we are fortunate to have dr christopher

chris currently serves as a reviewer in

the division of neurology products at

the fda

his interests include rare neurological

diseases he also teaches at johns

hopkins and the nih

chris received his md and his phd in

neurological science from the university

of chicago and completed his residency

and clinical fellowship at johns hopkins

he did postdoctoral studies in molecular

neurobiology where he also completed at

the university of chicago and johns

hopkins

im confident youre going to enjoy

todays lecture

hi

my names chris brader im a medical

officer at the fda in the division of

neurology products

and also a faculty in a program for

advanced academic uh programs regulatory

science at johns hopkins university

and today ill talk to you about a very

uh special topic which is the clinical

analysis of adverse events

adverse events are very important

because clinical research

as a whole is a balance between risk and

benefit

and the currency of risk is the adverse

event its actually how you monitor

for the risk in clinical research so i

hope you enjoyed todays lecture

the views expressed in the talk today

represent my opinions and do not

necessarily represent the views of the

fda

so today well use a questionbased

approach its always good when youre

hearing a lecture to fully understand

what

it is youre hearing about so first

well define

adverse events

and then i found its also useful to

understand why we collect adverse events

that really tells the story

for the rest of understanding

why and how we monitor them and then

well go on to hal which many of you
want to know and when they need to be
monitored
before we get into the substance of the
lecture well give you some
definitions that are very important and
the first of course is the definition of
adverse events and as you can see from
the
notes in parentheses this comes from the
federal regulations an adverse event
means any
untoward medical occurrence associated
with the use of a drug whether or not
its considered drug related
then the other definitions you need to
know which i will allow you to read i
wont read them through the slide is a
suspected adverse reaction
and another important concept is that of
reasonable
possibility
and then the final concept you should be
familiar with is that of an unexpected
event
to understand adverse events there are

