\*Disclaimer: All transcripts are provided as a resource and are not guaranteed complete accuracy

Oops he just started recording so while doing that sorry Hi everybody I'm I'm uh

Peter Schwartz I'm the director of the IU Center for bioethics and of the

bioethics program for the ctsi uh here and I'm pleased to welcome you to our

first of the 2023-2024 Academic Year our first treats talk the

translational research ethics applied topics uh talk series and um these are

introduction to key Topics in translational research ethics you know recorded and put online uh we come to

the Center for bioethics website to find those uh also we include references of

Interest often things the speaker spoke about we're lucky today to have Andrew Brightman who is the professor of

engineering practice at Purdue University but more importantly is a long-standing member a faculty member of

the bioethics and subject advocacy program of the ctsi and he'll be speaking us today on ethics issues in

design and testing of medical Technologies um the talks generally run about 30

minutes depending on the speaker and then we usually engage in a conversation after that about questions and

expansions so Andrew Professor Brightman thank you and off to you

thank you Peter thanks everyone for attending I hope this becomes a good

conversation at the end I will do some president I have a few slides more than I had imagined as always but

um there's a bit of a case partial case at the end we could use some discussions and certainly I'm open to questions

um during from anyone in the audience um that if I'm going too fast or not

clear about something I'd really appreciate that I'm taking this uh from

the perspective of being a engineer um focused on medical devices and

Innovation design and testing are areas that I'm most interested in and teach on

and particularly ethical engineering and so while there'll be some clear

Connections in translational research to clinical studies human subjects research

I'm trying to focus this talk a bit unique in are unique in the sense that

it's about the phase of this medical device development which is design and

testing so I'm going to share my slide here

I guess no one can see it yet um

let's make sure

is that visible

hey can I make that hopefully the little thing at the top will go away yes

it is visible okay yeah thank you I got you I'm trying to get the uh

bar at the top to go away but it's not anyway

um it's gone away on my screen so okay great it's showing up on mine thanks

Peter um so yeah so here's what I want to cover today I want to talk a little bit about diversity of medical devices

um there's such a wide range um some a little bit about the regulatory Pathways the regulation of

medical devices is really an ethical um analysis and ethical basis for that

in terms of safety and Effectiveness we'll talk about those pathways

um the complexity of the device development process raises um a lot of complex ethics issues and

we'll go over a few of those a number that come to mind immediately

in terms of device specific ethic issues as differentiated from maybe drug

development or other biologics development we'll do part of a case example and then I have a few references

at the end if people have interested in more reading

um as always these treat talks are meant to be just a primer a start of a

conversation not the full fledged information and if you want more

information advice and Consulting particularly on the ethics issues than

the center for bioethics is uh is ready and willing to provide ethics

consultation you can find the console request form at the bioethics and

participant advocacy program page and or you can contact Nick Oliver the program

manager Who's online here and His email is here the other uh advice in

Consulting opportunity is an organization a core program of Indiana

ctsi which I'm part and if there's actually two components it's called the

think tank and there's a think tank for devices and a think tank for drugs these are

advisory groups that help people who are interested in research and development of devices and drugs towards

commercialization so not sort of basic research Discovery but really going to the next stage of commercialization and

lots of Ethics issues show up there as well uh there's a link to the web page

for the think tanks and Dr Kara Garcia is the navigator for the think tank

device and her email is there as well

so I want to just remind us all of us have had interactions with medical

devices at some level whether it's for our own treatment or treatment of family members or hospital visits or even just

to the you know Primary Care Checkup

um because medical devices range from the most simple to very complex devices

they can have diagnostic roles to um to monitoring to assistive

Technologies to therapeutic roles they can be external uh you can think of

many wearable Technologies and that's a huge um growth area both for therapeutic

and Diagnostic and even in clinical studies now trying to understand human health as well as the more

um familiar implantable devices such as defibrillators or hip implants

devices can be simple mechanical tools to complex digital or Imaging equipment

ranging from disposable gloves or cotton swabs to large equipment like an

MRI instrument there's the range from everyday use to

Specialty equipment so the design and testing um is in lot needs to be in lots of

context unique to that particular use area and

then there's also clinical versus home use sorts of technologies that we have to think about ones that are designed to

