hello Im Rob bees and Im faculty at

Buffalo and uh I will be presenting part

two of a vignette on population

pharmacokinetic

modeling so in in part one of this

vignette we covered elements related to

the research question the nature of an

experiment the data that were generated

and then mainly the visualization of the

data in part

two were going to now is move into the

actual model building what are the

elements of model contexts to explore

what models that we want to

consider what do we look at in terms of

output and what are some very basic

elements of model

evaluation and how does how does that

allow us to generate inferences about

the pharmacokinetic characteristics of

the

drug again were going to revisit our

kopine example from the N imh funded uh

KY studies

so our general outline will focus on

model building approaches and this

encompasses the criteria for model

discernment things such as objective

function value or of information

criteria graphical

indicators then we consider what a

structural b or base model search looks

like how do we approach generating

initial estimates

what is an appropriate scope of

potential models to explore for example

one or two or three compartment models

linear nonlinear you know the target

mediated drug disposition based

elimination how should we think about

the between subject variability that

arises that we like that that is

critical in a population pharmacokinetic

analysis we wont cover in detail any

evaluation of the residual error

structure in this part

but one would evaluate any systematic

patterns in those residuals that would

help

guide model

selection were also going to assess the

impact of uncertainty in parameter
estimates and one may also evaluate
mixture distribution for parameters but
mixture distribution is a little more
advanced and they are outside the scope
of this
vignette we will touch on B basics of
covariant modeling so once you establish
this base
model you search for correlation between
normalized distributions of the
individual parameters we call those the
AAS and individual specific
characteristics uh one could consider
continuous versus categorical
variables and structures that describe
those relationships and then what are
the criteria for inclusion or exclusion
for the purposes of this part two
vignette we will cover the basics of a
step high CO variant modeling
strategy so lets start with the
criteria for model
discernment the objective function so
many statistical analyses will return a
numerical index of model

Fitness this is often referred to as an

objective function value and if youre

doing a nonlinear mixed effects modeling

population pharmacokinetic analysis for

example if youre using

nonm that objective function value is

based on the

likelihood actually the value returned

by Nom is minus times the log

likelihood and

why minus two times the log

likelihood well if youre comparing

models the difference in minus two log

likelihood values is approximately Kai

Square

distributed so what does that mean if

you have a population pharmacokinetic

model you can compare models if theyre

nested with different degrees of freedom

you typically make one change at a time

and you can evaluate whether or not that

change appears to have improved the

model description of the data

statistically by looking at the change

in that minus two log likelihood value

for example if your objective function

value changes by points because

its minus two log likelihood if its

points lower with one change in the

model IE one additional parameter then

that means that you have a significant

effect at the P equals 0

level if the objective function value

change is points with one change in

the model so one additional parameter

then its significant at the 00

level so it gives us some guidance its

not the only thing that should be

considered there are many elements that

one must take into consideration when

building

models another criteria for model

discernment is are the information

criteria I have two examples here the

AKA key information criteria which many

people may be familiar with this is a

function of that minus two log

likelihood or that objective function

value but theres a penalty added to

this and that penalty

is two times the number of parameters

that are in the models so if you have a

more complicated model if you add

parameters your information criteria

value will not be as low or as

optimal similarly the basian information

criteria sometimes called the Schwarz

basing

criteria is a function of the minus two

log likelihood plus a penalty that

comprises the the product of the number

of parameters multiplied by the natural

log of the number of data points so here

you have a combination of number of

parameters and number of data

points uh these information criteria do

not give a strict

basis for statistically statistical

inference based on statistical

significance what they do provide is

whether the complexity of the model is

supported by the observed data so its a

binary

decision what is better or worse but not

a specific continuous value that tells

you something is met a particular

threshold with respect to statistical

significance

so continuing along with criteria for
model discernment some other basic
graphical graphical indicators of
Fitness
include various goodness of fit plots
such as the dependent variable versus
the population predicted value the
dependent variable dependent variable in
this case is the concentration
measurement versus the individual model
predicted value so its adjusted for the
individual observations and individual
varant and then plots by individual that
show the time course of the data show
the time course predicted by the model
at the population level and show the
time course of the predictions from the
model at the individual level and then
of course residual plots but as I
mentioned in the
introduction I wont be covering
residual plots in uh this
vignette uh there are also Visual and
numerical predictive checks and again
those will not be covered in this
particular

