im excited to introduce the next

ethicist team leader of the office of

pediatric therapeutics in the office of

the commissioner at the fda

she has worked at the fda since 0

she received her medical degree from the

university of virginia and completed her

internship and residency at the

university of maryland

she completed a chief residency at sinai

hospital in baltimore and completed a

pediatric fellowship at johns hopkins

she is board certified in pediatrics and

a fellow of the american academy of

pediatrics im sure youll enjoy her

lecture

hello everyone

today our topic is ethical

considerations for clinical pharmacology

studies in children

the topics that well cover today will

be the basic ethical framework in

pediatrics

low risk and higher risk pathways for

pediatric product development

pediatric pharmacokinetic studies

pediatric extrapolation

parental permission and ascent

so over time weve evolved from a view

that we must protect children from

research to review that we must protect

children through research

we have an obligation to assure that

children are only enrolled in research

thats both scientifically necessary and

ethically sound

and children are widely considered to be

vulnerable persons who as research

participants require additional or

special protections beyond those

afforded to competent adult persons

this is a basic ethical framework in

pediatrics and it is as follows children

should only be enrolled if scientific

and or public health objectives cannot

be met through enrolling children to

children who consent subjects who can

consent personally

absent a prospect of direct clinical

benefit the risk to which children are

exposed must be low

children should not be placed at a disadvantage by being enrolled in a clinical trial and vulnerable populations unable to consent including children should have a suitable proxy to consent for them

the principle of scientific necessity is important to consider when we are thinking about enrolling children in studies

children shouldnt be enrolled in a clinical trial unless its necessary to answer an important scientific or public health question about the health or welfare of children and this is based on two principles that are found in legislation one is that of equitable selection that subjects who are capable informed consent which are usually adults should be enrolled prior to children and then we shouldnt enroll children unless its essential to the research that we dont have any other option we dont have any other animal or adult data to support

the studies prior to enrolling children

we also need to minimize risks in the
studies we should eliminate any research
procedures that are unnecessary that
dont contribute to the general general
scientific objective of the study
so when an irb looks at research and is
thinking about approving research in
adults
its allowable to enroll adults in
studies that are relatively high risk as
long as their participation contributes
to knowledge gained and the individual
is
willing to consent to the particular
research study however in children
theres a limit to the amount of risk to
which children can be exposed to and
this is defined under the federal
regulations that well discuss as part
of this topic today
these particular regulations are the
additional safeguards for children under
cfr 0 subpart d
and generally they can be thought of in
two categories research involving
children either must be low risk or