go home with a patient or to be set up in a home care situation or off-site

clinical care or in the hospital Universal to custom fit uh device design

is important um some require custom fit or custom analysis

stents for example implantable stents are now some of them aortic sensor being designed specific for the patient

versus universal and then and the most perhaps most important um

typography of medical devices is the low to high risk and this is how FDA

classifies devices and how it regulates them with different levels of Regulation

and evaluation based on their risk um here's a

diagram that just shows that the majority of medical devices are low risk

class one there's quite a number of medium risk class two that have a special

regulations and then of course the most risk

life-saving equipment often or life changing if they fail class three high

risk which require the highest level of clinical investigation testing and

trials you can imagine some of the different devices that we've mentioned in each of

these areas and in fact um the range of risk to benefit is a

key element at which the FDA is evaluating in which um the ethics are

looking at how much beneficence uh how much uh risk of harm or

non-maleficence is a constant design uh trade-off and a feature of the ethics

analysis and design and development and testing because no devices are without

risk they all have some risk benefit a risk of harm potential for benefit

profile so the FDA as a regulatory agency

um with under the laws of the government and Congress has some very specific

guidances on what is a medical device and I put this here not that we need to

belabor it but then the language is very specific but it just shows that the

dimension at which um when the FDA regulates medical devices they're being

very specific about a certain category it's an instrument apparatus and Implement machine contrivance implant in

vitro reagent or other similar or related article including a component part or its accessory uh which it has

the following three components and these are important to the FDA and to device

developers it has to be include one or all of these recognized

in the official national formulary uh or pharmacopoeia it's intended for the

diagnosis of disease or other conditions or in the Cure mitigation treatment or prevention of disease

in men and animals so in both human medicine and veterinary medicine devices

are have to have these components but a key differentiator from drugs is that

these are intended to affect the structure or function of the body with out having a primary chemical reaction

or not dependent on being metabolized so that separates out drugs and in many

cases devices do not include the software functions they're excluded into another category now

that's a very narrow definition and it's being blurred uh daily by new Innovative

devices um that uh include combination devices I'll talk about those in a minute but we

have many biological um components uh one of the technologies

that I was involved with was a based on a biological material but in fact it was categorized as a device because it was a

structure and structure function and not a metabolic metabolized biologic so it

was really interesting how that one got classified um

some other differences between devices and drugs they typically have an

engineered devices have an engineered set of components whereas the small molecule drugs are a chemical

formulation so the manufacturer is quite different direct mechanisms of action

usually um very clear readily apparent near-term responses versus a biochemical mechanism

of action that may have a time period of uh and kinetic response

um medical devices are often very organ specific or site-specific whereas small molecule compounds typically are

systemic um and the these differences really do change the way we do testing and design

and the way we think about the ethical issues that arise patient responses

um in in medical devices tend to be more similar um because of us the devices are mostly

the same when implanted versus drugs that are dose dependent both on their

benefit and adverse effects now that that those this this data in this table

is from 2010 from uh The Institute of medicine and I think there's some huge differences now in dose response of of

certain implantable like the brain implant can have significant dose

responses based on the signal and frequency that's being sent into the brain

um a key thing about cost in the financial is that most of these devices are are quite expensive right up front

um and they have a particular lifetime whereas drug costs can be much lower but you have to keep taking them and so the

costs accumulate with use um a key thing with a key aspect of many

medical devices is they require some sort of professional expertise um they often have complex instructions

for use or maintenance and that requires um specialized uh technical support or

training for those who are using them and they if they're a home use or a

patient use then there's some special concerns there for abilities of patients

to comply with those instructions whereas um drugs are often either

injectable or if their pills can be taken and applied rather straightforward

not always true chemotherapeutic agents obviously have some very specialized um

applications and controls another difference in devices and drugs the continued product refinement so

quite often a medical device is got to gets to the market in a sort of a

iterative process it's been refined over a period of time but often within a period of a few years there's a new

reversion out a new model an upgrade a change which can be quite challenging

for issues of safety issues of influence of Effectiveness

particularly if they're implanted devices that are intended for long-term use

um the development costs are are quite high up front for small molecule compounds and Discovery and development

but um devices have high development costs they just tend to accumulate over time

and then finally the quality control challenges um are really high with medical devices