vignette so lets go back to the basic

goodness of fit plots for model

discernment the dependent variable

versus PR plot so again the DV dependent

variable are our

observations threed denotes our

population

predictions so theyre B those are

predictions based on the dose time and

adjusted for covariant values if those

are in the model okay and these are

based on the fixed effects that are

estimated in the pharmacokinetic model

the PK parameters and the estimated

coari effects so this is also sometimes

referred to as the

thetas all right Al thetas are not

always strictly associated with fixed

effects they are typically

so so to Aid visualization in producing

this type of plot you want to use the

same range on the X and Y AIS

okay so here we have the observed

concentration and the population

predicted concentration so population

predicted concentration on the xaxis

and The observed concentration on the y

axis the dots are

the uh values for each of the pairs of

observe observations with

predictions this black solid line is the

unity

line and this dashed line is a smooth

through the data to see whether or not

there appears to be a major departure

from that line of

unity its useful for diagnosing

structural model Miss

specification and what youre really

looking for is whether or not theres an

even scatter of points on both sides of

the

line the distances are less of a concern

here because those are often adjusted

for with other factors when considered

the individual

predictions

okay uh and the again regression line or

smooth gives you should hopefully follow

that line of

identity so considering this dependent

variable versus population predicted

heres an example that shows a good

model on the left and this is from the

isop model evaluation white paper montre

at all that wases published in CPT

PSP here again on the xaxis are the

population predictions and in the y AIS

are the observations and you see in the

left

panel that we match this line of unity

quite well we have an even

scatter on the right hand panel you see

a missp specified structure and you see

some departure in that smooth from the

line of unity so something something

systematically not being

adequately

predicted or alter L predicted with some

degree of

bias another basic goodness of fit plot

is the dependent variable versus

individual predicted plot again the

dependent variable are the

observations the IAD are the individual

predictions so there predictions based

on the independent variables fixed

effects thetas and the adjustment for

the between subject random effects IE

Adas and

omegas

so conditional on a patients data and

the population

model the model can make an adjustment

to try to predict these values more

closely and these points should be

closer to the unity line as a

result uh again to Aid visualization we

want to use the same range on the X and

Y axis we want to include a line of

identity that would be the perfect fit

thats this black line on the plot on

the right

here um and you want to the locally

weighted regression line you can see

that follows for the most part it

follows the identity line and thats

what we we are uh looking looking for uh

specifically again on the plot you have

the observed concentrations on the y

axis and the individual predicted

concentrations on the

xaxis so here we have an example of the

IED versus dependent variable plot for

the true model and the IED versus

dependent variable plot for a

misspecified model and again this comes

from the isop model evaluation paper

Mont at all CPT

PSP and we you see that on the left with

the true model you have a line of

identity the locally weighted regression

line follows that closely the points are

very tightly distributed around that

line of

identity for the true model in the right

hand panel with misspecified structural

model you can see that points just are

systematically shifting around that line

of

identity and that the locally weighted

regression also departs from that line

of identity so it suggests that you need

to rethink your model structure because

there there is some sort of a

misspecification in this model and even

with the adjustments that fundamental

structural model is unable to describe

the pattern of the data Visa the

concentration versus time profile

the next basic plot to evaluate Fitness

is this population predicted and

individual predicted and dependent

variable versus Time by patient or by ID

by individual and this is a simple way

to visualize how well the model

describes individual profiles and its

useful for identifying observations that

Warren doublechecking for potential

mistakes could be about extreme values

and that sort of thing so what does this

plot look

like well here we have a

matrix of individuals so each of these

panels represents a different

individual we have concentration on the

Y AIS we have time on the x

axis and the dots are the actual

observed data The observed

concentrations in this

case and we we have two different lines

we have a blue line and a red line the

blue line is the population predicted

value and if we dont have covariates in

the model and were all and all the

patients got the same dose this blue

line is going to be the same for all individuals okay because its using the pop because it is using the population pharmacokinetic parameters the red line is the individual predicted lines these are adjusted for the observations so where we can see this most dramatically is an individual 00 you see that they have this one high concentration so the population prediction is this this blue line and it shows the same as every other Blue Line in all these panels but because this solution is conditioned on that on individual 00s data for this particular panel the individual prediction is actually closer you can see that its matching those points a little more uh a little closer at least its trying to match that that that higher initial value this allows you to to to evaluate whether you think there are there there are outliers whether individuals seem to be grouped into different kind of subpopulations in terms of the

