.

Winckler

that's a great dynamic Michael yeah Michelle please jump in

Michelle McMurry-Heath

well absolutely moving remarks K and I really appreciate it, I think what we have is an antiquated system.

That was designed to protect patients from being in clinical trials, you know our modern FDA is harkens back to a day, where.

The being in a clinical trial was the last resort, it was often disempowered patients that didn't have full consent that were being experimented on in a way that perhaps wasn't to their own best interest.

We have come a complete hundred and 80 degrees today your best hope if you have a serious life threatening disease is to get access to a clinical trial.

Your hope of getting cutting edge treatments that have the ability to make a difference we're nothing else can exist only in those clinical trials and with those experimental therapies.

And that is why we saw a patient storming the barricades during the HIV epidemic demanding accelerated approval, because they knew that their life depended on getting quicker access to these Barry.

evolutionary therapies, but that is not what we have set up our system to do and so now we have to stop letting the perfect be the enemy of the good.

have to start giving patients access to hope opportunity and survival and that's what accelerated approval accomplishes.

Now, of course, we need safeguards, of course, we need to make make sure that we are using our best science, but science has the ball to such a point.

That we have very good predictive measures very early on in our clinical testing to know whether something is likely to be safe and likely to be hopeful and successful.

And so we need to depend on that scientific knowledge and give more patients access, and this is important in the rare disease space it's also incredibly important, and if we want health equity and better diversity.

In who gets access to cutting edge therapies, because we know the clinical trial system we have set up today is overwhelmingly white and nail.

And because of the exclusion criteria not it's people think Oh well, we just have to put a little bit more forethought into it and, yes, if you spend more money and take more time, you can diversify your trials.

But that neglects the fact that we have non diversity sewn into the fabric of randomized control placebo trials, because we insist on the purity of the data.

And the purity of the data means and homogenous sample that has less complexity and that forbids access to so many diverse populations, so we have to realize that accelerated approval is giving hope and access to so many others, that would be excluded from it we're not available.

Winckler

Dr McMurray-Heath, thank you for that it amplifies you know we heard from Alberta in the HIV experience of their united folks who couldn't travel to it, but here.

it's not just about location, but it is about breaking through those silos that we've built that have have created a system where we we simply don't have health equity and so I guess it's another dynamic of accelerated approval, when you expand that access it helps us.

drive change in that inequitable structure

McMurry-Heath

yeah I mean people neglect the fact that our alzheimer's trials over the last 10 years on average of than 95% white.

So even along the clinical trial spectrum they've been incredibly non diverse.

And it's not because of carelessness it's because if you look at the exclusion criteria they exclude cardiovascular disease, they exclude history of cerebral vascular disease and many of them require patients to have a dedicated full time caretaker that can attend to their needs.

I can't think of a 70 or 80 year old African American patient who would meet those three criteria, no matter how hard you look for them.

And that but that's what it takes to get very pristine data, and we need to get off of that high horse and figure out how we help more patients.

Winckler

yeah it's a we often have said, you know randomized control trials are not real life, but then that means that some of the things we're learning more aren't available in real life to the broader broader Community really, really helpful, I want to turn to Dr Gralow.

You're here for our standing in the healthcare professional shoes and kind of that the player in determining how and when a patient would access the product made available under accelerated approval, because you hold the prescriber rule.

tell us how clinicians think about surrogate endpoints and even more generally, how to clinicians think about products made available under accelerated approval.

Gralow

Oh thanks Susan and since i'm representing providers or prescribers.

I personally practice does address medical oncologist and the clinical trials for more than 25 years, so I can speak directly to the impact of accelerated approval on my patients, I also.

Am assumed the role of the chief medical officer at asco this past year, the American society of clinical oncology.

Which is a professional organization of oncology specialists, and so I can speak on behalf of our professional organization and say that asco strongly supports the accelerated approval process.

Primarily because it provides patients with cancer, with the earliest possible access to potentially life threatening therapy and hope.