in part because the systems are often quite complex not for very simple tools

but if you have a complex electrical mechanical uh and biological or fluid

system that has lots of challenges we'll talk about

um okay so combination products or combinations of drugs devices and biologics I'm not going to talk about

these but you can think about a drug loaded stent or a drug loaded syringe

these are regulated differently and have their own complexity of ethical issues

I'm not going to go into those today but I think it's important to see that there's a lot of overlap

um the class one regulations are General controls these are mostly

um disposables or single use or tools that

are the safety and Effectiveness are fairly standard well known they need to

be manufactured with good manufacturing practices compliance with standards and performance and any Adverse Events get

reported to the FDA all of these General controls including registration of

devices and record keeping a require required for all the other higher level risk devices such as the class 2 Class 2

devices go through a pre-market notification that's a clearance many

people know it by its um by its regulation number of 510 code of federal

regulations 510 sub uh sub letter K these are low to moderate risk they have

specialized controls and have to demonstrate sub substantial equivalence

that is to illegally marketed device that's a predicate so these are devices

that are approved based on a predicate um this goes back to the 1976 medical

device uh authorization act um and they grandfathered in a lot of devices and then said okay if your

new device is essentially or substantially equivalent in safety and Effectiveness to that previous device

you can prove that we'll let you Market it without any further um uh

extensive clinical trials or clinical data now this has been

challenged and changed over the last several decades in part because

um you can get a chain of predicates okay well this device is predicate to that device and then and it goes down

the line and pretty soon the third or fourth generation doesn't look quite at all like the original uh predicate and

um sometimes there are predicate devices that have failed and then um how do you um ethically move forward

with approvals of uh of a device that has a predicate that has substantial

problems and you're saying oh ours is substantially equivalent in its safety and Effectiveness which doesn't mean

much of anything so this um process which is intended to speed devices to

Market and to clinical use where they can be effective without um incurring a lot of clinical evidence

costs and time um has stayed in in the process but is

being challenged every year and then the devices that have the

highest risk their life supporting a life-sustaining um or could have a significant risk of

of harm these require the high levels the highest level of scientific

regulatory review um so you need clear clinical evidence of safety and Effectiveness to get these

drugs into them uh into clinical use this process is expensive and it takes

um you know five to ten years in many cases to get a new device these are

considered not don't have predicates or have a high risk profile that can't be

measured easily in bench testing or animal testing there's two other regulatory Pathways I

don't want to talk about this time but it's important to know that there's a de novo pathway which allows devices that

are approved particularly in other countries such as this detectable device pill that detects

blood in the gastrointestinal tract uh developed in Ireland and and marketed in the EU has

been now allowed cleared for de novo um for use through the de novo pathway in

the U.S and then there's humanitarian device exemptions these are devices particularly uh for Orphan diseases or

benefit patients Diagnostic and treatment of small populations and a

recent approval was for a device that fixes the um

in neonatal patients a birth defect or the esophagus is not connected to the

gastric rest of the gastric system so I want to talk a little bit about uh

complexity of device development so in addition to all the regulatory controls

that help protect safety and Effectiveness or non-maleficence and and

beneficence those ethical issues um there's a complex device development pathway that ensures that by the time a

device gets to uh be submitted for regulatory approval to go to clinic

um a lot of um the testing and understanding of the device

functionality have been optimized so on the side is a

a diagram that shows you know you start with a great idea you have some user needs a unmet medical need or an

improvement on a previous device and you start quickly and immediately with understanding what's the regulatory

strategy what classes this device and what are the requirements for design testing and eventual approval or

clearance you go through a process of design uh planning creating design inputs which

this is how you determine okay what is going to be effective and what's going to be safe what will our specifications

need to be when we manufacture this those initial specifications get built

into prototypes the prototypes get tested um through multiple iterative processes

of design development and testing and when design outputs the testing of the

devices meets the design inputs that's called the verification stage at that

point it can go into the practice of validating whether this

device actually solves the user need or the clinical problem and that is the

validation step is often where the clinical testing or animal testing or human clinical testing come into play

it's not until that point that uh in the regular and development pathway that

it's considered a medical device and can be submitted for uh

approval for use that process is iterative can take a number of years and

that's where I want to focus discussion about design inputs and testing

of outputs to think about ethical issues because a key idea in the ethical issues

of design and testing of medical devices is that um early stage evaluation and

consideration of the ethics issues that are potential down the road in the full product life cycle

