todays lecture is by dr yoga gabriela

pharmacy in the school of medicine at

the university of maryland

between 999 and 0 he held various

positions at the fda and under his

leadership the division of

pharmacometrics was formed

yoga is a world recognized scientific

leader in the area of quantitative

disease models and their applications to

decisions

he is best known for transforming the

field of pharmacometrics across the

world into a decision support science

yoga earned a bachelor of pharmacy and a

masters degree from berla institute of

technology and science in india

he received a phd in pharmaceutical

science from north dakota state

university and then received an mba from

johns hopkins

please enjoy the following lecture

hi my name is yoga guburu im a faculty

at

school of pharmacy

university of maryland

before joining the university about six

years ago

i spent

quite a number of years at the

fda

and

my experience

in the realm of pharmacometrics and

it stems from the

need to

contribute to drug development and

regulatory

decisions

so

its all applied as far as i am

concerned

um in terms of pkpd modeling so what i

have done is that

we can briefly go over

the

concept of

modeling

and then im going to present to you two

case studies perhaps that should

give you a flavor

about the applications

of the

pkpd modeling

the underlying

premise

the underlying brains

of

pkpd modeling can be summarized in what

is called as quantitative

disease drug trial models

so there are three components here

disease drug and trial model

you see

the the

these three models

have the

input

in terms of the data that is collected

from experimentation

in the lab are clinical trial

data if you can see safety

pharmacokinetics and risk factors

they all constitute the data

and then you also have

previously available literature through

uh

through through journals

um and other sources

and then you you we have

diverse expertise in times in terms of

the domain expertise meaning we have

experts who understand the biology the

pathophysiology the pharmacology

the clinical

signs and symptoms

all that knowledge is also important for

developing these

disease drug trial models

then

in terms of the the the each of the

three components

disease models

generally pertain to

unquantifying the biology which is the

biomarker outcome relationships for

example

we have

uh for example we have

lets say were dealing with cancer

there is a like a solid solid tumor

the size of the tumor

and mortality

are correlated so a patient in general

qualitative terms a patient who has a

bigger tumor

is likely to survive less compared to a

patient who has a smaller tumor

but then how do we quantify that thats

what the disease model is about

same thing with respect to change in

glucose and how does that affect change

in hbc and how does that affect

the

probability or the risk of

myocardial infarction retinopathy

nephropathy

neuropathy

and

you know that that those constitute

biomarker outcome relationships

you also have a

natural progression if youre dealing

with

either cancer or for example

neurodegenerative diseases you have

parkinsons disease for example or

alzheimers multiple sclerosis these

diseases they progress over time

and

um capturing the

the trend and the variability the mean

and the variability of this natural

progression

also impo is important in

designing clinical trials in

anticipating what kind of a effect

a magnitude of drug effect

would constitute be

meaningful and such

and then the placebo response so you

have disease states

such as major depressive disorder the

placebo response itself is very big so

how do we quantify that and the

variability are there risk factors or

can you use

um some kind of a baseline

characteristic to uh to

to

enrich your population

as uh

um

super responders versus

uh versus uh nonresponders to placebo

and

so there is reason

for

our motivation for us to appreciate or

quantify disease models

drug model is pretty much

its its been something that we have

focused on in the past 0 years for sure

this constitutes the pharmacology so we

are very

proficient in understanding the

relationship between those

and concentration and concentration and

the

efficacy or safety markers speed

biomarkers outcomes um

and and such

we also know how to correlate or

translate thats what these days its

called translational research

the findings in a petri dish to

findings in a animal model

and then findings in healthy subjects

versus patients so we have

qualitative relationships and then there

are cases where you develop quantitative

relationships that can project based

upon healthy

subjects what happens in patients or in

animal models

and what happens in patients

so

these kinds of

pharmacology based models we are very

familiar with and that is going to be

the topic of this of this lecture

the third component of the disease drug

trial model is the trial model which is

often ignored you take a any of these

clinical trial publications table is

pretty much

the inclusion exclusion criteria the

baseline factors age body weight

number of males number of females and

and the disease

this is uh status

at the at the entry into the trial and

such right so those are usually