As we heard from Dr Mehta accelerated approvals are really incredibly important and oncology oncology accounts for about 85% of accelerated approvals and for the recent oncology approvals.

A third of that were initially an accelerated approval so it's a very important mechanism in oncology.

And as we've talked about throughout this whole chat accelerated approval is a balance it's a balance between how much uncertainty, we have about the effectiveness and the side effects.

versus benefit and the early access for the patients and the risks and benefits will differ across diseases across stage of disease across the indications.

So the risks are that the earlier treatment is available, the less safety information might exist, the less advocacy information we're not certain, it really works.

And earlier approval or access may make it harder to complete the confirmatory trials to get full approval, because it's out there already so you can't get people to enroll in the trial.

The benefits in oncology are clear, they provide patients with early access to potentially life saving therapies, instead of requiring them to wait for confirmation.

of longer term endpoints and let's talk about that you asked about the endpoint and after Corrigan caray overview endpoint so.

Accelerated approval is, by definition, based on what we call surrogate endpoint intermediate measures considered reasonably likely to predict the stronger clinical outcome so.

Overall survival is the gold standard and oncology the ultimate endpoint and does the treatment increase how long the patient lives so that's the gold standard.

That surrogate endpoints and oncology can include things like reducing the size of the tumor or delaying the time to progression or recurrent so giving more time.

Before a recurrence or progression and in a setting where there's no approved drug.

Just knowing that a promising new therapy can have a response, meaning, it can shrink the tumor that can be a reasonable surrogate when there aren't other options.

And he cancers our overall survival is very long and patient can live a long time with their disease.

On treatment for their disease, then progression free survival How long does the treatment hold to cancer and share without growing again that can be a very reasonable surrogate.

And Tiana's example of the benefit of just giving me more good days, the impact of treatment on quality of life that could be considered a meaningful surrogate endpoint to.

So we do have besides accelerated approval, we do have another mechanism to get promising drugs to patient sooner something called expanded access we sometimes call that compassionate use, but this is much more clumsy much harder to do.

You can kind of apply to get access to a promising treatment for a patient with a life threatening condition or serious disease outside of a clinical trial.

If there aren't alternative therapies, but it's not generally compensated.

it's very you have to get it approved across many levels.

And many smaller cancer clinics and Community practices just don't have the mechanism to be able to do a one by one by one, patient request for approval and then getting access to the drug and an experimental drug.

So it can't go through the normal processes and getting into institutional review board to review, so I just don't feel that practical i've done it.

But it's it's not practical and with accelerated approval far more patients will get access to the treatment when it becomes commercially available.

And we've had a lot of talk about these post marketing requirements and some concern over the regulatory structure for how do we review and what's the criteria, the timeline for withdrawing approval.

And, and what we've heard from Dr Mehta is set in oncology we found a relatively small number of withdrawals of accelerated approvals of drugs that didn't later confirm the clinical benefit, and if it been zero.

Then they should have bought out and full approval in the first place right.

And we talked a lot about these dangling approvals when the trials to confirm are conducted in a timely manner, or they don't confirm intended clinical benefit, but when when the drugs, whose clinical benefit isn't confirmed.

And we get withdraw, I just want to state that should not be a failure of the process, having some withdrawals is expected and it's a trade-off for getting exciting drugs available early and a failed trial doesn't always mean a failed drug.

It just might mean a very poorly designed trial on the wrong end point the statistical power and other statistics or inability to select a subset of patients that were in the overall trial they really are benefiting versus another subset who are.

So you know those are my thoughts i'm excited about the transparency in the oncology Center of excellence in project confirm that we heard about. I'm excited about the new innovative clinical trial designs less single on trials more randomized trials, where the a trial at an early endpoint can get a luminary approval and accelerated approval and that same trial can actually lead to the longer term employment, so my thoughts as a provider.

Winckler

Julie, thank you and you captured a I think it's an important point for us that if we're if all of the products made available under accelerated approval, then moved to approval we're probably might be being.