concentration time profiles and to

evaluate whether or not at the

population level beyond the DV versus PR

plot the predictions seem to be uh

reflecting the data with respect with

respect to evenly Under and Over

predicting these uh these observed

data

so the next component were to talk

were going to talk

about are the initial

estimates and these are basic principles

with respect to initial estimates and

some of this was taken from a paper in

TCP and I have the citation on on

subsequent

slides so all nonlinear regressions

require initial estimates as a starting

point for the search of likelihood or

search for an objective function and so

this

uh it doesnt matter what software

youre using you need to provide inter

initial

estimates so theres some strategies for

uh considering the calculation or

determining those initial estimates you could do a noncompartmental analysis on the data that you have for example the smooth we showed forthine maybe theres other literature maybe this is a drug that has already come out and there maybe in populations there are uh population pharmacokinetic parameters or even General pharmacokinetic parameters published the FDA uh website in particular the redacted andd uh reviews of clinical pharmacology review in particular are available as a result of the Freedom of Information Act and these these often provide average profiles from phase one and two studies with PK characteristics alternatively the drug labeling the clinical pharmacology section often has an indication of the general pharmacokinetic characteristics and those are all places that you can go to evaluate this now if this is a a brand new drug and youve got your then you you youll have to use your your your the data that are available to you from the study key challenges include

sparse sampling so you know you could do

time after dose and consolidate by

dosages similar to the plot that was

shown in part one for the

copine and we could have multiple points

create a smooth and do a

noncompartmental analysis on that

smooth curve at least give us some sense

of what reasonable clearance and volume

distribution parameters might

be so this is often a nontrivial issue

as poorly chosen estimates can increase

the runtime for any nonlinear aggression

problem or any nonlinear mixed effects

problem and in particular if youre

using nonm and youre using some of the

gradient methods and uh the first order

first order conditional first order

conditional with interaction in

theasian it takes longer for solution to

be discovered it can also result in poor

or incorrect final parameter estimates

some of these gradient base methods are

quite susceptible to local Minima and if

you dont have good initial estimates

you may end up with a solution that you

think is a is a stable solution but it

actually represents a local minimum in

terms of the the the estimated

pharmacokinetic

parameters so what parameters require

initial estimates well our fixed effects

values typically thetas right our

typical values so these are values in

the Nom Control stream and you also

probably want to provide some bounds so

for example if youre estimating a

clearance value clearance is a

physiologic process has has to have a

positive value uh its probably not zero

so you want to put some bounds in and

its probably not you know 00 million

liters per hour so you may want to give

not only an initial estimate but some

ranges one would one also must provide

initial estimates for the random effects

value so for the between subject

variability and between occasion

variability that you might pose in a

population pharmacokinetic model these

initial estimates are provided in the

dollar Omega block and it provides the

initial search for a value representing

how variable that parameter is between

individuals or between occasions

depending on which one it is bsv or BV

in the

population and then the residual

unexplained variability and for the

residual unexplained variability you may

want to start with uh values that are

close to the assay variability the limit

of quantitation and the CV of that

particular

assay

So speaking a little more specifically

about fixed effects Theta or typical

values or population averages this is

strictly the central Tendencies so the

population typical values youre not

providing any information on the

variability or dispersion or uncertainty

across the population and again were do

using a best guess and we talked about

strategies for that best guess again

literature is a good source of

information the authors from the TCP

paper suggested some general ranges for

linear processes or typical first order processes in pharmacokinetics for clearance and volume and absorption processes but it really will depend on your specific drug uh you know keep in mind that the values might be higher for the extravascular dose given the divisor of f these are really if it is if it is an extravascular dose its clearance over F and volume over F Etc so what about for our example of copine well we actually were multiple values available from the literature and that this table shows the parameter values so these were typically for one compartment models uh and there were three Publications in the peerreviewed literature uh isbister which was actually in a toxicology context with overdose Kimco which was an early evaluation that used the phase one and early phase two studies to generate the model and Z was from from actually the

