todays lecture is by paul klutz dr
outcome in the oncology center of
excellence at the fda he joined the fda
in 00 focusing on gu malignancies dr
klutz is a boardcertified medical
oncologist and internist he completed
his medical oncology fellowship at the
national cancer institute here at
bethesda dr klutz received his bs from
the university of colorado boulder and
his medical degree from the university
of pittsburgh he completed emergency
room internship at the university of
maryland followed by internal medicine
residency at the university of maryland
im sure you will enjoy his presentation
today
hello my name is paul klutz im a
medical oncologist and the deputy
director in the oncology center of
excellence at the food and drug
administration
and today im pleased to be able to give
you a lecture
about crossing the finish line in drug

development

and how evidence is generated for uh

review by the fda and hopefully approval

of a novel a drug or biologic therapy in

in this instance for cancer products

which is what i regulate

a little bit of background is that i

actually was a

medical oncologist fellow over at the

national cancer institute so i have um

familiarity with the nih and the nci and

so im really happy to be able to speak

to to you and

teach you a little bit about drug

development

i will tell you that the fda has been an

amazing place for me to work and so i

would urge

early career scientists to check out the

fda as an opportunity for either

fellowships or or even for careers its

been pretty remarkable

so i will walk through these slides um i

have no financial relationships to

disclose

my hope uh is that i give you a good

understanding of the fda

how we approve drugs and biologics using

again oncology as a therapeutic example

but i think the core principles that

ill be discussing you know you should

be able to use across therapeutic areas

so at the end of this lecture id like

you to be able to describe the fda and

its role in drug development

have an understanding of the two types

of approval pathways we use in the us

be able to characterize efficacy

endpoints and think about how to how to

look at the strength of an an efficacy

result

understand a little bit about

patientfocused drug development

measurement of symptoms and function and

what were doing to make trials more

patientfriendly and then end on how we

source our evidence and can we find

opportunities to make data generation um

more efficient from routine healthcare

my outline is as follows im going to

start with

just overview of fda and the review of

our products

well talk about evidence and endpoints

and then well get into the patient drug

patients and patient focused drug

development and then well talk about

real world data and learning healthcare

so im sure many of you are familiar

with the food and drug administration

its its a large agency where we have

many responsibilities um

we are responsible for the safety

efficacy and security not just of drugs

and biologic products but also medical

devices and food cosmetics radiation

tobacco veterinary we have a lot of

things that we do

but there are some things that we dont

do

we dont regulate the cost of products

so we dont know what the cost of a drug

or biologic will be before we review it

and we also dont regulate the practice

of medicine so that is to say that if we

approve a new drug

for a specific indication for instance

for prostate cancer

a

prescribing physician could use that

drug for another type of cancer its

called offlabel use we dont

regulate that

but it is something

that companies are not allowed to market

there are three key centers at the fda

that review a lot of the drugs and

products that are used in cancer

the center for drug evaluation and

research or cedar

evaluates drugs and antibodies

cbr or the center for biologic

evaluation and research regulates

cellular and gene therapies as well as

vaccines

and cdrh or the center for devices and

radiologic health

will regulate devices in vitro

diagnostics

and diagnostic and therapeutic

radiologics

now if youve been following cancer

research and development of cancer

products you know

that

cancer touches these three centers

and its a very active area we have many

biologic products like car t cells

therapeutic vaccines under development

clearly its been a remarkable decade in

drug development for anticancer

therapies

and with the advent of precision

medicine

identifying uh through in vitro

diagnostic tests populations of cancer

patients who will benefit greatly from a

targeted drug we interact a lot with the

center for devices and so

we have a new uh center the first inter

center institute uh that was formed

under the st century cures act called

the oncology center of excellence

recognizing

that this therapeutic area of oncology

really um was very active across the

centers that having um an intercenter

institute to coordinate the clinical

review

of all of these products will be helpful

and our vision is to create a unified

and collaborative scientific environment

to advance development regulation of

oncology products and so its been very

rewarding to work across all these

centers

for oncology products

now one thing ill mention as uh someone

who works for the food and drug

administration now for the last 0 years

is that it is quite a balancing act

and there are many people

that are either

concerned that we are being too cautious

or concerned that we are asleep at the

wheel

and its very hard to find the balance

so i like this slide because it really

shows on the xaxis specifically

that if you want complete certainty

about the safety and

the efficacy of a product its going to

require a lot of data and typically

longer trials and more trials and thats

you know can cause regulatory burden and

the more and more we ask to go down that

road on the xaxis to the right the more

we will be called to cautious stifling

innovation and therell be calls to

reduce regulatory burden on the other

hand moving down the xaxis to the left

you know if we expedite drug development

too much and reduce our certainty from

having very very early clinical data

clearly will reduce regulatory burden

but if we miss a small but important

safety signal thats infrequent you

could have a toxic death and then it

would be considered fda being asleep at