That it seems like there wouldn't be much uncertainty there right there, maybe our our our box of uncertainty is too small.

That we would assume that that looking at those surrogate endpoints some of them are not going to do to meet the standard, and then the back to the access component that Dr. McMurry-Heath mentioned.

You know that expanded access is a good way for a one off in one patient but but not, it really is more of a singular approach than accelerated approval and putting it into the Armor Armor men perriam of oncologists to to pursue

McMurry-Heath

Compassionate use bespoke and bespoke is always expensive and rare, so we have to keep in mind right

Winckler

Right and so it's it's a possibility but by no means a substitute right it's it's another of the tools and the things that could be could be done.

A couple that came up in our patient panel, and it has come up here a bit too on the payor perspective.

Dr Sherman I want to, I want to make sure that we hear more about the the payer dynamic and.

And you've been at the forefront of some of the most talked about pay for performance programs for drugs and biologics and and leading the way on real world evidence generation.

How to payors look at the last 30 years of accelerated approval.

Sherman

yeah and Susan, thank you for the chance to be here, I think it's an important topic, and let me acknowledge from the get go that I think payers probably have a bad reputation your broadly.

When patient advocacy groups talk about payers and physicians, the first thing that comes to mind is.

There the people saying you know we're making hard to get what I want, and I think we need to get beyond that and the reality is, and I think you've shown this here.

The data, the patient journeys etc these drugs are transformational more and more the reaction among payer should be not, how do we say no, but how do we say yes.

And and really that's the crux of it, but the fact, though, that payers do have a lot of questions as I alluded to earlier.

For many of the rare disease patients or excuse me payers don't have a lot of experience understanding what's impactful and what isn't and they need to depend on others.

And it's about having the right endpoints and also understanding what is not just statistically, but clinically significant so is a 1% increase in a certain measure.

of blood level or protein or something meaningful, it may be, statistically significant, but we don't understand that it's meaningful so.

there's often a lack of knowledge there and we need help being informed, second, and I think you alluded to this.

Clinical trials are done in very, very carefully on settings with the country you know really carefully selected patients physicians who.

Are reading or wrote the playbook and we see a lot of patients of those type everyone is followed by clinical research associate on.

And you know, and one of the downsides here and it's not just alzheimer's but for so many.

Trials they're not done in populations that represent what the broad populations appear to be.

So for those reasons payers sometimes they're skeptical now the again, the truth is, where we're saying drugs for unmet need delaying means lives.

And we should want to see more drugs for unmet need rather than another me to drug for diabetes or or other conditions where they're already maybe a plethora so.

That is important, so we need to get beyond that and one of the questions I asked is how do we create that access, how do we.

How do we provide real world evidence and what we've done in cases for for drugs and and also for precision diagnostics, where there is a lot of.

I would say confusion and consistent policies is try to figure out how do we, how do we help generate.

That real world evidence and how do we do it in a way which is fair to all parties and.

You know, and also creates a minimal financial risk for our stakeholders so we've done is a number of agreements for new drugs where we've agreed to facilitate and broaden access.

And in our population in return we they're generally is some sort of risk agreement that if the drug doesn't do what it's supposed to what it was approved for.

The manufacturers taking some financial risk so they're eliminating the concern among pairs What if there was poor value.

and in doing so, you not only come out with a financial risk agreement I frankly think that's usually the headline but that's not really the most important part.

The most important part is now we're introducing something into a broad and managed population.

Add into the wild with physicians you don't do trials all day but who actually are involved day to day and busy practices with all different types of patients.

And the that evidence truly is real world and be used by us and, frankly, hopefully by others across the country to make more informed decisions.

So we're we're proud to be able to doing that to be able to do that and there's so much opportunity we recently announced.

That we are covering the grail test for very limited population in the similar way.

there's a lot of confusion about how a pan cancer screening test might work but also tremendous promise let's work together to try to put as.

But at that data and determine what makes sense, so on and so I you know, in addition to the concerns I mentioned about.