univariate you give they give you the

mean median and a range perhaps or a

standard deviation and

these are univariate analysis but we

really do not know if you take a

parkinsons patient the

from that table

whether

the

baseline

updrs score thats the score used to to

uh

measure symptoms

in parkinsons patients whether that

score at baseline is correlated with the

age or age since diagnosis uh or you

know uh or any other

uh

pre

treatments that the patient has gone

through so that kind of a multivariate

uh quantitative analysis is required

its not a luxury but its required

really if you want to design a future

trial you want to perform simulations

you need to know those relationships

the other thing we dont pay attention

to is dropouts so this has to do with

two things one

understanding why the patients drop out

were more concerned about how to deal

with it statistically but we dont pay

attention to why the patient dropped out

and two is there anything we can do

to

uh

to minimize dropouts discontinuations

meaning is it because patients

um

have some kind of a

adverse event that thats why they

discontinued or they feel they are

completely cured of the disease that

there that theyre dropping out of the

study

understanding those using quantitative

approaches is important for us to write

individualized

dosing algorithms and compliance this is

a major problem i think i dont think we

even know how to measure compliance

there are some methods

but

they have not made it into mainstream

that we

can routinely look at compliance meaning

is the patient taking the

um

the treatment as prescribed

the are they skipping treatment

doses or are they skipping or are they

taking the

medication at a different time than they

were supposed to these all contribute to

the

understanding

of

uh the therapeutic properties of of the

drug as well as patient behavioral

characteristics so all these three

together

is that

all these three components together

constitutes

uh quantitative drug

disease drug trial

models okay

we will

focus on drug model

for the rest of this lecture

let us start with a case study

of a drug that acts on the hpg axis

so hypothalamic pituitary gonadal axis

we know that

in

the in the brain

hypothalamus is responsible

for

the pulsatile gnrh release

almost every two hours

the release

is pulse style meaning it goes up and

down like spikes

exactly like whats shown

on the slide

then that stimulates the

the secretion

or formation of two hormones luteinizing

hormone lh and

fsh follicle stimulating hormone

and then

a and and

and in the testes

is responsible for the for formation of

testosterone

so and then

excessive levels of testosterone send a

negative feedback to the hypothalamus

to go easy on the gnrh release so this

is a

tightly regulated

homeostatic

bio biological or physiological

phenomenon

and what happens in cancer patients is

there is a

there is

excessively high levels of testosterone

and those patients who are not

candidates

for

surgery

are radiation

the

they

go through

chemical castration how do they happen

it

there are drugs

such as dagger alex which block the gnrh

receptor

in releasing luteinizing hormone and the

follicle stimulating hormone

thereby suppressing testosterone levels

so thats the mechanism

in these prostate cancer patients

now lets look at the

clinical data thats available

for pk modeling actually pkp pd modeling

but lets start with pka there were

three clinical trials the study one

is single dose hour infusion study

which is placebo control seven parallel

treatment groups very unusual

but thats what it is

from and the doses ranging from

about one

microgram per kilogram to 0 microgram

per kilogram very wide range 0 fold

range

six to nine healthy volunteers healthy

volunteers per group

and theres a rich sampling schedule

study two

is a single dose

single dose short infusion study fif

either or minute infusion no

placebo control four parallel treatment

groups to 0 microgram per kilogram

dose

again

a pretty wide dose range

the third study included a single

subkudos so the study and were

intravenous and this is subcutaneous

study placebocontrolled

treatment groups

with doses ranging from to 0 mg flat

dose

and we have access to these data

for uh supporting or developing

a semimechanistic pkpd model

why do we care why why do we need this

the reason is

dagger relics

for its approval by usfta

requires

that

the

end point

meet is the end point for for the

approval is such that

90 percent or more of the patients who

receive the gorilla x in a clinical

trial

should have suppressed testosterone

levels and theres a threshold for that

0

um

i think nanograms per deciliter

so you have to meet that threshold

suppression from

day thats one month

through the end of the year so thats

for it for months

there has to be a sustained suppression

which means you want to get the

testosterone lowered as soon as possible

thats to do with the onset

then two

you want a that level to be

sustained

through the one year which means you

need to come up with a maintenance dose

and two and three

a

dosing interval should this be because

its a sub q injection that the plan

should this be given

[Music]