the wheel so where we are along that

continuum um you know is very important

and i think currently were striking a

very good balance

on the yaxis we also

need to be consistent in our regulatory

decisionmaking and yet flexible because

theres an everchanging environment of

new therapeutics coming out of new

science

and so thats a balance we have to have

we need to be thorough with our reviews

but we cannot take uh you know years to

review a product and so we have to be

efficient where is that line where is

the white space in that line and then

finally with respect to interacting with

the outside world we need to be very

independent and conflictfree at the fda

and we are

but we cant stay within our walls and

not reach out and understand whats

happening with patients with industry

with academia and so youll see that we

are especially in oncology quite

interactive uh working at uh you know

professional society meetings on panels

to uncover potential novel approaches to

drug development and thats actually

part part of the fun of our job

so lets talk about evidence and end

points so

the fda is really built on two laws as

far as drug and biologics so for drugs

the food drug and cosmetics act

requires that drugs be safe and

effective prior to marketing in the

united states and the public health

service act

requires that biologics be safe pure and

potent and while there are different

laws the fda modernization modernization

act was enacted to minimize the

differences in our review between those

two and so for all intents and purposes

for this talk uh you know

similar safety and efficacy framework is

used

and will apply to both biologics and

drugs

this is an excellent slide by my friend

and colleague mark thierry that really

shows a little bit about how drug

development has changed in oncology

this slide currently shows that the

classic phase drug development paradigm

where in yellow nonclinical studies are

conducted to identify a safe starting

dose for humans uh the company will then

come to the fda and present this

nonclinical information

and we allow a drug to be investigated

in humans through an ind

in early clinical trials uh we look at

pharmacology do dose escalation trials

to find the maximum the maximal dose or

several doses that we feel could be

further explored

and we move into the green section where

we look at phase two studies identifying

maybe looking at two different doses to

find the optimal dose to take into a

larger trial and then we really start to

understand

evidence for efficacy in a large

randomized therapeutic confirmatory

trial

maybe with a survival endpoint

to move to a regular approval licensing

application

this obviously is a stepbystep process

that can take quite a long time

now what has happened in oncology is

weve learned as weve learned more

about the biology of the disease is

weve moved more into a seamless

development paradigm and what it has

done is really collapsed

that sort of pharmacologic therapeutic

exploratory

clinical development

and this has been possible in oncology

because we have an early clinical

endpoint of benefit called response rate

the percentage of patients whose tumor

shrinks

and so with the advent of the

accelerated approval pathway which we

will talk about

it may be that theres such a

significant

signal of efficacy through response rate

and early clinical endpoint that we can

actually

bring that product for review uh in a

licensing application for an nda or new

drug application and granted accelerated

approval based on this early end point

and enough safety data to understand the

drug

expediting the access to patients for

this therapy that may provide benefit

over existing therapies

and then we further explore in the

postmarketing setting this larger

confirmatory trial set exploring more

safety verifying uh the efficacy and

eventually granting it regular approval

once those trials are completed so we

really have changed how we

develop drugs and regulate drugs in

cancer

i mentioned briefly uh the idea of an

accelerated versus a regular approval

pathway and indeed theres two approval

pathways in the united states

regular or accelerated approval and

which pathway

one takes is really dependent on the

endpoint

of the study

the magnitude of that result the disease

context and whether theres an unmet

need how many available treatments there

are and whether this is a larger effect

than available treatments among other

considerations so its not just about

the endpoint

when we think about regular approval we

think about endpoints that are typically

survival they could be symptom or

functional benefit

or an established surrogate and these

are usually larger randomized trials

that have larger safety databases

importantly when youre granted regular

approval based on the on these larger

sets of of evidence

we do not require a comparative efficacy

requirement so that is to say that the

drug simply needs to be shown to be safe

and effective

as safe and effective as an available

fda approved therapy so this allows for

noninferiority trials which are used

quite a bit actually outside of oncology

another thing that is sometimes

misunderstood especially for

for cancer is that overall survival is

not required a benefit in overall

survival is not required for us to grant

approval to a drug it can show benefit

based on

on tumorbased measurements as well

talk about

accelerated approval to get into this a

bit more is an expedited program that

was developed in 99 in the era of the

hiv

epidemic to try to exploit the delivery

of therapies with early clinical data

that appeared to provide

a benefit over available therapy

so for accelerated approval it needs to

be a severe and lifethreatening disease

there still needs to be substantial

evidence of efficacy and safety but that

efficacy could be based on an earlier

clinical endpoint thats reasonably

likely uh to predict clinical benefit

but because theres its earlier in

development as i showed you with the

prior slide theres less safety data

theres more a little bit more

uncertainty and therefore we often

require postmarketing confirmatory

trials which will add to the evidence

and verify the benefit

and importantly if that those trials are

not conducted their requirements if

theyre not conducted or if the results