What is what is meaningful and is the data indicative of what happens in the real world Paris worry about value and one aspect of this system is when these drugs are approved.

Frequently for a completely unmet need, which again is what we want to see there's no constraint on what they can charge and some manufacturers are very responsible, others less so, so when you have.

questions about how broad and how robust data is with what is what may be perceived as an appropriately high price payers tend to be concerned.

Let me also share that and again we are a pair with 2.2 million Members probably somewhat typical we serve medicare where.

You know, we may bear the risk, but if costs go up ultimately go a false beneficiary to the government.

We have half a million medicaid members and again that is really goes the state which have been managed a balanced budget anybody in the commercial side there's been a trend over past years for employers to go from fully to self insured so, which means instead of writing the insurance company check for $500 or whatever month they write us a check for 3040 hours or whatever that fee is and they pay the claims directly and and with that number increasing.

For our commercial population 67% of the membership is through self insured so when when there are costs without any benefit it's the employer is we're feeling that directly, so we need to be good stewards of the healthcare dollar.

And again, the best way to to assure that is to work together to start with fair pricing through some benchmark or showing your work or whatever.

And for going to risk coming at risk for the endpoints I think it's completely reasonable to ask.

The manufacturers go at risk of the same endpoints that they promised will work and are using to get the drug approved, at least in these kinds of settings until there's more evidence, and I think if we.

can work together, like this, we can balance access and affordability and and really bring more drugs to market, I always my litmus test is always knowing what I know.

What would you want for yourself or a member of your family and more and more, it would be to have access these so it's important to be part of the solution.

And being part of that solution, I think you pointed out it's you to want to you want to know more about that surrogate endpoint.

And, and what it means, and then you also want to generate help help if possible generate the data to say does this work, do you know we're all trying to navigate that uncertainty and payers.

want that uncertainty uncertainty, they want us to get through the valley of uncertainty, as well as that, yes, the.

best way to get through, that is, eliminate all of them, the access to better so let's say there is a new treatment that comes out for something.

Like alzheimer's a new drug and let's not rehash the past year let's say that again the what's been studied is on his plaque is amyloid where I think we've learned, there is not complete agreement.

What and i'm just going to throw this out, there is a hypothetical What if a manufacturer said to the payers, please cover this approved drug.

We won't send you a bill unless they not only have a reduction in plaque but if they have a certain improvement in cognitive performance, you know which is really the point here.

If someone were to do that, that would eliminate all barriers on the part of the payers and all concerns and would actually.

create a very large real world experiment which would would tell us at the end of the day, what How does this really translated into real world results doesn't matter.

McMurry-Heath

So Susan can I jump in there because absolutely it's incredibly important that we're having this clarifying conversation because accelerated approval gets.

confused with a coverage decision accelerated approval is an FDA purview and FDA is by statute not supposed to be considering the cost of the pharmaceutical it's supposed to be judging whether or not.

For significant patient population, there is the opportunity for the benefits outweigh the risks of the therapy period.

The rest of the conversation, is something we should have quite separately and distinct now, I agree that value of conversation is also incredibly important.

But we have to always be looking with the same aperture so a lot of our companies and bio we represent over 1000 biopharma companies are very excited about the opportunity for value based agreements.

But we also have to make sure that we're looking at it at the population level.

You know the speaker mentioned, that they should have the same endpoint that they have in their FDA trials, but FDA trials are looked at at a population level, not at an individual patient level.

And so, while meeting the same endpoints and goals and your trials at the population level is completely to be expected, and should be demanded meeting it for each individual patient is something that's just scientifically.

impossible to achieve, so we have to make sure we're striking the right balance.

And when we talk about what is the value of a break through therapy for an individual patient, we also need to have a very robust conversation as a society about what models were using to judge that value because it's it's.

You know, commonly accepted that many of the value assessment tools that we're using right now in the US.

tend to underestimate the needs of minority communities, they tend to underestimate the needs of patients with chronic diseases, they tend to underestimate the impact.