um it can really prevent failures down the road it can be costly to have to go back and to recall or redo tests or

redesign and remanufacture and certainly the potential for harm to patients if

this is not thought about in advance so when we teach engineers and researchers to think about the ethics we say all the

way through from the beginning to the end of the product life cycle which includes in many cases of product

recovery or retirement or the waste issues that are involved when you're

making millions of these devices and they're going out and being used and then what do you do with them at the end of the product life

um and monitoring well into and throughout clinical use so thinking about what are the potential ethical

issues that are going to be encountered is key so medical devices have a long um

life cycle of product development and their ethics issues at all stages to be

considered okay one more complex um diagram here and it's really not for

you to consume all the details but I it does show you that there's in the multiple phases of product definition

and design through testing and um and redesign uh into clinical testing

and into final manufacture before it goes to regulatory approval

um there are multiple phases and components within that which include usability studies technology

um uh development meaning the intellectual property and commercialization uh issues there's the

quality system that has to be in place the regulatory support for eventual regulatory approval that starts in Phase

zero and then there's um scale up for manufacturing you really have to think about how do you manufacture this from

the beginning and what might be the manufacturing issues now um the key elements or key places where

testing design testing occur um obviously we think of the final human

clinical trials where devices are proven for Effectiveness and safety these can

be multiple year studies multiple site studies involving all the issues that we think

about with human subjects and clinical trial um ethics but prior to that getting to that

stage um there's early stage proof of concept testing which often involves humans and

as well as animals um and there are ethics issues in when uh what's their ethical requirement for

oversight at those stages when is it a um just a simple device uh

proof of concept test versus a research and

generalized information about this that's going to go into the approval

documentation there's alpha or early stage prototype verification of design inputs

and validation of design outputs and then secondary or

um iterative process to the final product in the beta verification and validation

it's at this point that it's called a design freeze and the technology is then uh can't really be changed from here on

out through clinical study through approval and into clinical use if there's going to be a change a

significant change of of any sort to uh the way the device is designed functions

or manufactured or to even to the quality management system there may be a

potential you have to go back to uh approval stages um and document every change and its

impact on safety and effectiveness

so what are some device specific ethics issues I categorize these um in terms of

the four um principles of bioethics the

non-maleficence and beneficence we've already talked about that's what the FDA cares about regulatory oversight and

safety and Effectiveness is also what IRBs look at in terms of human subjects

uh research ethics but there's also issues of respect for autonomy under

consent and dignity and issues of Justice accessibility and usability for

medical devices that I want to bring up and would suggest that these are being

considered more now within the FDA particularly in diversity of clinical trials

respect for autonomy there's potentials for harm in both of these two additional

areas that are not what I would call primary areas of regulatory oversight

but need to be considered in early-stage device design and testing

um so I I would uh proposed that the complexity of these

medical devices um really support a wider range of potential harms than than drugs do and

so require um perhaps more rigorous or broader thinking about what the ethics issues

are including things like user areas errors at multiple levels I mentioned if

it's a complicated device the implantation may be complicated and require specialized training or if it's

a a participant or patient user control or monitoring then it may require

training at that level as well um there's issues of biocompatibility in

the body whether it's external or internal there's issues of sterility

um particularly for complex multi-unit devices complicated conflicts of

interest with industry uh Representatives sometimes required in

maintenance or in implant training or in explant issues

if it's a digital sort of Technology there's issues of data Fidelity and

security information privacy data usage transparency of third parties have to

manipulate the data before it's useful in a decision-making tool or before it gets back to a clinician or a patient

um uh there's multiple levels of privacy and confidentiality issues with devices uh you know a drug could be um

administered and taken and no one would know uh that that's happening but if it's particularly a wearable device or a

prosthesis or some other kinds of implantable devices that are attached

um it's often quite obvious uh that that's happening which can have psychosocial impact

um can have impact on autonomy and self-determination as well as issues of dignity and respect

um so I want to talk about some of these in the next few slides more specifically

breaking down um non-maleficent so the safety issue

um there's the iterative device design and testing that's required to evaluate

um and mitigate risk of harm it's really important to have a robust

risk analysis and management system from the beginning so you have to think about where the potential risks are whether