every week every two weeks every month

every three months six months

how do we come up with this

and

as you can appreciate

the

the the more frequent the dosing the

less likely

its going to be appealing to the

patients because you dont want to go to

hospital the patient doesnt want to go

to the hospital probably every every

week or every two weeks

so

you have to balance the the practicality

and the and the pharmacology in this

case

now

why do we need modeling why cant you do

clinical trials

and and then find them out well you can

but then you have to wait for one year

of trial

and different combinations of the

loading dose

maintenance dose and the dosing interval

and that could be pretty costly because

these are in prostate cancer patients

its not like you can recruit them

on the street

for your trials

okay

now

i advocate what is called as a dia

principle meaning any given project for

you you must should

you ought to

follow

dia principle if it were me i would say

must

dia stands for decisions information and

analysis and it is in that order

so i have shown you the data but i also

explained to you the key questions

that are the

motivation for the pkpd analysis so

you will have to write those key

questions which are not technical these

are decisions that you are to make

and then look for the information

that is available to be able to

support answering the questions and then

you design or engineer the analysis

based on the information and then come

up with some decisions then you will

have to negotiate with the rest of the

team because you will not have answers

to every which part of the question so

you negotiate um with the rest of the

team its usually interdisciplinary and

then maybe youll have to look for

further information and then maybe you

have to refine the analysis little bit

so on an average you have to go through

the cycle two or three times before you

come up with uh with the with the the

final decision to to move forward so

thats the dia principle so i really

strongly advocate that whenever you

start a pharmacometrics project that you

adhere to this principle otherwise it

becomes an academic exercise thats

futile maybe you can get a publication

but

there wont be any any influence on the

on the final decision whatever that is

here is here at the data

this is time on the xaxis degrees

plasma concentration on the yaxis this

is from study hour iv infusion

as you see the observed data

is shown

by the symbols squares and the solid

lines are the population mean

predictions meaning this is the average

model prediction for over the population

and the individual

predictions are shown

in dotted law by the dotted line as you

can see the model describes the

pharmacokinetic data very well what does

that mean

meaning

i can change the rate of input the dose

and such

and i should i would be able to predict

the pk profile under different

conditions that is the beauty of

pharmacokinetics once i know the

fundamental pk parameters clearance and

volume i can then change the input rate

to anything i want and i would i would

be able to reproduce or project the

pharmacokinetic profile under that

new dosing condition

this is the

this is the sample

representative subject from study

where the iv infusion is given over

minutes its the same thing

you see that the model describes the

data very well

the population mean which is the black

solid line is not going to ever

perfectly describe the data because

its the mean meaning therell be fifty

percent of the subjects above that line

and fifty percent of the subjects below

that line so the individual prediction

the dotted line the broken line is what

it signifies that the structural model

is accurate

and then you do the same exercise for

the subcutaneous

study study

and you see that the model describes the

data very well

now

let us look at some key differences

between these two

if you look at lets lets pay attention

to the to the

for example the minute iv infusion

the time scale there is two days

the time scale for the sub q is 0 days

okay

which means

the sub q

for the sub q administration

there is perhaps a depot

in the subcutaneous tissue

where the drug is released slowly

or drug is absorbed actually slowly into

the system and hence it takes longer

time

for the concentrations to decline over

0 days

and then this is the reason why

subcutaneous would be ideal for the

treatment especially when you want the

testosterone

suppression to be sustained over long

periods of time

and

that you want to keep your frequency of

dosing limited

or less

okay

so

the start difference between sub q and

the

and the iv

naturally the concentrations the c max

for example is much higher for the iv

compared to the sub cube but that can be

handled with dosing if necessary

each study represents unique pk profile

due to different dosing regimen and this

is the richness when youre developing a

new product if there is an opportunity

for you to

to

design or look at different dosing

regimens

uh starkly different you should do that

because that is where you will learn

the the properties of the drug that you

can use to extrapolate

in the future studies

and remember were only dealing with

health is here

you remember this this picture

what we did was we converted that