On families, when you have an individual with a long standing chronic illness.

And they tend to look at a very short time parameter rather than the impact, over time, and so we really do need to have a very important debate about what is the proper way to measure the value of the treatment.

And the other thing we have to talk about which we never discuss is the value of innovation.

You know our companies launched over 1000 research and development programs targeted at coded hundred and 81 vaccine development programs, we have around the globe now roughly 10 that have made it to the market of covert vaccines.

And no one talks about the cost of paying for this other 170 research and development programs that fail to ever produce.

a commercial product and yet I am so glad that we had 181 vaccine development programs, because if we had if the odds pickers had started at the beginning, as to which one they thought would win the race and be effective.

They would have been completely wrong 040.

So science is not predictable and yet we need robust science, so we need to come together, while shielding patients completely from out of pocket costs.

We, at the same time, need to figure out how we're going to come together as a society to pay for the innovations that patients are desperately need.

Winckler

Which is really helpful connection right in the distinguishing the FDA process, which then yields decisions for Michael and the other payors to make so they've got to understand and kind of think about how they think through that separate decision making process.

But I think there's a power here between actually among the patient, the provider the payor and an industry to be saying when you have.

You know, in an accelerated approval environment we're all trying to get through that valley of uncertainty and do that confirmatory trial, the idea of.

You know, empowering and gathering the real world evidence that is generated in that payer scenario, I think it is intriguing Dr Sherman I saw you unmute you and uh.

Sherman

yeah I know I I just think those are generally points I would agree with, and we need the right model on the problem is that if we do have.

High prices that are not commensurate with the value provided payors across the country will try to limit access which, which is bad for patients, which is what we should be thinking about.

The other point I would make is you know again for state medicaid agencies that you know that's for them it's a choice, do we pay a teacher.

Do we build a bridge, or do we pay for a drug and you're you're you know it's it's not an unlimited budget so we need to think about being fair to everyone.

Including the company's doing this cutting edge research, because it is high risk, and we do want dollars to flow to those companies.

I would also argue that we need some sort of objective assessment so let's agree attend even be the pair is making that decision.

But whether it's I, Sir, which is come up as an impromptu assessment entity, and that is unofficial in this country or others are showing their work, it is important and they're using accountable.

Well, you know they have farm at the table, and I will share with you that a number of pharma companies have gone to ice early and said, look at our drug tell us what it's worth.

And will price it there because there's empirical evidence showing that, when they do that pay or say it's a great value let's let's provide for that, but the other point I want to make.

If I may, is that the risk of not having these assessment frameworks is payors, will have a knee jerk response, and that is if they look at the price without the value.

They may say that $100 drug is preferable to $1,000 drug Yet if you look at the thousand dollar drug which may extend life more keep people out of the hospital, it may be the right decision, so the risk is without having that framework payers will make the wrong decision and they'll make inconsistent decisions, since they may use their own models.

McMurry-Heath

Complete that it needs to be out of the hands of both manufacturers and payors it needs to be independent, but it should be driven by the patient voice, because patients can tell us best what's the value that they that they really need and desire.

Winckler

So it will be helpful to think about the intersection of the FDA process, and then the subsequent payer piece, as well as this promise of potentially more data, I want to help us in our last.

15 minutes or so here to talk a little bit we haven't yet heard Michelle I want to turn to you to to say you know, without your Members and you mentioned that you know, without research and development.

FDA wouldn't have anything to review doctors and patients wouldn't have those therapies, to consider Michael would have less to evaluate in his payor decisions, so how does regulated industry, think about accelerated approval and, in particular.

You know we've talked a lot about we really want to see those confirmatory trials conducted.

How, how does regulated industry, think about this pathway and navigating it and and the important components there.

McMurry-Heath

Yes, so, you know it's so interesting to me I just was at the launch of elder corliss book about the code vaccine process, and he was talking about how he was so driven.

To try to find solutions for illness, because of his parents who had survived the Holocaust and how they really pointed in the direction of solving impossible problems it's it was so moving.