the uh company developed copine with

with with a larger data set we even had

some values from the ktie studies so

these appeared in a chapter reflecting

this of a book that was published from

the studies but were incomplete you see

theres no residual error

provided uh and uh was other limited

information so we we have quite a rich

set of information to start

with and we can use those as initial

estimates and also give us a sense of

what sort of model structures we may

want to

explore so what is the scope of a

structural model search well we might

consider the number of

compartments this could be one or two or

three compartments linear mammary models

with first order processes perhaps the

type of an absorption model is this A

first order absorption is this a zero

order absorption is this an llang

distribution with the catary chain uh in

terms of the uh delay in absorption is

there is there a lag in the

absorption in terms of elimination
Pathways is this does this appear to be
a linear elimination or a nonlinear
elimination uh there may be other
contributors to the drug disposition to
the pharmacokinetic profile is this a
drug that is subject to Target mediated
drug disposition what are The Binding
protein binding characteristics are
there Transporters that act on this drug
so lets go back to the profile that we
observed
for the copine study so here again we
have a dose normalized concentration on
the y axis and the time since last dose
on the xaxis and if we look at this
remember that there the these appear to
be linear processes there theres these
are multiple Doses and there are not
doses clustering above or below from
part one of the
vignette um and the general input and
offset look close to sort of straight
lines theres not a lot of not not a lot
of indication of a nonlinear process
here so we probably will explore only

linear processes and maybe one and two compartment models so we thought about okay thats the scope maybe for our basic structural model what about the between subjects variability strategy stry so we have parameters in this pharmacokinetic model and they may vary at random between individuals right because is are between subject variability and there are generally two schools of thought on the approach to this one is to put a between subject variability term on every fixed effects parameter so theres between subject variability on absorption theres a between subject variability onment distribution and theres a between subject variability on the clearance the other school of thought is to put no between subject variability and start with what is effectively a naive pulled analysis or naive pulled minimization and if you go back to the original lecture we discussed naive pooled analyses as one as one potential strategy and also highlight some of the

limitations

there in terms of the structural and

base model strategy if we add the

between subject variability to all fixed

effects

simultaneously we may be able to observe

where the bsv estimate is very very

small we can decide maybe we should

remove it maybe you know a half a

percent between individuals is not

really going to have any any

impact uh now this might also be very

small because this the data are so

variable or theyre multimodal and the

penalty for having an enormous between

subject variability estimate is greater

than the penalty for not predicting

those concentrations as well which is

the balance thats thats calculated in

the likelihood for these nonlinear mixed

effects popul phac kinetic

models similarly if the bsv is estimated

but extremely large maybe its not a not

a single distribution maybe there are

multiple modes for example if you have a

drug that is eliminated by cytochrome

p0

d we know there are poor metabolizers

that have almost no metabolic activity

we know there are intermediate and

extensive metabolizers which have sort

of have the typical elimination

characteristic that are noted for those

drugs and and we also have CL

individuals who are Ultra rapid

metabolizers and theyll have extremely

low level sat concentrations those Z do

not arise from the same distribution

theyre centered in

different positions in terms of the

relative

clearance now there are also

considerations of off diagonal elements

what are the expected correlations

amongst parameters and we should explore

those blocks structures exploration of

off diagonal elements would be beyond

the scope of the vignette

today so the other strategy is

to not put between subject variability

on in the initial analysis basically do

a naive pulled assessment and then add

bsv parameters one at a time and then
decide whether it should be kept in the
model do we use the statistical
criteria do we do we need to have
between subject variability on multiple
parameters perhaps theres a dependence
that we might miss if we do this again
we need to consider nonnormal
distributions in multi modal
distributions and off diagonal
elements so there are various also
residuals that we want to consider and
you can evaluate graphically using
residual uh patterns and Im will to
touch on this in a very superficial way
we have the Rees residual which is the
population residual
the W res which is the weighted
population
residual this is only really appropriate
for the first order estimation method
the conditional weighted residual which
is appropriate for the first order
conditional estimation the conditional
weighted residual with interaction which
is appropriate for the first order