restricted to minimal risk or a minor

increase over minimal risk if there is

no

prospect of direct clinical benefit to

the children

or if the risk is higher there must be a

direct benefit anticipated as participa

as a result of participation in the

study and the balance of this risk

benefit must be at least as favorable as

any available alternatives and in all

cases permission of the parent or the

guardian and ascent of the child must be

solicited

this particular slide lists the

requirements under the regulations again

weve actually already discussed the

first three bullets that are listed on

the slide the one we havent listed or

talked about this listed is um the cfr

0 part of the regulation and in this

particular situation there may be a

protocol that comes forward

that

may not offer a prospect of direct

benefit to pediatric patients and is

more than a minor increase over minimal

risk the irb may look at this protocol

and say that they cant approve it under

the 0 0 to or 0 categories

so in this case if they think that the

protocol is ethically justifiable they

would then refer the protocol to the fda

for review under a federal panel

so now well move on to discuss some of

the concepts that are involved in these

regulations that ive always already

discussed and the first is a prospect of

direct benefit so when we talk about

prospect of direct benefit we are

talking about a benefit that accrues

directly to the individual subject

enrolled in the trial and results

directly from the

research intervention thats being

studied and not from other clinical

interventions included in the protocol

so for example giving a drug in a study

is considered to directly benefit or

potentially directly benefit the child

but the medical procedures that might be

done as part of the study would not

directly benefit the child

we often modify the word benefit by the

word clinical to indicate that direct

benefit relates directly to the health

of the enrolled subject

and when were talking about prospective

direct benefit its actually based on

the structure of the intervention so

its not just only whether or not we

have a proof of concept but we also need

to look at the dose duration and method

of administration when were talking

about this

so i have a little bit more information

on this slide about prospect of direct

benefit the first question is what type

of

empiric data do we need

to support prospective direct benefit or

what proof of concept do we need and it

really depends on the particular product

under study we may have adults

information to support

enrolling pediatric patients in a study

but in some cases for example with rare

diseases we may only have nonclinical

data and that may be acceptable in that

case if there are no adults adults that

can be studied for that condition

do we think the data make us reasonably

comfortable that children might benefit

from the intervention or product

and this judgment may be similar to what

we might make in clinical practice again

as ive already mentioned the dose needs

to be sufficient and the duration of

treatment needs to be long enough to

provide benefit

and we need to think about the

procedures that are involved in the

protocol would these procedures be part

of clinical care or impact clinical care

and that will rate weigh into the risk

benefit analysis

the next concept to talk about is minor

increase over minimal risk

minor increase over minimal risk was

first discussed by the national

commission in the 90s as part of their

report and recommendations in children

and they talked about this because they

realized um when they were

talking about minimal risk that there
may be some other categories that might
be needed to be considered when were
talking about research in children
the defined minimal risk is those risks
that are normally encountered in the
daily lives or in the routine medical or
psychological examination of healthy
children and then they developed another
category called minor increase over
minimal risk and this category refers to
a risk which while it goes beyond the
narrow boundaries of minimal risk poses
no significant threat to the childs
health or wellbeing
in this particular case and in this
category
this is limited to children with a
disorder or condition or children who
might be at risk for a disorder or
condition
and this must contribute to
generalizable knowledge about the
childs disorder condition and the
reason for developing this as ive
already mentioned is that the national

