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hi everybody I am Peter Schwartz and I am the director of the IU Center for Bioethics

and more relevant for this talk the director our Bioethics Subject Advocacy Program and we are here for the next installment of our treats

seminar series translational research ethics applied topics this week this

month Dr. Mark Fox here Dr. Mark Fox the

associate dean and the director of the IU School of Medicine is out there and he is the bioethics and subject happy to

see programs liaison at the School of Medicine in South Bend and at Notre Dame

for us he helps us and researchers there with ethical issues that arise in translational research and so please

know I'm fast available for you work on research ethics topics today awesome

speech thank you none of the title see it's not about slides as he is pure talk

yet without slides but I believe the title is the little and the need when

you need a introduction to the new slide

because just reading text on slide I assume we'll talk through some issues

it's really focused on clinical research by non-clinicians what do we need to do

to safeguard actually and you know I

think at the outset there are probably a couple of caveats one about the nature of clinical research

generally and then also it's not I guess

it's not the full scope of clinical research that gets my attention so we ought to constrain that a little bit

and I'm not trying to just merge non-clinician either so I you know I'm not trying to

cast aspersions at anyone so I want to try to whittle down what I think what

issues it is that I'm really trying to force so to start with you know if you look at different definitions of

clinical research even across the NIH Institute's they don't really unified

definition so years ago my previous position I was appointed as the

associate dean for research development and director of our kind of branch

program of our clinical research center our GCRs and I remember a number

of disparaging comments from some of my colleagues that's it they range from either oh great they made an emphasis

the theme for research so as if that constitutes problem and it sure would be

nice to have somebody who actually does medical research as the director so I

mean I certainly have done clinical trials most of my work over the last 15

years has either been in research ethics or community health research and

especially epidemiology and social and behavioral research so it just

betrayed the fact that they did you social behavioral research or

epidemiology research as clinical research so II so I want to get a kind

of how clinical what is it that is clinical about clinical research or what

it what are the things that give me the cause of that clinical research kind of question so epidemiology research things

like that and I'm not so worried about that I'm thinking about yeah they're their default was

not really clinical research unless you're giving them a medicine and assessing that intervention or cutting

into them, there have to be some intervention like that that they're assessing so for my colleagues in Tulsa

I think that was biases that they brought and so that brings us to a

second caveat is for those of us who work in or I spend a lot of time around

medical schools and academic health centers these issues may not be as a

problem so now you know I'm at a regional campus so we don't have all the

accoutrements of a dick academic outside but we have basic scientists with that

research we have students we have you know postdocs and we don't have an army

of clinical faculty that are full-time at another school so clinical research

in South Bend is largely done in the hospitals and not at the Medical School

per se but a bigger challenge is to be in a place like a bar next to her neighbor University of Notre Dame who

they get really tired of them saying well since we don't have a medical school that says we don't have those since we don't have a medical school

they have a 50-year partnership with medical school that's a basement of their psychology building for 35 years

I've now literally across the street from the main gates when they say since we don't have a medical school what

they're really good moaning is the lack of an entity with a clinical practice

that provides 500,000 patient visits a year and sitting on mountains and

mountains amounts of patient data that's what they're really wishing that they

have access to I is my interpretation orally but the challenge I want to focus

on is you have faculty at a research

oriented institution that doesn't have you know armies of clinicians running

around in long that's and so what challenges arise in

that so the other the other piece I come

and I want to make again is not trained cast aspersions at I guess non-physician

what's doing research because I certainly don't think that that guarantees any either better

intellectual qualities to the research or any better human subjects protections but there are certain things but I think

just arise or more likely to arise in kind of the milieu of that for those

living and working there it would be easy to take for granted until you get

plumped and of course young and you know

an example of this came up for me again at my previous institution they were I think there are four different ironies

you know one was all about cancer clinical trials and another was all about social and behavioral research and

where your protocol went for review was ostensibly determined largely by the

discipline of the PI and you know I

couldn't my collaborators were social work human relations psychologists

architects they always wanted me to be the PM

yeah I'm fine with that it was because a lot of it was social behavioral research

if it went to an IRB largely populated by clinicians the same bias I suggested

at the outset it doesn't really count this clinical research if you're not doing something heinous to people and

assessing the in fact as long as you're not giving them chemotherapy you're not

really gonna be to worry about the risks associated with this whereas if it went to the board in the social and

behavioral research populated by sociologists and psychologists think it's been a lot of time you know for

separating out the trauma induced by certain questions about trauma so a lot

of our work on adverse childhood experiences the psychologists wouldn't worry about the harm we might be

perpetrating the cancer - oh so that's

why I owe the PIO so even within you know an academic center there are

certain pitfalls I think that exist there are certain times that obviously

physicians and other clinicians blinders on so I think that tries to set the

state's what I really hate about it is at least limited scope of clinical research where we're doing something

with or to human subjects but that are

done by people who are not physicians so I'll try and give that some context but

I think they're really a couple of areas where we have to be attentive to the

clinical implications of those types of research activities so so broadly I

think they relate to kind of the protocol design itself to the procedures

that are proposed in the context of the protocol and then

secondarily is how do we respond to adverse events or unanticipated problems

and lastly let's do with incidental

findings so I will just make a passing

reference so again I'm thinking about a

situation where clinical research done by non physicians especially in the

setting outside of the hospital so we

don't have an army clinicians around either in planning or so as an example

transcranial magnetic stimulation research done by psychologists many of

whom have trained in academic medical centers or medical schools so they they

have had again all the trappings to go with that and now we're in an

institution where they're not practicing in that same context and they're doing the same kinds of research the IRB may