several dimensions that need to be

described by typically the principal

investigator

or clinical coordinator in a research

study and ive listed them here the ones

ill talk about are designated with the

red star

the first event or the first aspect of

adverse events which is critical to

understand is time to onset and i would

say for each of these that

ive noted both as a medical officer at

the fda but also

when i was in industry

that these particular issues while

they seem very simple often cause a lot

of confusion

and

anxiety with investigators exactly how

to define them so i hope that this

particular section is useful

so there are some aspects of adverse

events which seem rather cut and dry

with respect to time to onset

of event it seems very clear on the top

scenario that if you have an event of

one intensity

or an in an event of just an increasing

intensity which then ends that that is

one event

on the other end it seems fairly clear

that if you have an event

with

a fluctuating intensity

over a single period if it completely

goes away thats likely

or could be

more than one event if it truly goes to

baselines but if that event as one sees

in the middle

scenario

changes in intensity over a continuous

period that could be very confusing as

to whether you should call those

separate events

one example you might think about is

headache where it starts out becomes

intense almost goes away but then

comes back again and its not always

clear whether thats one or more event

as with most of the

attributes ill talk to you about there

are very clearcut scenarios and there

are some that are not so clearcut

even in the eyes of the

reviewers

at the agency but i would say that if

you clearly define

how you are

designating events

and you also discuss those that seem

somewhat difficult to define that would

probably be the best scenario

another attribute which can sometimes be

confusing is that of resolution

which relates in a way to the last

attribute we talked about so

uh its very clear

that if the event goes back to the

baseline state its usually

considered

resolved

somewhat more

confusing could be an event that does

not change

that does not change to the last

inquiry an example of that

could

be

well also for the middle state something

like anemia where

um

it may hit a nader but then stay the

same without clinical consequence

through the rest of the trial

if an event continues to worsen

clinically

then that event would need to be

followed

definitely

and even outside the

time period of the study

but for example many adverse events

simply become nonsymptomatic

and one could say that if theyre

clinically stable that that is resolved

severity is the next aspect or attribute

of adverse events thats critical to

understand and at least at the fda

theres a common practice to

describe them according to one of two

guidances

typically people use terms like mild

moderate or severe so this is not

a very challenging

thing but there are other descriptors

such as

something known as the ctcae

common terminology criteria for adverse

events

that are typically used for chronically

ill patients and ive given you the

reference here

for more healthy subjects who are in

trials

the guidance on the describing adverse

events thats in the vaccine guidance is

typically used and ive included that

url as well

the next attribute is that of causality

uh

how likely was it that the drug caused

the adverse event and for that people

typically use

words like not related all the way

through its certainly related

and then definitions are given

to those different terms so that even

though theyre categorical terms and

they should be intuitive its good to

know exactly what is meant by that

and ive provided you with

two documents that discuss

how to assign causality and their urls

here

the next attribute thats critical to

record for adverse events is known as

serious adverse events

and this is actually

a term that is defined in a regulatory

sense this is not theres no ambiguity

about

what is meant when you check off that

something is a serious adverse event

and it would include any of the

following

things that ive listed in the bullets

here for example deaths

lifethreatening events

hospitalization either the initial one

or a prolonged hospitalization such as

if someone gets a hospitalacquired

infection

disability

congenital anomalies

or an event that requires intervention

to prevent permanent impairment or

damage

and then the final attribute to discuss

is action taken

which is very critical because it helps

you understand

uh

how serious or how severe

the event was

typically if some side effect happens to

you and nothing needs to be done

except maybe resting a little that is of

less consequence than needing some other

medication or some nondrug therapy like

physical therapy

you could have the test drug completely

withdrawn

which would be

considered a very important event in a

clinical trial

or the physician running the trial could

actually decide to discontinue you

from the trial so its very important to

know what consequence the event had

okay now that weve

talked about what adverse adverse events

are id like to give you just a few

slides about how to think about

adverse events before we talk about the

details

of analyzing the incidence and severity

of adverse events so youll have some

context

the first consideration is that adverse

events are just one of several means to

assess safety none of these are done in

isolation

and just

expressing my own opinion i believe

adverse events are one of the most

critical

or important of the methods of safety

assessments because its what

is important to the patient that gets

uh

discussed or the complaint of the

patient

the other

one that i consider

very critical

almost irrespective of all the others is

disposition

disposition

is whether the subject completed the

trial withdrew from the trial and if

they withdrew

why they

withdrew from the trial because its

really

as a

former director at the fda used to say

where the rubber meets the road once you

stop taking a medication and drop out of

a trial and stop getting the health care

that comes with the trial youre making

a statement about that therapy

so but the others are also very

important and need to be interpreted in

the context of their importance to the

subject for example ekg changes

lab changes or changes in vital signs

all important and

with all of these one needs to

consider the condition of the patient

for example a change in creatinine

for one patient the same change could

have a totally different meaning for

another patient

the other consideration

about drugs in general pharmaceutical

therapies