they're physical risks or emotional risks or psychosocial risks what kind of harm could happen and how will they be

mitigated all the way throughout the testing phase the manufacture phase the

deployment phase and ultimately monitoring as well uh into post uh post-market surveillance

post clinical use um an important aspect I mentioned is early phase testing for Effectiveness

often requires human participants so you have you have uh folks who are involved in early stage design to see if if the

device Works have to understand when to engage regulatory oversight of the IRB or the FDA typically it's earlier than

most researchers and inventors think and that's an important consideration

the complicated designs that are involved that have multiple components

have real sterility changes um typically if you have Plastics and

metals and electronics sterilizing that or if you have lumens or tubes or hidden

spots that might have potential for either bacterial endotoxin or other

kinds of contaminations these Pros unique challenges to medical devices for safety

all through the various stages of manufacture

um complicated devices also means that there's fewer devices that get made and tested and typically a smaller and less

diverse population it's a lot easier to make thousands of pills and millions of

pills and get them into huge clinical trials but early phase studies for

devices are often quite small and it's important to expand the size

and the diversity of clinical trials particularly as the complications of the devices show that there's increased risk

um and particularly if human anatomy is important or physical ability is important to use the device or to apply

the device if it needs to be specific to a particular

user's ability to manipulate it or to uh to fit in a particular Anatomy you have

to have a diverse clinical trial that covers [Music] the populations that are intended to

treat this limited clinical testing can also lead to undetected harms and early

market failures the case that I'll talk about is one of many that happen where

the first iteration of a device is tested on a small population and

um then some failures show up one two three years into device usage

and so post-market surveillance is really essential and finally in this category although

there are there are others that I can imagine um particularly smart and connected devices digital Health devices

um and even smart devices like implants that have um monitoring

um controls on them that uh feed out through RFID to

databases they have cyber security issues and so the design and testing has

to have a view to potential hacking and hacking trends that are uh that change with time

beneficence or the effectiveness of the uh the medical device for treatment or

diagnosis has a number of Ethics issues related to

that again physical human physical abilities in human anatomies

uh can differ widely across populations and thus influence the effectiveness so you have to have diverse clinical trials

for Effectiveness clinical trial design can also be complex

um challenges of sham Placebo or crossover studies with devices

have always been a challenge so you have to have careful clinical trial design if you think about implanting a brain uh

with a with a device or a or a hip or something that with a with a new design

how do you compare that you compare it to standards that of previous implants or if it's a completely novel device you

need solid controls to determine if it's actually more effective than the

previous version um clinical trial design can also be complex due to the learning curve uh for

the implanting surgeon if it's an implantable device or for the user operation and so a device

trial planning and preparation and training have to be part of that to understand is this a reliable data or if

it's a highly uh dependent on training and technique um how well will it

perform the device perform uh when it gets into General use this is also another reason for early failure in

clinical use is um the training or the preparation of for clinical use was not

clearly communicated or or carried out specialized manufacturing processes to

make some of these lead to potential quality and reliability failures this is

why designed for manufacturing and quality control it's really essential this is a huge ethics issue the device

developers need to think of if you have a unique manufacturing process that process has

to be evaluated just as closely as the device function itself because you have

to ensure that every device functions and is safe when it's manufactured and

then again the the significance trainings and Technical maintenance

um uh that are required for many of these mean that we have to design for that

usability we have to design for the repair and post-market surveillance if uh if you can't track where that device

is in the body or uh where you have to have a registration to know which ones are out there so post-market

surveillance can determine if there are Adverse Events and which ones are failing and in which populations and

that's important to um determining how to repair or uh

explant or in fact create a new device or take it off the market

respect for autonomy the consent and dignity issues um that add to beneficence and or safety

and Effectiveness and permanent or difficult to explant devices pose

challenges to consent once you get um a device in your body

um if you decide you don't want it anymore uh that's always a problem so

patients need to be fully informed um the problem is can you always predict

what the potential risk is long term if it's a new device on the market there's not a lot of long-term data uh but you

want patients who consent to a device to know what they're getting into if

particularly if it's difficult to explain um implanted neurological devices really

have challenges particularly if they shift brain function or hormonal activity or

um and people personality shifts or a sense of identity shifts this is seen

in some of the deep brain implants that are used to treat various

um both physical uh disease as well as emotional diseases depression and

other um I think some schizophrenic disorders as well being tested this complicates