do not verify benefit that accelerated

approval can be withdrawn from the

market

now as we get into the idea of the

strengths and limitations of efficacy

endpoints

since were using oncology as an example

i want to walk you through uh our

oncology endpoints so that you

understand a bit more about the typical

natural history so on this slide you can

see that this is tumor size these black

uh blotches are

is a tumor in a patients body

you can see that at

the initiation of therapy for a trial it

will be a certain size and thats called

the baseline size of the of the tumor

after about eight to twelve weeks

and this is actually true in clinical

practice oftentimes we will rescan the

patient and evaluate the size of the

tumor to see if the therapy is working

if if the tumor has shrunk a significant

amount 0

we call that an objective response rate

so we have an early clinical endpoint

um that we can use for accelerated

approval and indeed thats the most

common accelerated approval endpoint and

it occurs very quickly

as you can see unfortunately the natural

history of most solid tumors especially

metastatic solid tumors is that they

will continue to grow

oftentimes through therapy when theyll

become refractory to a therapy and

unfortunately grow to a size

greater than it was at baseline and

thats called progression

endpoints including time to progression

or progression free survival

either patients that have progressed or

have died

and then after progression the natural

history of that the tumor may continue

to grow may actually grow in different

places around the body causing

metastatic disease likely causing

symptoms and morbidity which we can

certainly measure as endpoints as ill

mention and then

unfortunately for for many patients with

metastatic solid tumors the natural

history of their diseases that often

results in death due to the tumor

now here i have written overall survival

as the end point i just want to touch on

that were not uh using the endpoint

diseasespecific survival were not

measuring only those events that were

specifically deaths due to the disease

and theres a reason for that

its because its pretty hard to

attribute someones death

to metastatic cancer versus to some

other comorbidity oftentimes typically

when a patient dies um you know they may

die from heart failure they may die from

pneumonia they may die from many many

things that could be related to the

cancer but may not be specifically

related to the cancer itself so theres

the

that problem the other reason though why

overall survival is useful in oncology

is because our our drugs are actually um

have significant side effects and some

of them actually can be can result in

death

so

it is actually a bit of a safety

endpoint as well so imagine a therapy

that does a pretty good job at treating

the the tumor and delaying the tumor

growth and theres some delay in death

and therefore survival benefit a

diseasefree survival or sorry a

diseasespecific survival benefit

but if the drug is so toxic that its

also causing deaths

toxis due to toxicity early

that may

make the drug not show a benefit in a

randomized trial because the toxicity

is overwhelming the incremental efficacy

so overall survival is an important

endpoint in oncology um both because

its its doesnt take attribution into

effect and because it is a bit of a

signal regarding safety as well

so when i think about an efficacy

endpoint result in a

cancer drug submitted to the fda i

usually think about it in three ways

i think about the end point what was

measured what outcome is measured in

this trial is it a tumorbased outcome

is it a symptom or functional outcome

which is more rare or is it overall

survival and how clinically meaningful

is that particular outcome

but i also think about how accurately

it is being measured what are the

measurement characteristics of this

endpoint and should i be concerned that

theres challenges with accuracy or

reproducibility or variability of the

measure

and very importantly how susceptible is

that to bias

how objective is the measure um

and thats very important and as ill

show you

finally after i understand whats

measured and

the characteristics of how its measured

i think about the effect how big of an

effect is this whats the magnitude of

effect and put that in the context of

the disease and available therapies

so just a quick slide on sort of

interpretation

i think of uh variability and bias as

related in some ways to how much

interpretation is required to for the

end point to be um met for the event to

occur

and here i have uh from low to high

my impression of sort of four examples

of cancer endpoints that require

increasing levels of interpretation and

therefore have increasing risk for for

bias and variability as i mentioned

survival is a useful endpoint

um

not only in its clinical meaningfulness

but in the fact that it has

very little variability and very little

bias and very little challenge and

interpretation so it is its a gold

standard endpoint for those reasons

but as we think about tumor measurement

we do have to interpret that the target

lesion has increased by 0 so theres

sort of measurement error issue we have

to be careful about how frequently we

are assessing the tumor measures and

that theyre symmetric

between the arms and so theres some

challenges there

even more challenging is when the tumor

itself isnt actually well circumscribed

and measurable so bone disease like in

prostate cancer you cant really measure

it on a ct scan in fact we have to use

bone scans which are even more variable

and challenging to interpret and so

theres even more uh i think variability

and bias in that endpoint

finally there are endpoints that include

clinical events that are driven by

clinician decision making and these are

perhaps the most uh open to bias and

variability so one example is skeletal

related events events that occur because

of metastasis in the bone

um one of the

events is

pain thats so severe that you need to

give radiation therapy as palliative

treatment and you have to think about

what needs to occur before that event

occurs an investigator needs to hear

that the patient is having pain assess

the patient and believe that the pain is

focal possibly get an imaging scan to

make sure that they think the pain is