biology

into

a pkpd model now we have compartments

the first compartment is gnrh

compartment there is a pulse style

release with a

a zero order formation rate of k release

of g n rh and

the degradation of the jnrh is

represented by a first order rate

constant k degradation gnrh the red box

then you have the

luteinizing hormone pool

and

remember the gnrh

stimulates the release of

uh luteinizing hormone into circulation

okay so the lh pool already exists and

gnrh only stimulates the release its

like switching open the valve uh for the

alleged to flow from this pool tank into

the systemic circulation

so thats why you have the pool

compartment and the plasma compartment

thats where you sample the plasma

and that rate is kl is a first order

rate constant depending upon how much of

the drug is available in the pool

then the the luteinizing hormone in the

plasma is what drives the stimulates the

formation of testosterone and then the

the testosterone the body also degrades

the testosterone ah eliminates it

eventually take a relax

it

counteracts the gnrh

in terms of

on the lh release into the plasma

circulation

and thats the

mechanism of action

so we

we implemented these models

in uh

in a software

um i think we use nonmem

and

lets see how the model describes the

data the placebo you have time

in days and testosterone concentration

on the yaxis

its pretty flat placebo theres no

action its pretty flat

and

as the dose increases so you have group

p here which is 0 micrograms per

kilogram this is from study

the group e which is about 0 micrograms

per kilogram and then group f which is

about 0 micrograms per kilogram the

higher the dose the lower the

testosterone suppression

or the higher the testosterone

suppression

ok

and the higher the dose the longer the

the suppression so look at here at the

the lowest dose group shown here

where you have a suppression which

occurs about one

um

one day and then slowly the testosterone

starts coming back in two and a half

days starts coming up

but then you you look at the

0 microgram per kilogram roughly those

the suppression is sooner

and

longer

because

the testosterone reaches the floor

sooner and it is even more pronounced in

terms of the duration of suppression at

the 0 microgram per kilogram this is a

classic signature of

bioflex based pharmacodynamic models

the question then becomes we had three

studies

and

there are different dosing judgments but

its the same drug and the range of the

exposures are similar

and the same biomarkers are are

collected in these healthies so could we

have predicted study two results based

on model developed using study one so

what we did was we took the pk from the

study two

okay the individual data

then we say well use the mean data

from

the

study one in terms of the

pharmacodynamic parameters and see if we

can predict without estimation the

pharmacodynamic profiles as you can see

here

we we we are able to reproduce the mean

uh profiles at through

0 microgram per kilogram dose

very

very well

in spite of the

fact that the time course of the

pharmacological response you see is

distinctly different from the previous

study

all right

then

we did the same thing

by asking could we have predicted study

three results

and again the the

answer is an overwhelming yes

again the signature the time course of

the testosterone is completely different

from the from study one and study two

so that is the power of having

a

physiologically based

pharmacodynamic model

that you change the input

you can

predict

the pharmacological response

for under these different scenarios

which

may not have been directly studied

so you can argue in this case they could

have gotten away with only one study

instead of doing these three studies

now what

now we have a model

that is pretty robust in terms of the

physio physiological basis

and two

we have done a reasonable testing under

i would say

vastly different dosing regimens yet the

model is robust enough to predict these

profiles reliably so i can now

use simulations

to

look at different combinations of

loading dose

and

maintenance dose and dosing interval to

narrow down my choices if not pick the

one

and then go for the clinical trial

but unfortunately the company did not do

that

so

what you see on the left hand side lets

start with the left hand side

you have the study numbers under

activity

and then the the development years 00

to 00

they have conducted

five studies the blue

the blue

uh

arrows for example cs0 through cs

they have conducted

from using anywhere from 0 to

about

00 subjects

patients that is

and yet they did not have a dosing

regimen until march 00

and then at that time based on these

analysis and and some other

sophisticated analysis

they came up with the dosing regimen

that was ultimately tested

in cs with a sample size of 00

patients

and then the drug is

approved after that its currently

approved uh based upon this type of pkpd

modeling

so

you can argue and perhaps this is a good

learning experience for you

that

you could the company could have avoided

most of these

studies the blue arrow studies

and

could have gone to market sooner which

means higher

revenue longer revenue

and also for the patients

perhaps its an another