is that all of them bring with them

adverse effects

theres a very famous person paracelsus

who was the father of or is said to be

the father of modern toxicology and he

said that

well he said in german but he said in

the the dose makes the poison and ive

given you a few examples where thats

true in the top

right you can see

warfarin

and one dose is a rat poison and another

dose

up till at least very recently was one

of the few means of

anticoagulating patients long term

but also simple things like caffeine and

even toothpaste have their toxicity

threshold

so

one should not be surprised with any

drug that they have

a toxic profile or adverse events

because all

all drugs for the most part do

i would also

say another thing to consider here

is that one cant study safety without

considering efficacy

theres been

some mention especially recently that

one could do away with the measure

of efficacy in the assessment of drugs

but just because of what paracelsus has

said

in the doses the poison

you need to know what dose is

efficacious to know

what safety is relevant one can always

pick a dose thats irrelevant that looks

very safe but has no efficacy so the two

really go hand in hand

and

to discuss the analysis of safety one

typically starts out with a discussion

of what efficacy is it always comes

first a drug that is not efficacious

cannot be analyzed for safety because

its irrelevant

and then the last general concept is

that of risk benefit

which ive termed here the adverse

exchange rate

the same

adverse event could have very different

meanings for

patients so if i have a drug

that happens to cause thrombocytopenia

with bleeding events

my consideration of that drug will be

very

different if

its something effective as a novel

cancer chemotherapeutic agent

in the same vein

it will actually not be too hard to know

how to think about it if this is a drug

which is the third or fourth line

therapy for a chronic disease and there

are other safer

therapies ill be much less likely to

want to use that drug

okay where it becomes difficult is

as one sees in the arrow in the middle

in the gray zone in the middle its

harder to know how to think about that

for

a firstinclass drug for a serious

disease but not quite

the same as a disease with fatalities

such as cancer

and also the first in

line for

most chronic diseases

however on the ends

its very clear if it offers a risk

most people with very serious and fatal

diseases are willing to take therapies

that have significant adverse events

tied to them on the other hands people

who are taking

the third or fourth line for a chronic

disease are typically not willing to

take a medication that has

very serious side effects attached to

them

now well move to

the how of how to capture adverse events

and this is a very important topic

thats of

discussion i know

around

at least universities

at this time

the typical way adverse events are

captured in clinical trials is are the

spontaneously reported events

and the upside of doing it that way

is that theyre typically more

clinically relevant if the patient is

willing to say something about that

there really are unlimited domains if

something is bothering you you can

generally figure out a way to describe

it youre not limited

in any means x only so much as the

patients able to articulate

you can inquire about them as frequently

as possible this sometimes becomes an

issue

because

in some clinical trials where the visits

are spaced very far apart

there could be a tendency to forget

adverse effects one has

of course one could say then that they

may not be as clinically relevant but it

is something to consider

okay

on the downside of the spontaneous

reporting of adverse events

there are very and ill start from the

bottom of my list here there are very

definitely cultural differences

in reporting adverse events for the same

drug for the same

event especially in domains like pain

ive noticed that to be the case and

thats very well known in the literature

its also thought to be a less sensitive

means

to collect

adverse events

okay its only

what the subject considers very serious

but

for various reasons they may not

complain about something which is

actually very important

on the

other side well go over to the right

side now there are objective based ways

to collect adverse events and they have

advantages and disadvantages

as well and objective means are

for example

lab values

and those are good because you can

define what you

measure

and

both a positive and a negative side is

that they have a threshold attached to

them so you can make it very clear as to

at what point an adverse event

is uh happening

that being said

these thresholds change with a number

of different issues they change with age

so uh

pediatric study for example of one or

two years duration the subject can go

through many

changes in the reference range can

your consideration can change uh with

the persons medical history

and at what stage the disease is

another

not positive aspect about objective

based measuring is that you can only

measure

what you define so if you measure

something very specific you could

miss

changes even within the same

organ system within the body

okay and then clinical relevance is

somewhere in the middle if you happen to

be measuring the exact

correct

thing it could be very clinically

relevant but all lab values are

surrogate

or surrogate assessments they dont are

not actually

looking at the clinical benefit or

clinical disability its a

an approximation of that so the real

relevance always has to be established

and then finally in the middle we have

scale based

measures of adverse events

and an example of that in the

field of antipsychotic therapy its

typical to use a scale called the aim

scale abnormal involuntary movement

scale

and these have some value because you

can focus

on some very difficult concepts

especially

some patient populations have a hard

time articulating certain types of

adverse effects so it allows you to

probe them

more

although

on the downside

again like objective

events they can be very limited in scope

and if thats all youre looking at

youll miss a lot of information

about the subject

there can be bias in the instruction

both to the patient and to the

to the person who is collecting the

events sometimes that is the principal

investigator sometimes that is a

caregiver

and sometimes you can direct them

almost to collect any outcome you want

depending on how biased the instructions

are so its not simple enough to know

that a scale has been used you would

also want to know how the instructions

were worded

and also how the training was given to

solicit that scale

in the middle something that well talk