due to a cancer versus something else

and then get the radiation oncologist to

treat the patient so theres a lot of

decision making along the way

and each decision could potentially uh

be prone to bias

so in in essence with endpoints

themselves they have multiple

characteristics and theres really no

free lunch theres no uh perfect

endpoint there are strengths and

limitations for each even survival and

as you look at overall survival in this

slide you see that it is very clinically

meaningful

perhaps the most meaningful endpoint

it has a very low risk of bias and great

measurement characteristics as ive

described

but the feasibility of this endpoint in

contemporary cancer drug development is

increasingly challenging

number one it takes a long time in a

large trial and requires randomization

because it is the final event in the

natural history of the disease but well

talk about other reasons why

contemporary drug development with very

high early signals of benefit with

response rate make it a challenging

trial

to not allow patients on the alternative

arm getting

regular therapy to cross over and have

access to that investigational therapy

which can really dilute a survival

result

tumor endpoints are very feasible

commonly used uh and you know theyre

also used in clinical practice as i

mentioned you know we get scans

for patients to follow them along to see

whether or not our standard treatments

are working

they have a kind of a lower risk of bias

not quite as low as low as overall

survival for reasons i mentioned there

is some measurement challenges and

variability associated with the endpoint

but we do

have source validation and verification

of the result because we can look at the

ct scans uh with an independent reviewer

and i think theres this sort of ongoing

debate about how clinically meaningful

tumorbased endpoints are um so i gave

it a plus or minus this is my opinion

but you know as a practicing oncologist

it is not it is a quite a meaningful uh

moment

uh in a patients life when you

unfortunately have to tell them that

their tumor scan has progressed and they

are going to have to be taken off the

therapy that theyve been benefiting

from for a year or so it is

meaningful to some degree although of

course its not a direct measure of

survival or symptoms or function

symptoms and functional outcomes are

obviously very meaningful to patients so

theyre quite clinically meaningful i

think they can can be incorporated into

clinical trials using either patient

afforded outcomes potentially wearable

devices increasingly but there is some

risk for bias

especially with patient reported

outcomes which are more subjective

measures its unclear exactly what the

magnitude or existence of this bias and

cancer specifically but it is uh you

know certainly a challenge i will say

that theres sometimes calls uh that we

should approve drugs based on symptom

improvement alone

but

my thought about that is that while

symptom improvement would be a very

impressive um a complementary piece of

evidence to a tumor

related endpoint if all you have is a

symptom improvement and theres no

evidence that the tumor has been

affected

then it raises questions as to whether

the mechanism of the drug is something

other than antitumor activity and we

are really regulating cancer directed

therapies and its important because

were accepting a higher level of

toxicity for these therapies so what

were really looking at is a supportive

care medication which is really just

palliating symptoms but not affecting

the tumor

we are going to have a very different

threshold for safety so thats important

to think about

finally theres clinical outcomes that

we can reduce that are sort of morbid uh

procedures like i mentioned in skeletal

related events or maybe reducing the

need for steroids and brain tumors etc

they are certainly clinically meaningful

i think theyre

relatively feasible to assess but i

think again when when this event is

driven by a

somewhat subjective decision by a

clinician we can have a risk of bias so

no free lunch uh theres pluses and

minuses to endpoints

so to wrap up how i look at efficacy

endpoints we talked about how important

it is to understand whats being

measured and how clinically meaningful

that is but its also critical to

understand the measurement

characteristics and be aware of bias and

ability of the uh of the measure to come

up with an accurate result

and i do want to touch on how much so

when we look at them at the magnitude of

effect from the result

certainly large magnitudes of effects

are great and they can certainly also

overcome some of the uncertainty about

whether its really going to be

meaningful to patients so for instance

progression free survival delaying the

progression

of a tumor for only two months or one

and a half months

is not impressive

because were not sure if thats going

to mean anything to patients however

when you delay a tumor for a year uh or

eight months or months in a tumor

that normally progresses in two or three

months uh you know you start to feel

more comfortable thats really going to

be meaningful to patients

conversely small magnitudes can even

you know make an overall survival result

meaningless and so you know a seven day

or

one week two week median survival

benefit in the setting of significant

toxicity uh may not be enough for an

approval

i would also mention that

even the uh the strongest endpoint like

survival if you have a large magnitude

of effects but theres some uncertainty

given the fact that maybe the tumor

measures arent really in line with that

survival benefit

you do need to make sure that you at

least think

about whether or not the effect that you

see is due to the drug or some

confounding influence or bias

it doesnt mean just because you have a

large result that is due to the drug and

not something else and so what are some

of those things especially for time to

event endpoints the time it takes a

tumor to do something uh whether that be

progress or lead to death other than the

drug theres all sorts of things that

can cause uh one arm to live longer than

another

that has nothing to do with the drug it

could be that one arm has an imbalance

in uh you know good prognostic factors

so its a its a slower growing tumor

just naturally

it could be that the demographics are