drug available for their consumption

all right

now let me present to you a different

case study

this is on the

a genetics based pediatric warfarin

dosing regimen derived using

pharmacometric bridging

warfarin is one of the top five drugs

that is prescribed in us and perhaps

the world

today

yet

this drug is not approved for pediatrics

and there is

some need

of this drug in pediatric patients

what you see here is

uh

from the publication that is shown here

so if you want to have more

details you should go to that

to this publication

lets go through facts about warfarin

pharmacotherapy

its my most widely used

anticoagulant

more than 0 years in use one million

prescriptions per year in adults

it has a narrow therapeutic index so

there is a monitoring of

inr

which is supposed to be around to

if you fail to

meet the inr meaning youre below then

your risk of thrombotic

embolism

increases

or thrombose formation

and if the inr is

you know uh importantly greater than

three

then the risk of a hemorrhage bleeding

is higher

okay

and we now know which we did not 0

years ago

that there are two mutations

that

govern or contribute to the variability

of warfarin that is c9

poor metabolizers

in um have higher exposures than

the um

than the

extensive metabolizers

and then

with respect to the

weak or c

its about the sensitivity of

the

patient

to the same concentration of warfarin so

even if you take two different patients

extensive and poor poor metabolizers and

lets say that you control the

concentration to be identical in these

two patients yet the patient depending

upon the weak or c status could

have a

inr

that is

off because of potential mutations in

weak or c allele

there is no

formal approval in pediatrics and i

dont think that anybody would do a

study that will support the approval at

this time

because its off patent forever

but there is a need in patients with chd

cvl wall replacements

and more infants than adolescents than

children

need

warfarin

but there is very limited clinical data

so

what do you do when you are dosing

pediatrics its i guess anybodys guess

so we wanted to plug that gap and this

research is about deriving

warfarin peak

dosing in pediatrics using pkpd

approach

so the what is the but what is the

problem you know people should be able

to figure out the dosing by trial and

error well survey in 00 of

pediatric hematologists who treat

pediatric patients with warfarin showed

that 9 positive response for need to

develop new pediatric dosing regimen

because of this problem what you see

here is

day 0 to day 90

and

you see the warfarin dose on the yaxis

as you can see the recommended daily

warfarin dose for a hypothetical 0 year

old child weighing 0 kilograms could be

as low as

um i would say

one or milligram um

to

more than 0 milligrams

so depending upon whos treating

depending and and depending upon the

variability

uh different patients get different uh

require different doses

and this also shows

that

even on day zero

um

you you see very vast range of doses

that are used

which means the practice also is

different depending upon who you see

so the objective is to derive a

potentially useful

dosing algorithm based on mechanistic

principles and

modeling and simulation

so you have we have very rich prior

adult pkpd model

we also know the contribution of the

the polymorphism in terms of the

metabolism as well as v car c and we

also know the mechanism of how warfarin

acts on the anticoagulation system

then we have pediatric model derivation

which is meaning you would bridge the

exposures between pediatrics and adults

using

body size and

you know and

ontogeny the maturation of of liver

enzymes

that is also known

we also have real data from pediatrics

from the los angeles hospital chla

to verify if our predictions are

reasonable

and then you would do perform simulation

cts stands for clinical trial

simulations to estimate starting dose

and come up with a titration algorithm

and and then you would

look at the

uh

you you would

we can discuss what happens with that

with that dosing algorithm

all right

this is the picture in terms of

therapeutic index uh two to three is

widely accepted there is some gray zone

or pink zone in this case

about where the bleeding risk starts i

think its and above and gradually

the bleeding risk starts

to increase and below there is

risk of thrombus formation

and

usually

in clinical trials in adults you see

that the therapeutic goal is to have

at least 0 percent within the

therapeutic window

by two weeks

and there would be

less than 0 percent of patients who

would be above

and less than 0 percent who would have

inr of less than two this has been the

empirical observation

in clinical trials among adults

we know the form of kinetic model which

is there is a first order absorption to

the plasma there is distribution into

the tissue and then elimination from the

body

c free is a concentration in the free

concentration that elicits the action on

the anticoagulation

synthesis

and the pharmacodynamic model is

provided here which the pca in this case

will translate into changes in the inr

and then for the for the metabolism

clearance and volume clearance you would

have the effect of sipc9 genotype and

for the ic0 for the pharmacodynamic