about in future slides as well and that

are the best

scale

properties or how you administer it

okay you should use a patient reported

outcome

a caregiver outcome

or a physician or a clinicianbased

outcome in some fields this has been

studied at least in the pain field its

felt that patient reported outcomes are

better than the physician collected

outcomes

and then

that being said how

should you inquire to the patient should

you

give them a categorical scale or a

visual analog or vas scale to fill out

in this slide we see an example of a vas

scale a hypothetical example

for

nausea

you could go into a trial and at

baseline be asked to place an x that

describes the magnitude of how you feel

at the moment and ive

this hypothetical patient has placed one

right to the left

place their x of the midpoint

and then at at end point

or lets say at the end of weeks

theyve checked off how they felt and it

was just to the right of x

so this

presents the problem of how to interpret

collecting adverse events such as this

whats clinically meaningful

if on a 00 millimeter scale thats a

difference of 0 millimeters

is that meaningful and does it matter

where that 0 millimeters is

on the whole scale so

the relevance of collecting adverse

events by these methods that seem

more objective can

uh can be very problematic

this is something of a busy slide it

comes from a

publication that ive listed below but

it presents changes one can see

with the method of acquisition one

column

being either by patient interview or the

next by looking through their medical

records

and what it shows is that for different

demographics

of patients or depending on what youre

trying to collect there can be a very

big difference between what you get out

of a patient interview or by going

through their medical records and so

one needs to stop and think

you know which method will give me the

most

accurate picture of the patient am i

concerned about the patients recall

and our inability to articulate or could

it be that the caregiver

or

physician has possibly over interpreted

the relevance to the to the patient so

this is a a real life example of this

issue

okay

now ill talk about data quality

and ill start out by saying ive been

giving lectures like this on

analysis of

safety data and data that goes into

ndas for the last eight years

i would say in the last two or three

years ive really switched my focus

to emphasize data quality much more

because its

often more the case that the data

quality has an issue on the outcome than

people had appreciated beforehand and

as the proverbial

idiom goes garbage in garbage out you

cant interpret

quality into very bad quality data so

its very important that the data that

goes into these analyses is of the

highest quality

so in this slide id like to first

discuss some technical aspects

of adverse event

submission and study and that is the use

of medra

medra stands for the medical dictionary

for regulatory

activity

and it is used to code adverse events

for submissions to the usfda

now there are different

and other languages for coding adverse

events for other purposes

but we wont talk about them today

as of today if you wanted to make a

submission either to the biologics or

the drug evaluation branches

of the fda

you would be required to use medra in

your ndas

which are for generic drugs and for

certain commercial biological license

applications or blas

come december they will also be required

for commercial

inds or investigational new drug

applications which is the application to

study

drugs in humans in the united states

postmarketing submissions have had this

requirement for somewhat longer

one may ask although i think its

intuitive why does one need to focus so

much on data quality and this has been

studied

fairly systematically and its been

found in the study that im reporting

here

that even small deviations can lead to

very significant differences in the

interpretation of clinical information

the picture i have

to the right provides one example of an

adverse event term

and that term is procedural hypotension

and as i mentioned medra is a

terminology system used to describe

adverse events it has several

levels

of hierarchy

it goes

from the bottom what the patient

reported or the verbatim term

up through several several levels to the

top which is known as the system organ

class

such as the cardiovascular system or

respiratory system

and as it turns out procedural

hypotension depending

on which track you choose as the coder

for the clinical study can go into one

of either two

system organ classes and so

one can divert

these

adverse events and split them up so the

signal could actually look smaller

if the reviewer is simply looking

at the level of the system organ class

so this shows you just how important

this is and well come back to this

example in future slides

theres

evidence in the literature that the

variability even for very simple things

is about and a half percent and ive

noted that

percent as well in my own reviews of

lists of coded adverse events the

variance i had with the original

versions but it can

vary actually quite high depending on

the difficulty of terms if its a very

difficult concept then the variability

can be quite high

the next two bullets discuss

some of the pr common problems of

adverse event data sets

with any data set missing terms can

present a problem

and

especially for adverse events

using nonstandard variable or column

names can

present an issue as well

for those of you who are familiar with

adverse event

analysis im sure youve heard of the

concept of lumping and splitting and

well talk about that in the slide to

follow

so on the topic of data quality lets

talk a second about how

adverse event terms get coded or put

into the language you see

typically what happens is the patient

makes a statement

for example i have a headache that word

headache is the verbatim term

then

the site coordinator or investigator

will decide

which term

on the lowest level of medra

that corresponds to and that lowest

level term is called just that llt or

lower level term

once

the

lower level term is picked then the

hierarchy

for all the terms that follow

are fairly set although some terms can

go into either

one of two

different organ systems for example and

well talk about that

but pretty much the

terms that follow which is the next

level the preferred term which is where

most of the adverse events are analyzed

at or the higher level term

and then next higher level group term

and then finally the system organ class

are fairly defined so once youve chosen

the lower level term

the course for that adverse event term

is fairly set

so there are some

[Music]