imbalanced and that you know these are

younger patients or higher socioeconomic

status or they have very few

comorbidities

um increasingly it could be that theres

an imbalance in subsequent therapies

because theres so many more therapies

available that are effective in cancer

now maybe more patients got uh you know

an effective therapy on one arm versus

the other

this is why

randomization is so critical

for time to event endpoints like

survival because

it is the best that we have

to balance

not only the known

prognostic factors and other confounders

but the unknown things that we dont

even know about maybe its you know poor

care at one site versus another et

cetera

i want to touch on the benefit of

response rate as

a important endpoint and increasingly

important endpoint in cancer drug

development

and it has everything to do with what i

just said

assurance that the effect that you see

is due to the drug versus something else

uh

in cancer

solid tumors metastatic cell tumors for

the vast amount majority of disease

states tumors do not shrink on their own

tumors inexorably grow unless you

intervene with something thats

effective and so if you see uh a tumor

shrink

after the initiation of a therapy um in

the absence of some other therapy that

was given

you have a higher certainty a high

certainty i would say that the tumor

reduction is due to treatment and so

this allows the patient to be their own

control and so this is why single arm

trials can be

used uh if you use response rate and

thats so important because increasingly

in

cancer drug development were

identifying smaller and smaller

populations through biomarkers through

in vitro diagnostics

that its becoming increasingly

challenging to to find enough patients

to randomize thats one problem and then

the other problem is a loss of equipoise

which ill talk later about um as to

whether or not you can even sort of

ethically

conduct a trial

with the survival benefit

but with a survival endpoint

and maybe ill just give you a little

history as to how this is happening so

back in the 90s uh in cancer

therapeutics we had few therapies um

really uh this is about the 0s and the

0s

tumor shrinkage or response rate was

used frequently as an efficacy endpoint

for approval

for single agents and then uh in the 0s

they started to put uh therapies

together and were getting some

incremental benefits of maybe 0 or 0

percent of patients having some

radiographic

tumor responses but this was in a

setting of

increasing and increasing toxicity

and not a great uh set of supportive

care medications at that time either and

so

you know it was really thought after

discussion that um ideally in these

at this time at least

the outcome should be a direct clinical

benefit a randomized trial was survival

which became kind of the

common design in the 0s 90s and even

into the 000s

and this occurred until science began to

advance and things really changed and i

think this was a pivotal moment for what

were calling precision medicine or

targeted therapies where the new england

journal report of macnib and interferon

refractory cml was reported

that out of patients had a

complete hematologic response

and so that is a super high response

rate right a tumor reduction that is

just was unheard of and uh dr drewker

and his colleagues wrote that their

results demonstrated the potential for

the development of anticancer drugs

based on the specific molecular

abnormality present in human cancer and

that of course

heralded

well what has happened uh subsequently

over the last you know 0 years and you

know

what has happened as you see those sorts

of response rates in in the earlier

clinical trials has really forced that

change in the drug development paradigm

in cancer so more of a seamless oncology

design and it has challenged equipoise

for large trials so

when i talked about clinical equipoise

what i meant is that when you have

equipoise theres uncertainty

in whether one arm is going to win or

not you have enough uncertainty in that

investigational drug that you feel that

it is ethical uh to run that trial

and so what early

sign of clinical benefit uh allows you

enough equipoise to run a trial you know

back uh you know years ago when we were

looking at solid platinum and cytotoxic

chemotherapies you know 0 response rate

uh where we may have given accelerated

approval that was a decent enough amount

of uncertainty to say yeah we need a

randomized trial to confirm that that

level of response rate is going to

confer benefit

but in the contemporary drug development

paradigm with things like crozotinib for

nonsmall cell lung cancer therapies

that are targeted at enriched population

with a target that this drug

specifically will address

youre seeing response rates that are 0

0 0

with durations that are longer

and side effect profiles that are often

better and so equipoise has been a

challenge

and this just continues uh these are

just at least nonsmall cell lung cancer

the many

uh im sorry this is across cancers

these are many targeted agents in

comparison with sort of chemotherapy

typically twice the response rate um

certainly you know

0 0 0 higher response rates for these

targeted agents

and in addition to the loss of equipoise

based on really large signals of early

clinical endpoints

were also seeing our populations

available to randomized trials shrinking

and shrinking so this is uh a great

slide by my former colleague kidan

blumenthal that showed you know

nonsmall cell lung cancer 0 years ago

was thought of as a single disease and

as we understood the biologic

underpinnings and genetic

drivers of these cancers we were able to

identify science was able to identify

small subsets of this that were able to

be targeted by

drugs that address that specific

mutation and now we have you know one

percent of lung cancer and thats a lot

smaller population to be able to

randomize to a trial

one may ask and it has been asked

whether approving drugs based on

tumorbased endpoints like

progressionfree survival uh or response

rate is really helping patients in the

long run and a great study was put out

in the womens journal last year uh by

folks of the nih

regarding um

how nonsmall cell lung cancer

survival to your survival had increased

um

higher than the incidence of the disease