the consenting process enormously and so have to think about these before the

device gets fully approved um I mentioned that visible external

wearing devices uh wearable devices uh especially those with user interactions or alarms or controls

uh these can involve stigma or social impact if they're highly visible or

require attention during social activities um patient-centric design or co-design can

be really valuable early in the process getting participants to help understand how

it's actually going to be used and what might be the failure modes or what might be the potential ethical issues

that are faced and how comfortable people are either physically or emotionally with using the device

um and then finally this co-design and usability testing um has challenges around particularly

around neurodiverse participants and there's some ethical concerns

related to vulnerable populations so special IRB oversight participant advocacy should be considered in those

cases if if the device is designed to treat certain populations

and finally Justice um we're talking about accessibility usability issues of uh and just

distribution again back to human anatomies and physical abilities differing wildly across population so

diverse clinical trials for usability are critical getting making sure that populations are comfortable using it

understand how to use it are going to be successful using it um Custom Design devices often provide

better safety or Effectiveness but then uh tend to cost a lot more and that

limits accessibility so determining a cost Effectiveness design trade-off early in the design and testing is key

to having a market that is uh ethical distribution

complex devices uh with a high cost as

as many of them do and that require training and maintenance

um we'll often limit distribution to rural or low resource communities and thus limit the just distribution of the

health care access to um to various Target populations so you

want to think ahead to determine what the ethical distribution or market value might be for populations that would be

limited in their accessibility and finally um these complex devices that require

training often required device company representatives to participate in the

patient procedures you know implantation or explantation or adjusting or

affecting the the treatment values that raises ethical concerns about

patient privacy data Fidelity industry influence and significant conflicts of

interest it's clear that if if the industry rep is in the in the room with the clinician

in with the researcher in the clinical trial evaluation there is influence

there so there's a important need to ensure transparency about that um

potential industry influence or conflict of interest with the participants with the public who learn about the device

and how it was tested and certainly the clinical trial evaluators

so uh I got a case about Esure uh but I want to just pause here to see are there

any questions about all of that

that was a lot of information downloaded quickly um I wanted to have a bit of a

background go ahead Peter yeah I was not saying by the information is the is the multiple stages and multiple sets of

issues that come up at every stage I think when probably I even invited you to this talk I thought oh we'll just talk about trials but of course um as

young says in your teaching I know and I'm reminded now as you emphasize here the planning for ethical testing starts

with piloting and um has some very unusual characteristics for devices which you've described so well so

uh I found that incredibly helpful thanks yeah I think it's important that um it's

clear to folks clinicians and Engineers both that want to develop a technology

that would solve unmet and medical need that it's very early in the process you

have to think about these regulatory issues as well as the as well as the ethics I mean I consider regulatory

issues to be ethically based

yeah so yeah I wanted to just talk a little bit about Esure we're not going to dig deep into his succumb kind of a

complex situation some of you may have heard of this um device medical device

it was uh highlighted in a 2016 2017 uh

documentary called the bleeding edge it's been in the news for the last uh

eight or nine years um and a complex situation but I think the

question is um you know could some of the problems be prevented uh with more ethical uh

analysis and um more rigorous uh clinical testing design and testing

um so easier for those of you who might not know about it is a non-surgical non-hormonal medical device it's

intended for permanent contraception or sterilization it was developed by conceptus originally

went to got approved for Market in 2002 is sold to bear in 2015 I think it was

maybe 2013 now I I'm should have checked that number um but the issue device is uh you can

see in that picture it's just a little metal coil um and I chose that picture in part

because um if some of you uh know about another medical device of failure you

know this is definitely a failure um the theranos case uh the diagnostic

device case um I'm really concerned about marketing that shows some medical device

that's held between the fingers and marketed as this is an important device

you can hold it in your fingers it's real um anyway that's an aside but this device is um a medical spring like uh

nickel allium nickel titanium alloy uh and stainless steel

um it gets inserted into Fallopian tubes uh through the cervix and um it's

intended to create scar tissue and close the Fallopian tubes around the inserts to block uh and uh prevent conceptions

um contraception um so permanent sterilization is uh the

second most common contraceptive approach for women in the U.S according to reports in 2015 about