jargon terms that people in the coding

industry have

for different inappropriate ways to code

terms and ill start on this slide in

the upper right one is known as

inappropriate lumping

where you take

several

preferred terms the patient has a

certain diagnosis and you split it up

into

well

the patient has a certain diagnosis that

consists

of

adverse event terms

some of which are seem very bad

some are not so bad for that particular

diagnosis and

they lump them together so that you

dont know that

the patient has some of the very bad

terms

on the other end of the spectrum

a patient could have a very bad

diagnosis

and the coder could split that into

many symptom terms so that you dont

appreciate that they have the full

diagnostic

syndrome and then the last

event that i alluded to in a previous

slide was that some terms can go to more

than one system organ class

so if for example a subject has

hypotension its very clear that that

goes to the system organ class for

vascular disorders

but if its in the context of an event

they could be coded as having procedural

hypotension which could go to either the

vascular disorders or the one listed in

the orange

ball

there so one needs to be very accurate

and consistent in how one codes

these the slides that follow are just a

few examples of tools that are available

publicly and are also used at the agency

and used

to look at the data quality one tool

is something known as j review

and if one looks in the bottom

of the slide here you can see that you

can make whats known as a cross tab

which is a fancy word for a table and

that you can

create rows for the different

medra levels if you see at the bottom

going from the ae term or verbatim term

up through the system organ class

and then you can

look at that by treatment which is in

the columns or any variable

you want

and one does this because one wants to

create whats known as an ae map or an

ae coding map

that allows you to look at how all the

terms are coded

and there are at least two different

ways that this is done these days one is

through

the example ill show you in j review

and the other uses a program

thats called jump jmp

although you can do it in almost any

any type of program

so in j review if you

do what ive demonstrated here

that will produce

an ae map

that looks like this

where on the right side you have all the

verbatim terms

that were given in the trial

and in successive columns going to the

far left side

you will see how they are assigned to

the different levels of

preferred ter lower level term preferred

term

higher level term higher level group

term and then system organ class

so if as you go across the next box is

missing that means you go up

to to see what group that belongs to and

this is actually a very fast way to take

huge data sets and check the coding

to make sure

that the coding makes sense to you

not mentioned in a previous slide but

about to 0 percent of verbatim terms

are not

found in medra in any given trial and so

many of these are

what one calls hand coded

where a lower level term is assigned but

its more or less the judgment

of the person coding the events so the

purpose of the reviewer is really to

make sure that especially

those terms that are hand coded are

accurately

placed into the medra system

here is an example of the other program

i was talking about if you look on the

left you can see what could be a very

complex and confusing part of a

adverse event data set in the program

known as jump which is a sas program

and these are not arranged in any

particular order although you may

recognize from the column headers

the same

variable terms ae term which is the

verbatim term from the patient

the lower level term

then the variable name for preferred

term is a e

d cod or d code thats the next

if you sort those terms as you see in

the lower right box thats a jump sort

box

by

medra level you can

put them in such an order that its much

easier to see which preferred terms that

ae terms correspond to

and thats how one

checks out the data quality and jump

and then finally i had mentioned in a

previous slide

or shown you a picture of the medra

browser the previous slide

had the example of procedural

hypotension

and this is an example of an

investigation

into the term

of foggy for example sometimes when you

take a medication

that makes you feel confused you as a

patient may say you feel foggy

but if you put foggy into the medra

browser which will tell you what the

hierarchy

will be youll see that the system organ

class

turns out to be general disorders and

not anything in the nervous system

so you may choose

then to recode that term into something

that will group with other words like

confused or disoriented so that you

dont split that signal in the system

oregon classes

in this segment of the talk i will

discuss how

adverse events are typically analyzed in

premarket submissions to the us fda

premarket submissions is

a long expression for what people know

as ndas or new drug applications or blas

biological license applications

and then out later in the talk i will

discuss

the postmarketing analysis of events or

what happens after a drug is on the

market

one point id like to make is that

adverse events can come from many places

in a drug development program and ive

listed them from whats typically the

beginning

until the end and ive also shown you

what i believe the advantages and

disadvantages

at each point are now

because they come from different points

in the development program doesnt mean

theyre

any less

important its just that if one is only

analyzing for example a phase one trial

youll get different sorts of

information than you will from a large

simple trial

when a drug development program begins

the first study is typically known as

the single ascending dose or first in

human trial

and as with all the monitoring in that

trial

there is very intense detail and focus

on the patient these are often conducted

in clinical research labs or dedicated

hospital units

the difficulty of

using adverse events from these trials

is that

first of all the sample size tends to be

very small

and also theyre typically in normal

subjects who dont have the disease so

the actual relevance to real life

is not so clear although it gives one an

idea of

of what could happen with the drug

the second source

of information