But there's so many people like that in our industry, and I think what saddens me the most as both a scientist and the physician, and someone said, the opportunity to be both an FDA and an industry is the presumption that.

Companies are not trying to get to the answer I think we need confirmatory trials, I think, companies want to have that.

Complete assurance that they know from beginning to end, that their products are helping a patients that they intend to help.

But in the accelerated approval context the science is evolving incredibly rapidly.

I remember once over seeing a trial, where we were being asked to confirm a trial, where the science had surpassed that product, and it was no longer actually the preferred clinical choice.

What is the ethical responsibility of completing a clinical trial when the sciences move past it.

And the science has already said that there are other options that are better for patient Is it better to keep on enrolling that trial.

and exposing patients to that clinical option, where it may be good for a small sub population but not good for patients overall.

Or is it better to say let's move on and figure out what the next breakthrough is and what is the next evolutionary step, we need to take, and if you look at the HIV example.

We constantly saw an iteration of new and credibly improving drugs at each iteration and that's what we want to see that should be our benchmark that and.

The withdrawal rate of accelerated approval products not outstripping that of normal approval and that's what we see I think in the normal.

approval process for the last 10 years the withdrawal rate has been around 5% and an accelerated privilege and about 7%.

So it's not like accelerated approval is letting through floodgates opening of unsafe products it's that it's giving patients access to incredibly cutting edge science quicker than than it would otherwise.

and cutting edge science, that we can then continue your navigate and answer those questions that we didn't.

sciences iterative, and so we should be taking, if we are really moving to a model of real world data which we should reward data that is actionable immediately.

Then we should be capturing the data as we go, we should know as much as possible whether we're seeing adverse events that we were not expecting or we're seeing a decrease in.

The can see that we were not expecting and then we should put it, we should not be wedded to a clinical protocol, we should be pivoting to the next great iteration based upon that knowledge.

And we have to strike that balance we need to make sure that innovators are fulfilling their commitments, but we also need to not stand on formalities in letting the science stampede ahead.

Winckler

Science stampeding ahead, makes me think of speed, which is one of the components, the accelerated part of accelerated approval and and we know that speed can make people nervous, we certainly heard that you know in consumer reaction and questions about the development of a coven.

vaccine, I want to give each of you the opportunity to to share, how do you think about the.

Accelerated part of accelerated approval and and how the FDA industry and providers and payers kind of maintain that high standard of review, while also.

moving quickly what what what strikes you about that moving fast part and you've touched on it a bit, but who wants to unmute first and and provide a quick response there.

I've got it okay go ahead, Michelle julie's next.

McMurry-Heath

Well I'll just say I was, I was withdrawn Crowley, who was a patient Father turned innovator.

Of a rare disease and he his company was able to come up with a cure for that has saved two of his children.

And he said to me, you know if you are battling a rare disease or a terminal diagnosis, time is the enemy.

And I think that is so clear when you talk about fear of speed, that is not usually coming from patients who are struggling.

With a life threatening illness that is coming, maybe from payors, maybe from regulators.

Maybe from public sitting on the sidelines, but it's not coming from the patients and the families that are desperate for a solution.

And so we need to keep that in context coded vaccines are unique because you're getting a product to a healthy population that's a distinct situation.

But, in most cases when we're talking about accelerated approval we're talking about something that is desperately needed and that people are waiting for.

Gralow

It really so you are understanding of cancer and its treatments is just changing every day is accelerating the amount of new information, the number of new targets, the number of new drugs.

Under study and our regulatory systems need to be able to respond and adapt in ways that need this rapidly evolving science.

You know, so that we can deliver cutting edge treatments quickly to patients and appropriately balancing the at risk, so accelerated approval process works it's not perfect.

You know, we can absolutely make some changes to make sure it's possible to complete those posts approval.

confirmatory trials and you know knock off the few that don't meet the criteria but um, we need to support it it's working and the accelerated approval process has now been around since the early HIV eight states it, it has evolved and its continuing to evolve and we need to support so that we better meet the needs of our patients.