conditional estimation with the

interaction option the individual

residual which is the newer versions of

NM is now being automatically calculated

in the older versions one had to incorp

break this into the error block and the

individual weighted residual and the

waiting depends on the error structure

that you select helpful visualizations

include the population residual versus

dependent variable this will tell you

right away if you cannot use an additive

model youll see a fan structure this

with increasing uh distance from that

unit from the zero line with increasing

dependent variable the conditional

weighted residual versus dependent

variable conditional weighted residuals

versus time individual residuals versus

dependent variable and the individual

rated residuals versus the dependent

variable so lets look at some model

output so we talked about selecting

model structures and having a scope of

search so this is a game this is from

our analysis of the copine data set from

the KD studies on the left table we have

output from a one compartment model

analysis linear absorption linear absor

for absorption in first order

elimination on the right panel is a two

compartment model for the same data set

the numbers are the parameter values you

see the units are provided here for the

thetas these are the fixed effects okay

these are your typical values the

population value of clearance 0 for

the one compartment model for the

two compartment model for example we

have volume absorption rate for the two

compartment model V V because its an

extra value dose and this is the coding

in in in Nom and then the interc

compartmental clearance is

Q the omegas are the between subject

variability on those parameters so you

can see that the we have the Omega

clearance right this is the between

subject variability on clearance the

value returned by nominum is the

actual when we convert that to a

percentage between subject variabilities

about so the values in Brackets are

the

percentages between individuals

between individual variabilities

again these are the between

individual variabilities and in Brackets

we see the actual

percentages and the numbers returned by

n are presented as the main numbers here

these are basically like a CV not

exactly depending on which estimation

method youre using you have to do a

different back transformation

and then we have our residual

unexplained variability this is our s

these are these Sigma values and at the

very bottom we have our ofv the

objective function value and you can see

for the one compartment model this is

the value of

0 9 and you remember that the

objective function value is minus two

times the log

likelihood and the lower the better

these values if we compare this to the

two compartment model

we see that this objective function

value is one is

00

thats almost over 0 points lower you

remember for one degree of Freedom right

a change of

points was sufficient to deem this a

statistically significant

Improvement now here we have two degrees

of freedom because we are

adding these uh extra volume of

distribution B and the

intercompartmental clearance or you

could argue four degrees of freedom if

you are including the between extra

between subject variabilities but the

0 points on a Ki Square even for four

degrees of freedom is highly significant

so

this would point us towards selecting a

two compartment model structure now this

is in conjunction with evaluating

graphical patterns uh residuals

Etc now were considering between

subject variability you see that the

estimate for the between subject

variability on the peripheral volume

distribution here Omega V is extremely

low right 0 between individual well

that means its probably not having a

significant impact on the disposition

and its an extra

parameter so if we basically remove this

parameter fixing it to zero in the right

side side table here we see that the

objective function value actually got

better so the estimation was more

stable it was and the other parameters

actually are all reason reasonable as

well and youll see this V value

actually starts to get a little bit

lower and closer to what was reported in

the

lature well what about model uncertainty

we can also

consider the parameters with respect to

the model uncertainty this is often also

referred to as the relative standard

error of the parameters its basically

how well do we know those parameter

values we do an analysis and we

determine okay

well can we rely on that parameter

estimate so youll see that most of

these value these are these are the

values in Brackets or parentheses next

to the main numbers here in both of

these tables

and what we see is that theyre

generally relatively low with a couple

of exceptions but the major exceptions

we left in now this is the between

subject variability of Omega V okay we

have a value of in this case but

the uncertainty in this estimate is

000 plus which suggests that that

that value could assume just about any

any number any value and you would get a

very similar solution so these

particular uncertainties or relative

standard errors are calculated using

something called the fisser information

Matrix what is the fer information

Matrix if youre running most nonlinear

mixed effect modeling

software a variance covariance Matrix of

the parameters is determined that Matrix

is inverted and it allows one to make an

inference about how much worse the model

fit gets if you change the parameter

value and that is the basis of the

determination of these uncertainties in

these parameter

values in very rough terms in very rough

terms uh one can also obtain these

values using a nonparametric

bootstrapping approach but thats

outside the scope of of this

vignette so essentially if we remove

again this between subject variability

we really get no change in the objective

function and the model stays about about

the same and estimates are all

reasonable so theres no reason to

include this so the uncertainty in this

case on this parameter estimate pointed

Us in the direction modifying the model

OKAY by removing this this

element so lets talk a little bit about

basic covariant modeling and the

technique Im going to touch upon in

this part two vignette is stepwise

covariant model building and this

involves steps called forward addition

and backward elimination so you start with our base model we talked about building the base model and and making those selections and then you test the covariant to determine which one improves the model most significantly so you test each covariate individually you get a set of objective function value changes or differences and you evaluate which ones are significant and then rank order which you know the level of significance how many points is this change by and you can add this covariant to the to the model starting with that most significant covariant and you add the second most did it get did the model get better or not if it didnt get better then you remove that that second goarant you had the third one you check did it get better or not oh it got better so you leave that one in for example and you keep doing that until you have no further Improvement then you have this full model with coats and then you start