are

either phase two or three adequate and

wellcontrolled trials thats what the

awc means

and the adequate the concept of adequate

and wellcontrolled trials is described

in the federal regulations the exact

place

cfr

it describes the different ways

to do an adequate and well controlled

trial

the good thing about these trials for

adverse events

is that youre studying patients

and also i mentioned earlier you cant

study safety without knowing the

efficacy of the drug typically the

primary objective of these studies is to

study the efficacy so the context is

just right

and because of the concept of

randomization and blinding

you can decrease the bias in these

trials

the downside of gaining information from

these studies is that they are powered

for the efficacy endpoint which is

typically much less than you would want

for studying the safety

although the analysis of safety data the

statistical techniques used do not

speak to causation rather they speak to

association the exact statistical

testing

and then finally

patients may drop out in large numbers

from these trials sometimes for reasons

related to the adverse effects so you

could lose

a lot of valuable information from these

trials

typically following a phase two or three

trial there is something known as an

open label extension

where the trial is not blinded and its

conducted in a much more naturalistic

fashion

which is good because events that happen

there

may be very clinically relevant and also

it allows one to see events that take

some time to develop

however one needs to realize that these

are actually

enriched populations because the pa the

patients who couldnt tolerate the drug

have already dropped out also its

unblinded

so there could be bias from both the

patient and the investigator

and no comparator for context for the

incidence

of the event

one of the best methods of assessing

adverse effects is with something thats

not spoken of very much known as the

large simple trial

and its just that its a large

simple trial that has very few

objectives

and very few visits

so it can be conducted in a much more

naturalistic fashion its powered

typically for the safety event

of interest

but unlike the open label trial its

controlled

so it does not have quite the expense of

the phase trial

but one does not have the context of

efficacy within that trial so these are

best for drugs where the efficacy has

been

established

and then finally

one can gain information about adverse

effects from metaanalyses and these

have the benefit of having very large

populations

and one can do many types of

techniques to analyze

the data however

there are problems when one study may

have an unduly

large effect

on the outcome of the metaanalysis

and also pooling methodology can be very

challenging

one can describe the analysis of

premarket

adverse event or medra data in

as uh going through three phases when

one first gets adverse event data one

wants to screen the data to get the big

picture

and one uses tools

such as something known as the

standardized measure query or smq

or one can perform what are known as

force plot analyses and ill show you

examples of both of those in slides to

follow

one

also does what i call verifying and that

is one looks at the

table of common adverse events thats

submitted for the

package insert or labeling its one of

the most important parts

of the premarket submission

and then finally one can

do analyses related to hypotheses that

one comes up with based on your

evaluation of the data

ill first talk about standardized

measure queries or smqs

by definition these are medical term

lists related to specific diagnoses or

medical concepts such as hepatic failure

anaphylactic reaction or

thrombocytopenia

and i like to speak about smqs

metaphorically like a fishing net

so these are lists of about 0 to 00

terms long

used to capture

events from adverse event data sets that

can be many hundreds of thousands

of terms long

and just like any fishing net you may

catch what you would like in the net but

you will certainly also catch other

things just because you matched

on one term an example of that

is the smq of acute pancreatitis has a

one of its terms being nausea so if you

cast out the acute pancreatitis smq

and theres nausea in the data set it

will turn up as positive however

everybody who has nausea does not have

acute pancreatitis

so that is something that one needs to

be cautious about

ill also talk about something known as

made which you may start to see more in

the literature

thats a tool known as the medra adverse

event diagnostic system

its primarily a tool developed at the

fda although theres discussion

of its programming in the external

literature

and this is a serverbased program that

can take

all of the smqs theres about 00 and

analyze them simultaneously in each data

set

and then the final aspect of the slide

ill point out

is that recently my group at hopkins

has published a very comprehensive

review

on the use of smqs for all of the

approved drugs at the fda and ill

present a few slides

on those findings

in the next few slides

first i want to just emphasize the

practicality and importance of using

smqs in adverse event analysis and for

this slide id like to thank

dr mary doy who was formerly a safety

reviewer at the fda and is now the lead

medical officer in our office of

computational

sciences and for this drug

what had happened is the applicant had

submitted a package insert with certain

warnings and precautions

she had used the

maid

server to evaluate their database and

had found

that the smq of hostility and aggression

had come up with a very high

relative risk and so the final package

insert ended up having a boxed warning

for serious psychiatric and behavioral

reactions so one can see that

this isnt just a theoretical

application but has real real world use

in the publication that i described to

you

all of the

submissions to the fda were evaluated

for their use of smqs for

a number of terms that you can see in

the

table here

and it turned out that smqs have been

used since 00

and

over of the ndas and blas have used

smqs for analysis for a total

of over

0 investigations

so each investigation would be

for a single smq within an nda or bla

this slide demonstrates two

findings from that study

the first

is

who initiates the analysis