has been decreasing suggesting that

that therapeutic advances specifically

in precision medicine over this time

frame

really did drive uh an improvement in

the whole disease as a as a whole

you might say well maybe that is just

because people are smoking less and

theres less incidence of lung cancer

but

in fact when we looked at or they looked

at small cell lung cancer

which is a

cancer that unfortunately has had very

little drug development or drug approval

in the same time frame they did not see

that

degree of improvement and survival

so im going to move on now to

how we are sort of moving more towards

incorporating patients and thinking

about patients and drug development

and improving trials

so this is a slide by my colleague

theresa mullen um that ive adapted

where you know the question is where and

how how do you involve patients during

drug development and so i think she

suggests and i agree that you can

incorporate patients all along the way

from very early on before trials were

even started to understand the disease

natural history and whats important to

patients and can you measure it uh

so it may be if theres certain symptoms

that are important to patients you would

then need to identify a tool that you

can measure it with in the clinical

studies area there are two things we can

address number one is how are we running

trials right now and could we make them

more patient friendly and the second is

when we heard what matters from patients

in the translational phase are there

tools we can use in deploying clinical

trials to

assess complementary information on

symptoms and tolerability and functional

outcomes

and then how can we incorporate this

patient related data in our fda reviews

in the premarket review and then

finally even in the postmarketing

setting when the drug is out on the

market um you know can we communicate

this this patientcentric data out to

further uh sort of inform the drugs

risks and benefits and is there are

there easier ways to generate even more

data in the post marketing settings to

understand the drug in in the

generalized population

most of our work actually has been up

front and i think weve made some

strides i just wanted to mention so when

you talk to patients and we have in what

we call patientfocused drug development

meetings that are formal meetings at the

fda but also just in my everyday work in

in a lot of the uh sort of conferences

that i attend i speak to a lot of

patients i speak to a lot of advocates

um and really what matters to patients

in addition to controlling their tumor

and

living longer is they want to know how

theyre going to feel and function

better

before they take a therapy how did

patients

experience that

treatment while theyre taking it and it

has a lot to do i think with what

theyre going to give up for for the

benefit theyre going to receive whats

the quality

of their progressionfree survival its

its been a long asked question and

typically sort of drove the health way

to quality of life field

so theres a big interest in measuring

symptoms and function better now

why now i think

one of the drivers is that theres so

many more effective therapies that are

approved and itd be

uh better to have information uh to make

an informed choice where theres two

choices to be had

i think theres technological

improvements that are making this easier

whether thats electronic capture of

surveys or patient voted outcomes on how

theyre experiencing symptoms

uh or whether it be more novel

approaches to measuring function and

activity like wearable devices fitbits

apple watches etc

we have work in both of those areas

also i think clinical care is actually

starting to use patient reported

outcomes more

to monitor patients and intervene and

provide supportive care specifically

symptom side effects sort of patient

reported outcome measures that have been

advanced by ethan bash at the university

of north carolina and others

and there are new pro instruments like

the pro ctcae by the national cancer

institute which are just more flexible

libraries of specific patient reported

symptom questionnaires that you can

custom tailor to the to the drug that

youre studying so theres a lot of

things that have come out recently that

have helped

advance this field but when were asked

to use it the fda is asked to use

sort of quality of life types of

measures

we really thought carefully about what

was it that was going to help inform our

regulatory decisions because as i

mentioned

just because an end point or a measure

at a trial is meaningful

doesnt mean that its a good endpoint

from a measurement characteristic

standpoint so it has to be important to

patients

but it also has to be sensitive

to informing the intervention that were

studying whether whether its a drug or

biologic and if we can find that

it can inform our regulatory decisions

so what weve done is created a core set

of of symptom and functional outcomes

that we feel um are a general starting

point a core set that we think could

inform our trials they include things

like disease symptoms

symptomatic expected symptomatic adverse

events

a global question about how bothered

patients are about their side effects

a measure of physical function and then

a measure of how patients are able to

work or or enjoy their leisure

activities so its a pretty

narrow group of outcomes compared to

larger health related quality of life

instruments and their disease modules

and what we hope to do

is expand our palette of evidence when

it comes in to the fda for safety

and efficacy review so what we do well

now weve been talking about in blue is

our standard

efficacy markers of survival

progressionfree survival and overall

response rate

we have

very good standardized safety data that

are reported by clinicians

common terminology criteria for adverse

events ctcae safety data its very

standardized

we we know about dose modifications

during a trial and we know something

about hospitalizations and ed visits and

some of the sort of uh healthcare

utilization so i think we can do better

in yellow but i also think we can add

that core outcome set of symptom and

functional outcomes that are sensitive

to the intervention for for a better

totality of the evidence get a better

sense of

quote the quality of a patients uh