removing

covariants but in a different order so

you dont start with the you dont

remove the last covariant that you added

you add you remove a covariant maybe the

most significant covariant that was

added during the forward Edition and you

evaluate whether or not the model

Fitness got worse IE that objective

function value went up and if go and

typically you have maybe set an alpha

threshold for forward addition of 00

so that would be points and in the

backward elimination phase you change

that threshold maybe to 00 go

points you keep on doing this until no

further worsening is observed and you

have your final

model now this is sort of the most basic

technique there are lots of other

techniques but again they they are

outside the scope of uh of this second

vignette what are the strengths of

stepwise cant modeling well allows

selection of cant relations from a large

set of candidate relationships it has a

reasonable predictive performance

theres lot of experience with this

approach iss an economy in which models

to test and avoids many problems

associated with search based on

empirical base estimates for example it

allows to you to account for varying

amounts of information between subjects

time varing covariant and a single

framework for model

selection like oh this is terrific

except there are some substantial

weaknesses here theres no guarantee

that youll find the best model theres

a selection bias theres a an increased

risk of false selections for relations

with lower power and if youre

covariant right with power to detect the

coar less than 00 And The coefficients

are generally overestimated IE the

impact on the parameter

value and the confidence intervals are

underestimated youre doing all these

different tests and youre getting

different sort of differences and

objective function value and Crossing

thresholds but often multiple testing

penalties are not applied and we do

dont know what the appropriate penalty

would be to apply in this

case uh its not designed really for

generating predictive models and many

runs may result in unsuccessful

terminations or local

Minima so stepwise Cate modeling is

shown in this figure here starting with

a base model looking at diagnostic

information test all the suspected

covariates by adding them to the base

model independently one at a time pick

the model with the most sign ific Cate

add the CATE to the base model okay then

you repeat come back and say take take

the second most significant and add it

did the model can get get even better if

it didnt remove if it did keep this and

keep cycling until you have your forward

Edition model there at the bottom of the

First Column of boxes

here and then our backward elimination

you test the effect of removing all

covariates independently one at a time

maybe start with the most significant

covariant from the model just dont do

the exact same order that or verse of

the same order that you did in the

forward

direction and you end up eventually with

the new coar based model and you keep

repeating this removal until you get no

further worsening in the model and you

have your final

model so to

summarize uh our model building vignette

we have multiple

considerations we have to come up with

rules for Discerning what we think a

good model is uh we have numeric indices

to help guide this things like objective

function value Val information criteria

parameter uncertainty there are

graphical indicators such as residuals

and uh these various plots we

discussed uh we have to come up with

initial estimates we can go to the

literature or do a noncompartmental

analysis of average profile over the

population from data that been

generated uh we have decide on a scope

of the model search what is an

appropriate space to search in terms of

number of compartments and different

processes linear nonlinear elimination

absorption processes how do we handle

the stochastic elements of the model the

between subject variability do we put

this on every parameter to start with or

do you one at a time there was a dual

unexplained variability what is an

appropriate model there is it additive

is it proportional is it a combination

of the two and then we start to consider

covariants how do we incorporate these

how do we look at potential

relationships and what does that mean

are we in danger of missing certain uh

uh dependencies amongst covariates and

as we you saw from the part one

exploratory data analysis vignette one

has to be very careful about covariates

that are correlated amongst different

arms or uh even within different

characteristics because what is the

characteristic that is driving the

relationship with the response and if

you have correlation thats very very

difficult to tease apart so there were

some elements that were not covered in

this part two vignette that is a more

specific evaluation graphical evaluation

of residuals bootstrapping technique

visual predictive checks numer numerical

predictive checks and numerical

predictive distribution errors and that

would be the subject of future

vignettes again I would like to

acknowledge Kristen BOS at Johns

Hopkins University a faculty member

there in the in the division of clinical

pharmacology and uh an MS candidate in

the lab haranga who has been uh working

on the the M the model Direct

me thank you very

much