350 women per year uh would undergo this surgical treatment and the standard

surgical is a laparoscopic tubal ligation um time cons assuming

um complex fairly complex surgical requires hospitalization

um and so there was a medical need for something that worked better was easier to uh to treat and perhaps uh and

certainly equally effective perhaps even less complications so Essure was

developed with that market need in mind helping uh

people not get pregnant without having to spend a time in the hospital so be

cheaper and less pain or complication potential

and the idea was that if these devices could be inserted in a in a doctor's

office with a simple um insertion uh

device then outpatient leaving the clinician without

entering the hospital leaving the doctor's office uh and with a follow-up

within three months and in fact between uh 2002 and 22 over uh 750 000

women receive in the U.S received the Essure device um however the FDA received during that

same time almost 70 000 medical device reports um the majority of those were reported

by the women themselves who had been implanted until about 2015 when

um uh when the FDA convened a second

um panel to evaluate all of these uh Adverse Events and required reporting

from the company so medical device reporting is not required in most cases of adverse advice it's

voluntary except in certain cases that it's part of the approval for the

highest level risk or devices that have enormous um reports of adverse failures and so

this this was a problematic case it went for um you know 13 12 years before the FDA

stepped in uh in 2015 is when they reconvened uh

the device panel that initially evaluated safety and Effectiveness

um and they wanted to look at the post-market studies so far and they

wanted to um require some additional post Market surveillance of what's

happening to these women the safety concerns raised um included a wide range of tubal

perforations so basically these devices were getting shot through uh um the

tissue ending up in other places in the abdomen uh or in in the cervix or even

into other parts of Fallopian tube across the fallopian tube leading to intractable

pain bleeding eventual hysterectomies because this was a device designed not

to be explanted and in fact it turns out that trying to remove it with a surgical

procedure often fragmented the device it broke leaving fragments

um then um attractively embedded and even more

complex related health problems so the question is

could these Adverse Events been detected sooner or avoided altogether if there'd

been a higher quality pre-marketing and as well as post marketing evaluations and more timely

and transparent disseminations of study results so in in 2015

um actually 2014 15 there were a number of folks starting to look into this

problem um including news agencies lots of people

were getting on board and eventually in in 20 uh I think it was 2016 the documentary came out but but a CNN

analysis uh showed that between 2013 and 2017

yeah 2013 was when bear acquired it 2013 to 2017 um bear was paying lots of doctors to

implant this and for Consulting fees to increase the usage of issuer despite the

fact that as you can see they're thousands of Adverse Events were being

reported including um the unexpected pregnancies dislodged devices device

breakage migration surprisingly a wide number of nickel

allergies or uh alloy allergies even though the device um

uh was used by a pretty standard um alloy for medical Technologies

medical devices perhaps something about its placement in the uterus in the

Fallopian tubes was causing a specific reactions it's still not clear and then

other weight fluctuations fatigue headaches irregular menstruation and

abdominal pains were highly reported so in 2016 FDA eventually put a black

box warning on it they allowed it to continue to be sold it was actually continued to be implanted until 2020 I

believe in in Europe but in the U.S bear stopped selling the device in 2018 and

recalled it in 2019. completely so all the devices

um so how did this device fail so badly um obviously it had a lot of problems

even though it was very effective for a large number of women you know six seventy thousand uh is uh you know less

than 10 percent of the women were having problems uh 90 were being successful but

is that an acceptable uh device failure um is that ethical to allow that out

there onto the market eventually was determined no um but um some looking back at the approval

process um in 20 in 2002 when Esha was approved in the pre-market approval so at the

highest level uh pre-market approval is that class III device highest level of evaluation but it was only based on two

clinical studies non-randomized non-blinded prospective studies lacking

a comparator group even though this was a completely novel device the total enrollment was 900 a little over 900

women the FDA concluded from the clinical

uh information that um 97 of the women uh who had bilateral

issue replacement could rely on the device for contraception however even at that time the data shown to the FDA

described up to 14 failure rate for the first attempt at bilateral coil

placement now you've got to get this coil in exactly the right place in both fallopian tubes for it to work and um

clearly there were lots of failures of getting it local placed and in fact

multiple studies uh multiple situations in this clinical trial in both these

clinical trials showed that um the device was deployed sometimes two

or three times in each fallopian tube trying to get it into the right place um and so it wasn't actually described