Sherman

Yeah, you know I would again nothing, where we disagree with their it's just such a poignant stories about people for whom delay means lives.

That you know that speaks for itself, the important thing is to have a robust process, as we do for validating afterwards and proceeding with full approval or or or withdrawal and, as you, you know demonstrated that that's fairly robust, so I think we're all on the same page here.

Holcombe

And I am I think it's important to remember that our focus.

Traditionally, I suppose, has been on.

Speeding up the review of an application so something has happened it's handed into the FDA let's make the FDA do it in 10 months instead of 12 let's make them do it in six months instead of eight let's make them do it in five minutes.

But this is about something that everybody acknowledges is a problem which is drug development is too long and it's too costly and it's too difficult.

And what accelerated approval is about is about recognizing that there may be a way to get into that development process itself and then.

Quote unquote accelerate it or shorten it and then prove later if you've really made a big miscalculation but it isn't like somebody can walk in the door with something they've scooped out of their bathtub and say you know this cured three of the guys on my block.

There are data that are required to demonstrate this reasonably likelihood that we're looking for it's reasonably likely to predict a clinical benefit so reasonable.

FDA knows what that word means I can assure you, but I think anything that we can do to understand how to intervene in the development process itself.

Particularly in the longest and most expensive part of it, which is phase three clinical trials, we ought to be thinking about doing it.

and doing it well, obviously doing it carefully doing it responsibly, so that we can say to patients, yes, this is reasonably likely to work for you.

We are going to prove this within the next two years by some additional studies we're going to be doing.

And there are now so many ways that we on the outside as as Dr Michelle McMurry-Heath has just said, that we can bring in and understand how to use real world evidence.

But there are also ways that patients are bringing real world evidence to bear patient registries natural histories of diseases, these are all real world.

pieces of information that can be built upon and added to so that we can say we can move from reasonably likely to yes, this does predict a clinical benefit.

McMurry-Heath

Kay, i'm so glad you had hit hit on that point of, let us like take a breath and ask ourselves, are we doing clinical trials, we should be doing them.

You know I i've had company leader save me, you know clinical trials or 90% of the time and 90% of the cost.

of developing a new drug So if you want to talk about how to make innovations more within the financial REACH.

Of of more and more payers let's try to use the science, the big the it the big data, the real world evidence.

tools that we have at our disposal today to evolve that into something that's faster cheaper and safer, to me, I think it's a crime that actually for our covert vaccines, for example, we.

agreed with absolutely every conclusion of the Israeli data Israeli real world data uncovered vaccines along the way.

That means that are huge trials that we paid for, and all those other settings actually added no scientific information that was incremental to to those studies those early studies.

So we need to ask ourselves, are we being redundant, are we being wasteful, are we putting more patients at risk because the main.

difference for really sick patients between saying come into this phase three clinical trial of 10,000 patients versus accelerated approval after 2000 patients and will continue to collect data.

is really who pays for it because there's calculated risk in both of those situations and which patients get access to it.

Winckler

So you all helped us kind of come through the story of of.

Why, we would pursue accelerated approval, you know the the patient reminding us of doing this in an area of unmet need Kay, I think you captured it really.

brilliantly, and the idea that this is not about making FDA move faster, but rather about saying, where are their points in the research and development process.

That we can broaden access and then continue to learn broaden our ability to learn and and Julian Michael from the professional and the parent perspective thinking through, how do we, how do we incorporate and put the context around accelerated approval.

But I want to give each of you a final word, so you now are going to have 30 seconds to one minute to say thinking about all of the conversation that we heard today.

sometime this weekend or next week, when you think back to what you did on a Friday afternoon and you something's going to come to mind and you're going to say oh yeah you know, it was not a deep powerful story about having his infusion and his arm or.

The power of Tiana and the and the other patients or or thinking through this idea of earlier have accelerated approval being about access and equity.

i'm going to turn to each of you, and let me tell you the order that i'm going to go in and then we will be right at the end of our time so i'm going to go K Michelle Julie, Michael and i'm going to keep you to under a minute each Okay, what are you going to remember from this afternoon.