treatment journey with respect to how

theyre functioning how theyre being

able to take care of themselves

and what sorts of symptoms and their

impacts theyre feeling

in addition to measures like patient

reported outcomes and improving symptom

and functional uh measurement

we can and should and are making trials

uh more patientfriendly

um we are certainly getting there we

have done some things like looks to

broaden eligibility criteria to allow

patients with a broader set of

comorbidities uh to enroll on trials and

weve had multiple collaborations uh

have been successful in that regard

were looking to

improve trial access and reduce

disparities and the ability to to get on

to clinical trials and there are several

ways we can do that that ill discuss

some of the ways that we can get trials

more out to patients is to improve

digital health technology

so we can remotely assess patients so

that they dont have to travel so far to

get to clinical sites

and that is called decentralized trials

so conducting trials closer to where

patients live and finally you know what

role does just standard clinical care

and and learning healthcare systems play

in our ability to deploy you know more

practical pragmatic trials even

prospective randomized trials all those

things are being evaluated

so lets talk a little bit about what

were doing with evidence generation in

the trial in real world settings so a

decentralized trial is a clinical

investigation where either some or all

of the trial related procedures and data

acquisition take place at locations

remote from the investigator so we are

trying to move

some of the aspects of the clinical

trial out closer to where the patients

live

now

there are lots of potential benefits to

decentralize clinical trials

a lot of it centers around the reduced

burden on patients so many patients have

to travel

you know 0 00 several hundred miles

if they live very remotely to the

tertiary or quaternary health care

centers that typically are clinical

sites for

trials

when you reduce the burden on patients

you can access more patients

you can improve accrual because theres

a larger catchment area which may make

for faster trials and lower costs

you may keep patients on trial and

decrease attrition because its just

easier to be

enrolled on that trial

because of the remote assessments

they are not as onerous to

for the patient to go and have them

assess going to the site so maybe you

can have them more frequently

and in fact maybe you can query them in

longer term followup and get some more

longterm followup data easier

but i think one of the biggest benefits

of

gct possibly is that we can access a

wider

swath of patients and therefore

hopefully obtain a more diverse and

representative population in our

clinical trials thats more reflective

of how these drugs will be used once

theyre

approved if theyre teams safe and

effective

well look theres so many benefits to

decentralized clinical trials why have

we not done it what are the barriers

there must be some barriers and i think

probably one of the biggest barriers is

uncertainty and risk aversion

in the clinical trial uh especially

commercial clinical trial realm and its

understandable these trials are very

expensive

um

they have a lot of um of work and

preceding science that are packed into

these single trials

and so

understandably sponsors know that this

is the way that drugs have been approved

in the past and theyre reticent to

change things if its been successful

theres also things that are sort of

outside of of our control like

jurisdictional state laws about

telemedicine licensing which could

hamper decentralized trials and then i

think if you decentralize trials um to a

large extent you may need to do some

training uh and certainly supervise

these remote healthcare providers or

other personnel

but i think really it is a lot about the

uncertainty you know how will

remote conduct affect uh data in

clinical trials so you know thats the

big question

you may have been seeing talks at

various conferences about covet 9 and

what it has done to uh

existing clinical trials that have that

were ongoing and i think you know its

been termed the grand experiments and i

think this is this is accurate it

certainly is the silver lining to an

otherwise terrible public health crisis

because what it has done is is forced

industry regulators academics

uh and even patients outside of their

comfort zone

to deploy rapidly these remote

assessments that weve been talking

about that

are key to decentralized clinical trials

because the risk of traveling and going

to a site where there may be a high

covered rate because they were being

hospitalized

that risk outweighed the risk of

changing what had been done uh before

and so remote clinic visits through

telemedicine remote labs remote imaging

remote administration of investigational

product and site monitoring were

deployed

or at least permitted across a wide

range of trials during kovic so what can

we learn

and what were going to be doing is uh

is looking at that data as it comes into

the fda and we hope that well learn uh

how to continue to deploy some of these

remote assessments postcoded

and and deploy them in a way that

maintains patient safety and maintains

trial integrity

another thing that has been looked at a

lot is whats called real world data

what is real world data real world data

is data relating to patients health

status or the delivery of health care

thats just routinely collected from a

variety of sources that are not clinical

trial sources so this is electronic

health records its claims data its

disease registries

possibly patient generated data from

from apps and iphones and things like

that

and mobile devices

so theres been a great

deal of interest in this data and how

can we use it to inform regulatory

decision making

but i would you know suggest and i think

this has been made clear by the fda that

real world data

is not real world evidence and so work

needs to be done to assure that we

understand enough about real world data

to allow it to be considered evidence

that will help us understand the risks

and benefits uh or other regulatory

questions for medical products

some of the ways that real world data

could be used and actually you know are

are being used now are in the sort of