and the

fda

initiations are the black bars

and the

industry or corporate investigations

that were initiated are in the lighter

bars

almost all of these are known very few

were unknown who initiated it based on

the review language

but you can see a trend youll see in

slides to follow that this the use of

smqs is increasing very dramatically

and at least at the fda you can see it

really picked up around 0

which is when

maid really came into use at the agency

and made it

forgive the pun much easier to do smq

analyses

now one issue thats been very important

to me

is whether the socalled diagnosis of

the smq was verified by either the

applicant

or the fda reviewer and by that i mean

if one gets an

smq hit at all

it said that that

case is positive for the smq

so in the example of acute pancreatitis

if one simply had nausea one could say

that they are smq positive for acute

pancreatitis

but that wouldnt mean that that person

necessarily had

had a acute pancreatitis so we looked at

whether the finding was evaluated

further by looking at labs or other

adverse events and one can see by the

table

here that the rate of following up to

verify

whether something was truly positive or

not is fairly high

around uh i would say on average

percent but there are still about of

cases where there really was no

further evaluation of the cases so that

would not be acceptable

another item of interest was

what effect these smq analyses had on

the regulatory action

uh during the review and by regulatory

action im speaking of

did the smq analysis have an effect on

the labeling which is very important

or did the smq analysis

was it

somehow related to assigning a

postmarketing study requirement

and so this

example like almost all the other trends

show that with time

theres an increasing trend towards smqs

being an important

tool in the

regulatory toolbox of the reviewer

here the conclusions

from the study of dr chang chang it all

published this year

is that first of all smqs are a tool for

screening

rather than one used to make actual

diagnoses

the second finding

is that its best to use descriptive

rather than inferential statistics to

describe the findings

because the adverse event data sets and

the trials that they come from were not

designed for this type of hypothesis

safety testing

also more regularity is needed for

people who modify these

smq lists and

here im

quoting uh language that says about the

same thing for the

for the medra organizations

instructions on how to use smqs

and then finally the last important

point is that its very important to

verify that cases when comparisons are

drawn between

treatment groups or when one plans to

use these findings for

important regulatory actions

the second example of

using adverse events and safety analysis

ill demonstrate is the production of

what are known as forest plots

and the tool one does

that is called j review its been out

for quite some time even publicly

until recently its been known as i

review

j review provides

many types of statistical analyses

using the metra language now there are

system organ classes that it does that

in

and

you can

do this function known as risk

assessment which produces what ive

termed as forest plots which you can see

in the figures on the right

and in the center

well the first thing one notes is the

column to the left

when before you click on anything has a

series of plus signs

and then on the top all of the system

organ classes

and then if you look on the right you

can see the

the point estimate

of whatever statistical variable youre

interested in odds ratio risk difference

etc and also the confidence intervals

the larger that

circle is you can see a rather large one

about two or three lines down the larger

the population was for that assessment

or in that of that system organ class

you can then click on the plus signs on

the left and open it up from system

organ class all the way down to

most people look at things in the

preferred term level

but you can look at the point estimates

and the confidence intervals for any of

the system organ classes one typically

goes after

those that have

the largest center point estimate

bubble

there and this is a very easy way to

screen for

safety signals in the data when one

first gets a a data set

now well move to the

adverse event tables and verifying their

incidents and

you need to look at these

both

the fda does but if youre interested

in a drug and are looking at the package

insert you need to be interested

in this table and try to verifying it

because

its the main source of information or

one of the main sources in the package

insert and often there are discrepancies

one may have with the coding but my own

philosophy is that if you are going to

suggest any changes

that its really preliminary on your end

youre not with the patient so one needs

to communicate with the sponsor and

agree on the most reasonable

coding for adverse events

this slide shows an example and jump how

its done

youll recall in the upper left before

id shown you an example of an adverse

event table with columns representing

the different

medra levels one then

summarizes them

in a twostep procedure to get the

incidence

which eliminates double counting the

same

adverse event for the same subject its

a twostep procedure and one can then

easily using jump calculate the percent

on each treatment and

and see which adverse events occur at a

frequency greater than placebo and then

decide also on the threshold for

reporting

many adverse event tables one sees

report

at an incidence of two percent but they

go as high as 0

or as low as one

that having been said

i tend to look at the entire data set

because even an event that occurs at a

very small

frequency such as

stevensjohnson syndrome

dont typically happen

in nature and so even if its a small

amount it could be very important so you

need to follow up not only on the common

adverse events but on the very important

adverse events as well irrespective of

their incidents

this slide shows you

a table generated in the tool j review

also an adverse event table

thats

sorted alphabetically just to show you

you can generate these tables to to

look in almost any way you want and this

is useful if you have many events and

youre interested in certain ones so

that you can very quickly find the event

in the table