it was considered a an effective delivery if at least one of those devices uh ended up in the right place

um a couple of other challenges uh was follow-up um only 85 percent of the women who

actually had what they called successful placement uh were followed up at one

year for Effectiveness and uh um 92 for safety

and safety was considered um was it uh was it causing any uh adverse outcomes

um at one year and only 25 of those women were followed

up for a second year it's a very short timeline so um my question is uh could something

be done here this is a case where clearly there were not um effective studies done early on and

before this was approved and the device manufacturers had limited knowledge uh

with a small population and the ability to implant this device

was much more challenging than anyone understood so they had not done

effective usability studies uh they also had not trained anyone for removal and

um and therefore this device failed and was removed from Market

um there the FDA did um ask for us in 2015 asked for a second

study um this study was not fully published um it stopped enrolling after 500 women

and reported fairly High um uh procedural device malfunctions and

adverse effects even still um in 2015 it was still deemed as a

successful contraceptive I have to warn you Andrew people will be stepping away at two

o'clock which is a couple minutes um okay I think you're good I'm done oh yeah there you go

thank you yeah but no of course everybody needs to leave please feel free we can continue the conversation with five more minutes praying responses

I think that's that case is absolutely missing my face as you presented I'm not sure if I was laughing or crying over

the disasters there and certainly brings home the way in which the ethical design and testing of devices really falls on

the a burden on the on the researcher and the person developing it because you may not be able to land regulation to

really um make sure things are done right there's a lot of concerns now about this sped up FDA regular you know

approval processes in many areas including pills and some questions there but this is a horrendous

horrifying story to tell Andrew um any anybody else with questions uh

for Dr. Brightman uh yes I had a question

um would you mind going back two slides this one

um I think it was the next one but it's all

right uh my question is this um did the researchers consider the um

I guess skill issue uh of implanting the device successfully is that one of the

the issues that they considered uh prior to marketing

um I can't know what was in their minds but clearly they did not prepare uh

um even the folks who were participating in these two clinical studies that they did because there were a number of clear

failures during the study uh attempts multiple attempts so um I think even at the design level they

must not have understood um how this was going to work they had some imagined

um uh idea and didn't do enough usability studies to see if it actually would be

delivered the way they imagined it and if I might follow up on that has

there been any regulatory change in response to this case

[Music] um not that I know of specific to uh it's

certainly specific to this device but specific to a classification or pre-market approvals no uh I think those

um those remain it's still mostly voluntary for adverse event reporting it's still

mostly voluntary you have to designate what kind of training you're

doing but it doesn't you don't have to prove that your training is effective which is a problem

um so you just they assume that if the clinical trial works then your training was affected

those are good questions thank you and this is you know I picked this case but it's it's just one of many uh cases

that have uh in the last 10 years really failed uh sort of extraordinarily

um and that's I pick out a failure case because it shows the importance of

doing it right often uh device um developers do it right and we have

effective devices on the market but when they don't do it correctly and they don't consider these it it has dire

consequences more questions from the group again I

know we're at two o'clock yeah sorry for going along no it's a lot of information to convey and really is

amazingly it's again I was struck uh by how extensive and continuous the

pressure the necessity of doing the ethical review and the um plans visibility accessibility the

all the way from the piloting phase all the way through the testing although the one you're giving us a horror story is a

high it was classified as a class three device then Andrew is that right yeah that's the most extensive testing I'm

also fascinated what you mentioned earlier about the ones where there's sort of a telephone problem where the first one is uh approved to this

analogous to an approved previous one the next one gets approved because it's analogous to that one and eventually you

have you know robots doing surgery when the one that was approved before was just a fancy scalpel or something so um

um so that's just that's just a fascinating story too and those cases must be interesting and again they

point to the necessity for regulation we're not regulatory I see Chris is on here and Kristen probably tell us the story hours of overseeing regulatory

approval for devices but of course if the ethicist we are here to like you

said the beginning uh Andrew it's the beginning of a conversation as people are developed these devices call us off you probably end up talking to Andrew uh

as you as you get advice on ethically planning and designing and testing

devices so again thank you so much Andrew thank you all for being here our next treats talk uh will be advertising

that soon that's in October of our professor Ott will be doing that um and we'll uh

we'll see you then thanks everyone thanks again Andrew