low risk areas where you really dont

necessarily need you know a significant

understanding of the attribution of the

outcome to the drug which is something

ill talk about and that is you know um

sort of understanding just the outcomes

in general

of certain populations uh to

characterize

you know what they look like in the real

world

um obviously you can get important use

data what kinds of drugs are used and

what kinds of ways

and that can be very important even to

monitor for things like drug shortages

we can certainly look at safety in the

real world and we have done that through

our office of surveillance and

epidemiology for several years now

but i think whats maybe the more bigger

challenges is people are interested in

using real world data to generate

efficacy data to generate data on

benefit outcomes

that are related to the drug itself so

that is where we need to focus most of

our research

i think you know to sort of close what

were seeing at least with respect to

source data uh and making trials more

more efficient and data acquisition more

efficient

is

at least some shift

from

traditional randomized controlled

clinical trials

which which really are protocol driven

health care at uh at trial sites

that have you know their prospective

trials are randomized they have a

standard assessment frequency of both

for both

safety and efficacy theyre very highly

monitored to keep data quality high

but they suffer

from a narrow population and a challenge

with generalizability

but we feel pretty comfortable and

confident

that the outcome in these traditional

randomized clinical trials uh is due to

the drug versus confounding influences

the whole point is to reduce the effect

of compounding influences

and you know as we move down more

towards routine healthcare moving trials

out more towards routine healthcare we

we can decentralize at least some

aspects of the randomized control trial

which is sort of the next step which we

talked about it can still be a

prospective randomized trial we can

still have a standard assessment

frequency but we can do it remotely we

can still monitor the trial for for a

data integrity um and i think maybe the

population will be broader as a benefit

even further along to routine healthcare

we could actually deploy a randomized

prospective clinical trial

in sort of more of a routine healthcare

situation where there are very little to

no standard assessments and patients are

just being treated and sort of followed

along as we normally would

clearly less monitoring clearly a

broader population but you know you lose

some control and and confounding

influences could could be an issue

obviously this may also require that

these are already approved drugs or

there may be other some other

considerations

finally what we just talked about is

true real world data which is really

about just

looking at information thats just been

sort of routine routinely collected

from a health care system this is all

routine healthcare data

currently its mostly retrospective its

almost always not randomized

there is certainly no standard

assessments its not monitored theres a

decent amount of missing data

its certainly the broadest population

has its big benefit

but

when youre looking at things like time

to event endpoints like we mentioned

survival

the major limitation of real world data

at this time

is that it lacks randomization and we

have a very hard time interpreting any

kind of survival difference between a

real world cohort and a trial cohort

based on

our

high uncertainty that that those

populations are balanced for known and

unknown prognostic factors

so i think

uh moving forward what were very

interested in is is identifying

opportunities in the real world

to create some kind of

real world response rate some kind of

understanding thats thats uh you know

entered into the system that the patient

received the drug

their tumor

was you know

was reduced

by by you know significant amount and

the clinician felt like it was a

response

that would be helpful because as i said

if were going to use singlearm cohorts

the one endpoint that we feel

comfortable with with respect to

assuring that the outcome is due to the

drug

is tumor shrinkage and thats just not

an end point we have right now in the

real world

so in conclusion

uh both regular and accelerated approval

uh require substantial evidence of

efficacy uh in the setting of acceptable

safety and whichever you use has to do

with the context and the endpoint that

you use

i mentioned that no efficacy endpoint is

perfect

um we take lots of things into

consideration when we look at efficacy

uh that includes the meaningfulness of

the outcome the measurement

characteristics of the outcome how large

of an effect uh the safety and also the

disease context in available therapies

i want to hit home that randomization is

so critical

uh not just an oncology but in any

therapeutic area where your outcome is

the time it takes from randomization for

something to happen when you have a time

to event endpoint thats driven by

progression of a disease

like survival and cancer

we need to have confidence that the

effect is due to the intervention and

currently the best way to do that

is randomization to assure that arms are

balanced

i would say theres significant momentum

to make trials in general more

patientcentric thats both by assessing

and measuring more sort of patient uh

experienced data

such as symptom and functional outcomes

but also the trials themselves need to

be more patient friendly

expanding eligibility somewhere patients

can participate moving trials more out

to our patients live so that they can be

less burdened by the trial itself and

finally i think there is emerging

opportunity for for more efficient

evidence generation um i like the idea

of prospective randomized trials that

are conducted uh you know in a more sort

of decentralized or even more practical

pragmatic

way

i think real world data true real world

data which is not prospective and not

randomized

you know is currently limited when we

look at efficacy

with that i will end i really appreciate

the opportunity to to speak with you

about topics that i i really enjoy

i want to acknowledge my colleagues and

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