model you would have the influence of

the haplotype weaker c on on the ic0

so patients some patients would have

um

higher ic0 meaning less sensitive to

the drug and some patients would have a

lower ic0 which means they are

sensitive relatively more sensitive to

the drug

there was a separate trial i dont want

to go into that but this model was used

to design the dosing arrangement for

that trial before the trial was

conducted and as you can see

the

the

observed and the model predicted data

purple and the gray are pretty

consistent

for inr less than two two to three and

greater than so which shows that the

adult model was prospectively validated

from this clinical trial in adults this

was conducted by harvard

um

and then we know

that if you looked at related

anticoagulants

the

exposure response those response

concentration response in terms of for

example here antifactor 0a

for heparin and low molecular weight

heparins

lmwhs

the adults and pediatric data are highly

overlapping as you can see here the

the filled symbols versus the hollow

symbols they follow the same trend in

terms of higher the concentration

higher the effect on antifactor 0a so

this means that pharmacologically there

is no difference between pediatrics and

adults so

as long as i can scale the dose such

that i can manage the same

concentrations in addition pediatrics i

should not be expecting a different inr

changes for a given concentration in

pediatrics compared to adults

and that is also shown for this direct

thrombin inhibitor ergotrobin

where you have a turbine concentrations

all the way from

shall we say one microgram per ml to

0 000 its

you know five orders of magnitude

unbelievable range of concentrations and

on the yaxis you see aptt in seconds

and blue and the red are the adults and

pediatrics they are they follow the same

trend in terms of the data in fact the

adults are healthy is here and the

pediatrics are patients in spite of that

they still follow the same relationship

in terms of the

pharmacology the exposure response

okay so

then the pd model is basically

the same

as adults

and the pharmacokinetic model the

relation the relationship

meaning the the difference would be to

bring in body weight to to scale the

clearance and volume

and the effect of age because were

going all the way to neonates um in

terms of the ontogeny of cc9 which is

also published in the literature so you

take the allometric scaling

and the ontogeny model

and we already have the pd model

that was actually developed by us at an

earlier point and and and other

researchers also you pool all these

different sub models together

to

start predicting the

um outcomes are inr at different dosing

schemes in pediatrics

we do have the observed data also from

subjects this is very hard to get

data in terms of warfarin and pediatrics

and the dosing was empirical basically

every investigator decided how to dose

that kid

by themselves there were no protocols or

whatever to follow per se

the age range is months to years

and the body weight ranged from seven to

eighty four kilograms and the target inr

the two to

uh was about five to was

of them and to was

why do we have a different cut for the

inrs that is how they they looked at inr

in in this

in this observational study

and

naturally because you have only

all the genotypes and haplotypes are not

going to be represented so for example

you have ship to c9 star star which

is the the

wild type 0 of them are the patients

are of that and star star is about

0

there is no kid who was among these very

rare mutations like star star

and in terms of the weak or c genotype

they are pretty evenly distributed one

third each gggan

what we did was we used the model for

the pda the adult

extrapolated

pediatric model meaning we did not

subject that model through the data or

the we did not subject the pediatric

data chla data through the model so it

was kind of a prediction of what happens

if we predicted the outcomes the inr

results from the pediatrics and then see

if the pediatric chla study gave you

similar range of exposure inrs so what

you see here is

the

the predictions the black lines are the

median predictions because you can never

predict without some data from each

individual

that in that patients data its just

impossible um

because of variability so we

repeated simulations for what in other

words if you recruited a hundred

subjects like id like id like id

0 like id9 you did you exactly

recruited such

match matching patients

um

and a hundred of them and you gave the

same dosing to all of them

this is the best or the mean

inr profile youll find thats the black

line

and the red lines are the

th and the 9th percentiles

of these

virtual hundred kids

okay

then

lets sprinkle the data

the model

by and large

uh describes the

the data pretty well except in some

instances we wanted to show you both

good and and not so good predictions

like the lower ones id 0 and 9 theyre

not so good but and pretty good um

so we counted based upon this kind of a

visual display

0 0 of the followed

the the predictions were on dot

for 0 of the the predictions did

not follow the uh

the the the predictions did not follow

the observations

why is that

thats because

um

there was uh the records here