or you could

use the same tool to present it by

percent percent often is a better

indicator of the clinical relevance and

you can decide what the cutoff is in

your table

and then

put all of those that occur at a certain

percentage and greater than placebo

into your package insert

and then finally for the premarket

analysis

heres an example of the hypothesis

driven analyses

one does these when one

has small data sets you may choose to

analyze them not at the preferred term

level

but at the higher level or higher level

group term

level

and you can also put different adverse

event terms together

to come up with syndrome complexes

such as is seen here

i looked at a data set for both

people who had falls and people who had

a higher level group term of mental

impairment for a drug

that caused confusion in people to see

if they actually had clinical sequelae

from that

now id like to briefly talk about

postmarketing safety analysis

and for this i would like to thank dr

christian cowell whos a

safety team leader

in the

group known as the ose at the fda who

donated most of these slides on

postmarket safety monitoring

well begin with by saying

there are two main systems used now for

postmarketing safety analysis

the largest system is a passive

surveillance system known as fares the

fda

adverse event reporting system and well

talk a little bit more about that in

slides to follow

its

receives very large numbers of adverse

events

and since they come

not from studies but from the marketed

drug its more naturalistic

the problem being that

they are very

underreported one says that at the best

one gets about 0 percent

of events that probably occur

you dont really know the denominator

for most of these events because its

hard to know everyone whos using the

drug even if you have prescriber

information

and the quality of the reports is quite

variable

another system which has

arisen quite recently is known as the

sentinel system im sure many of you

have heard of that its also a

naturalistic system with large numbers

comprised of a number of centers

around the country that aggregate their

safety information

but as with any naturalistic system

its hard to know all of the confounding

factors or missing information

that you might be receiving

as i mentioned fares is the main adverse

event monitoring

system for post marketing

now it is comprised of

reports that are submitted by the drug

sponsors or companies

as you can see from the

graph here as with most things related

to the pharmaceutical industry

and safety monitoring the numbers are

increasing steadily

since the 90s

one limitation i described before is

that

the reporting

from

the standpoint of the patient

is voluntary but once the manufacturer

gets the report its required to be

submitted to the fda and there are

specific regulations that relate to the

timing of when that needs to be received

based on the severity of the

adverse event

as i note on the bottom of the slide

one often has very incomplete

information so

its hard to tell whether the adverse

event was actually due to the product

as with the reporting for the marketing

submissions

there are requirements now that adverse

events are coded

in medra

and uh with the use of electronic

reporting its much easier to process

this information compared to when they

were

purely coming in by paper

the next slide shows the form that i

mentioned at the bottom

the 00 form

and this shows you what needs to be

filled out by the sponsor

and at the very least one needs

information such as the patient

identifier or number

what drug products youre referring to

a description of the event

and the signature of the reporter

but as you can imagine

even with this information its very

difficult to tell

uh causality of the event

uh one thing that helps here is that

since you have millions of reports

generally those large numbers help

whereas clinical trials may have just

thousands of numbers but the data

quality is much higher

when the group the ose

folks get this information or even

companies get this information they

engage a certain search strategy to see

if a safety signal

is arising

the first thing they do is decide what

specific question

they would like to focus on and then

develop a search strategy

and

the ose folks also use the smq tool

or they develop what is known as a case

definition so if theyre interested in a

specific diagnosis they determine which

criteria are important for that or they

could come up with any number of

different custom search strategies

heres an example in real life of how

safety data mining is used for

monitoring

and this has come from a publication

this is not just a tool

for

the regulatory industry but is one

thats used very widely by

the regulated industry

and also people in academia use it

highlighted in this slide

is

the middle row that has

about eight boxes of different

analytical techniques with many acronyms

such as poisson method for very rare

events

or

[Music]

on the right side

there are

bayesianbased techniques to analyze

safety data or on the left side

very crude frequencybased techniques

based on case reports so all of these

analytical techniques are used

to see if there are signals

and then

the

if an event is of interest then for

extra monitoring is applied for that

sort of safety event

ill close the

lecture now with just a few slides

emphasizing that information on this

topic

is available from

many guidances from the fda ive

highlighted

two of them here that i find very useful

the safety reporting

guidance

on the bottom is being revised and i

would say within a year

what will be available will be very

cutting edge and up to date

this is just a a picture saying the same

thing one of the tasks

at the agency besides reviewing this

information everyone is really involved

in producing these guidances for

industry

and

so

one should be on the lookout for new

guidances and as ive mentioned theyre

updated

on a regular basis

so well close with this slide

emphasizing how important it is to have

good quality and standardized data

because as you can see if youre not on

the

same page

you will not just be analyzing adverse

event but your analysis itself

may turn out to be an adverse event

thank you i hope you found this

information valuable

if you have any questions please contact

the program coordinator