But you have to unmute or we won't be able to hear you.

Holcombe

gotta remember to turn off my mute button.

i'm going to remember that rare disease patients need and deserve for all of us to be looking for ways to make their access to safe and effective therapies more.

quickly and more.

more quickly.

Excellent Okay, I think I have the adverb really, really.

Winckler

Well, confirm and tie it down in in the recording Michelle.

McMurry-Heath

Kay, you have been so eloquent I don't think anyone is worried about that.

i'm going to remember how hard it is not to conflate the issues between making a regulatory vision about whether patient should have access to therapy or how we're going to pay for it because we keep conflating the two, and they are distinct questions both important but not related.

Winckler

Helpful and we did some conflating earlier with kind of conflating was a failed confirmatory trial of failure of the drunk or failure of the trial and needing to distinguish that so conflating might be end up being my my word.

I was going to do Julie and then Michael does that work Julie.

Gralow

Yeah, so I think what i'm going to remember from this, more than anything is a very powerful stories from the patients that we heard today.

You know that so sticking in my mind that's what's impacted me most, and how you know patients might not be alive to get access in a year or two.

We, we know that the process isn't perfect, but we are getting promising drugs to our patients sooner, and that is giving them hope.

And i'm going to be keeping a careful eye on to new bills that were just introduced into Congress this week.

To give the FDA some additional tools to advance this pathway and i'm going to commit to working with the FDA and all of you on helping keep this process in place that evolve it and make it even better.

Winckler

Thank you Julie. Michael.

Sherman

And you know I actually had the same thought as Julie did on it's a patient stories, you know that you have different stakeholder groups that don't always get along together, and there are probably good and bad examples of.

Patient advocacy groups and biotech companies and payers, but you know being here together hearing those stories hearing the strength and humility.

That that we're showing I mean I you know I don't know if anyone check their email during different parts here, but not not during those stories, it was compelling and it's a reminder, why we're all here and why we need to work together so on.

You know I just I really was humbled hearing them.

Winckler

Thank you all so very much for joining us.

we've come through our arc of telling the story about accelerated approval from the FDA perspective, the patient perspective and then this chat to help us put all together, Dr Corrigan-Curay could I turn to you, to close it out close out our discussion of deliberate uncertainty.

Corrigan-Curay

Yes, well, yes, thank you and wow what an afternoon, I really can thank everyone enough for joining us and Susan for your just wonderful moderation.

You know, we started with our prospective FDA navigating regulatory standards and procedures, and I know it's tough times that could be a bit arcane.

And so, then we were followed by such moving personal experiences from our courageous patients, Mr Rubio, Dr. Singh, Miss Woolford, and Ms. Couvillon and then we heard from our next panelist just now on the importance of accelerated approval to provide access when we use our best science and ideas and maybe we can improve how we find our confirmatory.

data, and I want to emphasize, something that Kay noted that accelerated approval does not mean that FDA accelerates review we give it the same attention.

As any application, and then we need to know that we have the scientific evidence to meet our framework.

And we know there's going to be challenges, and we know there will be failures that's inherent in a reasonably likely standard and it's sometimes in our nature to focus on where we come up short.

And while we should not and i'm going to use another “d” in this in this theme dismiss our failures and as Dr Mehta notes, we learn from our failures.

We need to continue in our disciplined way to get that data that patients and clinicians need and there may be improvements, we can make, and the oncology Center of excellence is providing more transparency.

But importantly, we need to continue to embrace our deliberate uncertainty when the science is there because it's such it's so important that we continue to give.

Mr Rubio, Dr Singh, Ms Woolford, for Ms Couvillon beyond and many, many others and new therapies that will provide hope break shackles allow freedom to live their lives and, importantly, provide them more days.

So with those thoughts I'd like to thank you again for joining us and wish you all a wonderful weekend.