observational study

for several of these

six of

were not straight meaning the inr as you

can see for these two patients was low

but if you looked at the charts the

dosing

they kept increasing the doses so its

not clear

how this can happen in spite of

increasing the doses the the inr starts

dwindling down

um so that part is is not clear

so so its we dont we cannot say that

the model doesnt predict the data very

well um

perhaps there is some uh uh

some of this can be attributed to poor

records

uh im not saying that just to justify

uh and defend a model

but

0 of the subjects it was very good in

terms of the prediction so and these are

the six who had questionable records so

it is possible that the model is not as

bad as it may seem if you only looked at

these two subjects

chla dosing

led to poor inr control as you can see

here which

actually lets look at only this graph

the the time days to to

to 0 are shown on the x axis and

percent of the patients uh i

of the total inrs measured

uh in the in in the range

e and outside below and outside the

range are shown here the green is good

meaning within the target which is about

and it goes in

to about fifty percent

uh uh only after day twenty two

the patients who are below the target

are about fifty percent

um

you know roughly and they go down to

about by by week three

the number of patients who have higher

uh

inrs increase over time from five to a

tad over 0

in three weeks

so

by and large if you compare it with the

adult trials

this is

a poor inr control

and if you if you parse the data based

upon genotypes you can see that some

genotypes have

worser outcomes compared to the others

but the numbers are small so i dont

want to spend too much time on that

then we have the model and the model

performs reasonably well so we we

simulated

pediatric data under different dosing

regimens and then

looked at the output of inr

those are the demographics age one month

to years

weight five to eight kilograms and then

we

simulated a thousand kids per genotype

so what genotype would be six variations

in two c9 three variations in weaker c

which is eighteen variations times

thousand eighteen thousand kids

and

look at how many of these subjects met

the target

inr

okay the same principle here to is

what we want

ill skip that its just to narrow down

the the

dosing um dosing scheme and we found

that it is best to separate out less

than 0 versus 0 and greater body in

based on body size kilograms

because you cannot get a

same per kilogram dose for all of them

because the elemetric scaling the body

weight clearance relationship is

curvilinear so you will not be ever

able to get

one per kilogram dose for

the full range of five to eighty

kilogram patients so we made it into

kind of two linear mg per kilogram is

linear right mg per kilogram two lines

uh below 0 about 0

and thats the titration scheme

then

we found and we simulated both genotype

based and genotype independent dosing

and as you can see

the just by looking at the two panels on

the on the

right hand side genotype based and the

left hand side genotype independent the

greens are taller you dont need to look

at anything else the greens are taller

and the reds are smaller the reds are

larger on the left hand side

so by this you can

conclude that genotype based dosing is

more appropriate in terms of therapeutic

achieving therapeutic success

so

now

there are some

challenges the lowest strength

administered

in pediatrics is 0 milligrams that too

you crush the tablet and you give it

with apple sauce because these kids

cannot swallow tablets

and success of the proposed dosing

because some of these doses we assumed

dosing is not an issue but it is an

issue in practical in practice so there

has to be some other formulation but

then who is going to do this because

nobody is going to make money out of

that probably

in conclusion

this is to our best knowledge first

reproducible scientifically based

pediatric warfarin dosing regimen

and there is successful use of prior

information bridging from adults to

pediatrics this is the other thing

mechanistic models allow

using prior data efficiently if all you

had is a pvalue theres no

actually theres no utility of pvalue

other than just looking at it and then

maybe celebrating it and then youre

done with it theres no carrier of

knowledge from from that and we took

advantage of the pharmacogenomic advance

advances

and and the proposed dosing perhaps

should be studied in a clinical trial

and maybe

they we should think about coming up

with a pediatric friendly uh formulation

if possible and

thats it folks

so

so in essence what is pharmacomatrix

what is pkpd modeling pharmacomatrix is

not about number crunching its a

culture of discipline decision making

youre taking all the available

information youre using making the best

use of it to guide the the next research

sometimes you do not have to do clinical

trials again meaning if i were to treat

a

patient that i know i care about

pediatrics i would go with the

recommendations that ive shown you

before i dont need to wait till i see a

clinical trial

because i have confidence in the pkpd of

of warfarin and the knowledge that we

accrued so far

so with that i would

end this talk thank you very much

you