commission realized for treatment

protocols or protocols where we might be

studying drugs that it might be

impossible to limit studies to those

that were either minimal risk or

offer direct benefit to the child

so another important concept to talk

about is that of component analysis when

we look at a clinical investigation it

doesnt just involve

the treatment with a drug product but

often involves other interventions

within the protocol and when we look at

these interventions in the protocol we

also need to look at the risks of those

particular

interventions when were looking at the

risk to pediatric patients

so with each intervention or procedure

we need to evaluate it separately to see

if it holds out the prospect of direct

clinical benefit to the child or whether

or not it falls under the minor increase

over minimal risk category and this

approach also was

consistent with recommendations that

were made by the national commission in

the 90s

interventions or procedures that hold

out the prospect of direct benefit

should be considered under the

regulations under cfr 0

and interventions or procedures that

dont hold out the prospect of direct

clinical benefit should be considered

under 0 or 0

and the reason we need to do this is

because if we fail to carefully

distinguish the different components of

a clinical investigation we may end up

letting studies go forward where the

risks in the protocol exceed the risks

that are acceptable for involving

pediatric patients in the study

so now well move on to talk about some

examples and pediatric pk studies that

relate to the concepts that weve

already discussed

first of all the administration of a

single dose of an investigational

product or whats considered to be a pk

study generally doesnt offer a prospect

of direct benefit to pediatric patients

one exception might be the situation

where you might give a drug to treat

pain we may we know that one dose of a

drug to treat pain may treat the pain

and in this case you might also collect

a p a pk sample but in most studies for

chronic conditions where several doses

of a drug are needed to provide clinical

benefit a single dose wouldnt offer a

prospect of direct benefit to a

pediatric patient

there is another possibility though in

terms of looking at on pk studies we

might look at them under the category of

a minor increase over minimal risk as

weve already discussed these particular

studies would require a drug that has a

very well designed

welldefined safety profile we have

existing safety data on them on the

product

potentially in adults or in a product

that may have already been

out on the market for a while um and um

the but in this particular situation the

children would still need to have a

condition or be at risk for a condition

and then theres a third opportunity for

collecting pk data in a study and that

would be within the context of another

study that offers a prospect of direct

benefit so for example you might have

an open label study

thats using a product to treat a

particular disease and during the course

of that disease you might decide to

collect pk samples and use that so you

can study the

pharmacokinetics of the drug

so ive included a few examples here to

specifically look at this

so in this particular example a study is

proposing to administer a single dose of

a product being used to treat depression

in children they plan to collect serial

pk blood samples to evaluate the pk of

the product the project is a new

molecular entity so theres no data on

use in children and very limited data in

adult in adults

several doses are needed before a

clinical effect on depression is seen so

theres no effect with one dose

in this particular setting the use of

the product and study offers no prospect

of clinical

benefit to pediatric patients

what the researchers should consider is

conducting a singledose pk study in

adults and using the data to support a

multidose study in pediatric patients

that is designed to offer a prospect of

direct clinical benefit

the second example is a study proposing

to collect pk information after a single

dose of an overthecounter cough and

cold preparation

in this particular case the product

safety profile is well characterized

and the study has defined children in

the study to either have or enroll

plaster and rolls children in the study

who either have an upper respiratory

tract infection or are at risk for a

future uri based on certain criteria

such as the frequency of past infections

number of people in the home or exposure

to others in a preschool or school age

setting

the use of the product in this studies

is acceptable and although the children

who dont have a uri yet dont benefit

the use of the product is low risk or a

minor increase over minimal risk

the third example is a study that

proposes to collect an occasional sample

to look at the pk characteristics of a

drug in children who are already being

treated with the drug as part of

standard of care so the study itself

doesnt involve giving a drug but only

involves collecting blood samples and

data collection

samples in this particular study are

planned to be minimized in order to not

overly burden the children limited to

one or a few samples and collected as

possible at the time of other blood

draws the collection of pk data in this

sample i mean the study could be

considered to be minimal risk or a minor

increase over minimal risk depending on

the frequency of the sampling and the

volume of blood collected these studies

are often con can refer to as

opportunistic studies

so i included a slide on acceptable

pediatric blood volumes because i think

its important to consider when were

thinking about pk studies in children

because

we need to draw blood to to collect that

information

so these are the points that i think are

important to consider

the blood sample volumes needed for

these studies should be limited to the

least possible volume and frequency

required

to minimize the risk and burden to the

child the blood volume should be

considered in the context of other blood

draws needed for clinical care

existing guidelines for blood sampling

volume limits range from one to five

percent of the total blood volume within

hours and up to 0 percent of the

total blood volume over eight weeks

these are considered to be consistent

with some the limited evidence we have

now on minimal risk to children and when

youre thinking about these blood

volumes you do need to think about them

again in the context of other bloods

that might be drawn as part of the study

for clinical care

and we should also consider even lower

blood volume limits for critically ill

children and neonates

so i included some slides on the

substantial evidence of effectiveness is

needed to determine whether or not

we have enough information to approve a

product

under fda regulations

and initially in 9

under section 0 d of the food drug and

cosmetic act congress intended that we

needed at least two adequate and

wellcontrolled studies each convincing

on its own to establish effectiveness

but over time fda has recognized that

this might not be practical in all cases

so in 99 congress amended section

0d to make it clear that fda may

consider data from one adequate and

wellcontrolled clinical investigation

and confirmatory evidence from from

other areas um to um to allow

establishment of effectiveness in in uh

for the approval of products

in doing so fda confirmed

or congress confirmed fdas

interpretation and statutory

requirements for approval and weve used

this flexibility in

many cases for pediatric product

development particularly to approve

drugs for rare diseases

so now well move on to discuss a

concept called pediatric extrapolation

and what pediatric extrapolation is is

that we may allow adult information on

efficacy to be applied to pediatric

patients the use of extrapolation was

first introduced in the 99 pediatric

labeling rule and states the following

if the course of the disease and the

effects of the drug are sufficiently

similar in adults and pediatric patients

fda may conclude that pediatric

effectiveness can be extrapolated from adequate and wellcontrolled studies in adults usually supplemented with other information obtained in pediatric patients

a study may not be needed in each pediatric subpopulation of data from one sub population can be extrapolated to another so for example you might collect data in adolescent patients and then you can extrapolate that data to younger pediatric patients

efficacy can be extrapolated but dosing and safety cant be extrapolated so we still need to have studies to collect that information

this particular algorithm comes from the guidance thats listed at the bottom of this page and it describes pediatric extrapolation and fda is actually moving away from defining extrapolation in terms of full partial and no extrapolation but whats important to note on this slide is the importance of collecting pk information and exposure response information to

support pediatric extrapolation

so finally when discussing pediatric

extrapolation the selection of an

appropriate dose and the assessment of

pediatric specific safety cant be

extrapolated and when were thinking

about extrapolation of efficacy it

requires an understanding of the disease

pathophysiology and the mechanism of

therapeutic response to the

investigational product in addition

sometimes bridging studies may be

required to support extrapolation in

terms

in addition to what ive already

discussed

and one further concept that i wanted to

mention is that with pediatric

extrapolation we do need to think about

appropriately designing adult studies to

support pediatric extrapolation and by

appropriately designing adult studies

and thinking about these considerations

that ill go through on this slide we

may be able to better inform those

pediatric studies some of the things to

consider are understanding exposure

response relationships in adults at

potentially more than one dose level to

support pk studies in children

establishing a pharmacodynamic endpoint

by exploring exposure response that can

be correlated with clinical response

establishing a clinical endpoint in

adult clinical trials to to extrapolate

adult clinical results to pediatrics

and if we have sufficient proof of

concept to support prospective direct

benefit to justify risk include

adolescents in adult trials to allow

extrapolation to younger children

all these considerations wouldnt apply

to all studies but are things to think

about in designing adult trials

so finally well talk about when does

subpart d apply and subpart d applies to

children so we do have regulations in

place that define children under under

statute but one important thing to think

about is that in all

jurisdictions generally defined by state

in the united states

the age of majority is not the same its

generally in most states but in some

states its 9 or older

also there are situations in research

where a child

or an individual who might be considered

to be a minor or a child in some cases

may be able to consent for themselves

for example in cases

of

getting

information or treatment for

reproductive health issues and in these

particular situations those particular

individuals can consent for themselves

in the research situation as well

so finally when were talking about

parental permission parental parental

permission is required for nearly all

fda regulated research there are a

couple of waiver options one is under

the exception from informed consent or

ethic for emergency research and theres

a new one area for waiver for research

involving no more than minimal risk

which is defined

under cfr k

or

0 the the guidance is actually

listed at the bottom of this slide there

are four criteria that must be satisfied

as per this guidance in order for

research to go forward under this

regulation

and its important to note that we

actually think that there will be very

few situations where this will apply to

fda regulated research

so finally when were talking talking

about child assent its important to

talk about

whats required affirmative agreement to

participate in research on

in terms of ascent is needed for um for

in the research context so mere failure

to object isnt construed as ascent in

the research setting adequate provisions

for soliciting a childs ascent need to

be

solicited so when a child is capable of

providing ascent they should provide

ascend and we need to look at the age

maturity and psychological state of the
child while making that assem assessment
ascent can be waived in certain
situations if the capability of the
child is so limited that they cant be
consulted
or in situations where the study offers
a prospect of direct benefit thats
important to the childs health or
wellbeing and the opportunity to obtain
this treatment is only available in the
research setting
or in certain cases a minimal risk
risk research where its impossible or
not feasible to
conduct the study without the waiver of
ascent of the child
so finally in summary there are unique
ethical considerations that impact the
design of clinical studies intended for
children
pediatric pk studies must be designed in
such a way to offer a prospect of direct
clinical benefit or be no more than a
minor increase over minimal risk unless
of course reviewed by a federal panel as

we previously mentioned

when appropriate adult clinical trials

should be designed to support

extrapolation of adult results to

adolescents and or younger children so

that children are not exposed to

unnecessary or overly burdensome

clinical trials

and finally parental permission and

child assent are required when enrolling

children in clinical studies

thanks for your attention i hope you

enjoyed this presentation if you have

any questions please ask the program

coordinator

you