or may not have content expertise or sophistication even to know that what

kinds of human subjects risks they ought to be thinking about looking for and so

there's the risk that the IRB takes at face value whatever the investigator says this is a blue risk procedure well

you're not cutting in somebody's bringing about good brain biopsy ceremony you know what's the assessment the risk

and this the look risk look different if it happens in the context have been acted on because anywhere you've got

everything around you nurses if you in an undergraduate institution of

higher education so and I think this relates to you know the screening

process of thinking about the kinds of questions that we might ask to determine whether someone is eligible to

participate in a particular research protocol if your workforce is made up

largely of undergraduate research assistants maybe a handful of graduate

research assistants who have no clinical training at all and yet they're asking a

variety of questions about your past medical history or clinical status you

know so you're teaching first-year medical students how to take a history and they can't and that stage can't

ferret out what are the additional questions that you need to ask - if you say yeah I mean history of heart disease

well does that mean have you had surgery on your heart have you ever been diagnosed with anything funny as your

heart never fluttered your flip-flop in your chest yeah what do we mean is do you carry a

diagnosis so what's the rationale for asking the question what is the risk

that you're trying to avoid I don't feel confident that I can convey that to first to medical students I feel even

less confident that I could convey it to an undergraduate research assistant so you know TCMS protocol one of the risks

it's seizures and so it's creating questions do you have any history of seizures do you take any antidepressants

to mania is another potential risk of

trance so if yes do you take any antidepressants no you know but I take

one of you trying to help me quit smoking right so yeah medical

students won't necessarily know that that has an effect on seizure threshold that it's used for antidepressant

effects as well as smoking cessation thing so unless you have a really robust mechanism for contract with the

medication classes off-label uses and all sorts of things it'd be really easy

to miss something so again it has to be clear why these questions matter how

much detail you need to go into and trying to ferret out these questions so

you know medications and reports of medical history if they matter in the

screening process how do we ensure that you know there's enough training for the

staff implementing the protocol and appreciation for what's at stake so

again in the TCMS you know the Bible of T CMS guidelines it suggests depending on the protocol

that's used and what's being evaluated they have some guidelines on what

setting they should be in outpatient

medical setting versus what can be done elsewhere but I clearly suggest that

there should be a physician involved someone with expertise in this area involved in initially conducting the so

another to you know the screening elements that good that are outlined in

in the protocol itself is one here and then the procedures that are implemented so again to draw on another example was

an engineering professor doing diffuse optical spectroscopy for gather

data about tissues brain and vascular tissue so it's essentially the same

technology that goes into a pulse oximeter so trying to advance that to think about

how do we assess tissue composition at least ourselves so it's not for clinical

application and yet it's really just describing those characteristics but

screening questions that ask about vascular disease things like an again the same questions about how much

sophistication or you know why do these questions matter what is it you're trying to avoid and being clear about

that who should not be allowed to participate in this research and then a protocol called for measuring you know

this activity and distal tissues following inflation level blood pressure cuff to 200 or up to 220 millimeters of

mercury and leaving in a plated for up to 5 minutes so

you know the scientific rationale for doing that isn't articulated but what

the real risk is of that greatest risk assumption oh my god

nothing in the consent form that outlines that as a risk no real sense of

other than people with documented vascular disease who else might not like

we want to exclude it from participating so you know certainly there's nothing in

the protocol to suggest either an appreciation of the experience for the

human subject undergo 30 seconds but

then you know I think the screening question for that was is there any

reason you shouldn't have blood pressure measured in my breast cancer something

you said I section things like that somebody with a human dialysis maybe a

fistula or something but again if we ask

patients what medicines are on what they're for what they have done very often they can report that in the most

reliable way and it can take an experienced clinician to try and tease

that out and understand what their one

of the one of the things we're most worried about that we want to ensure that they have not had that would be so

that students could do that reliably even less confident than somebody without any clinical training so you

know really reviewing what the procedures are but the but the potential risk to the human subject is but also

ensuring the second category is room that I want

to think about are you know adverse events were unanticipated problems so

again back to an example from the TCMS protocol reports of two otherwise

healthy college-age females that participated in a protocol and

lightheadedness is one of the risks that's documented associated in in one

report the woman was instructed to put

her head down between your legs and take some deep breaths and another one she was laid back not on a stretcher but in

a chair that partially reclined and was given orange juice and crackers and I

presume that the orange juice and crackers was to treat perceptive hypoglycemia but I'm not sure whoever

implemented those responses to these side effects really had a clear plan of

what they were intervening to address or that they've been given any training

about what the protocols so thinking it

down you know whether we're treating hypoglycemia or pre syncope and thank

God neither of those procedures because of what at least in that case the

medical thing one wonders so then the last category I want to think about and

again I'm not going to go deep into this, but you know there are some unique

incidental findings issues so again back to the engineering and diffuse optical

spectroscopy study it has blood pressure cuff for five minutes they wanted to

record the heart rate and they suggested that they were going to use an EKG

to determine heart and a different place than protocol talk about an EKG machine

versus an Apple watch versus by palpation and their oscillations so you

know if you use an EKG machine and your purpose is simply to get a heart rate

most EKG machines will give you a presumptive diagnosis up there that says

based on your age and gender this is a possible ischemia right so so you might

get a lot more than just the artery and unless you have a clear plan of what

you're going to do with that and I would suggest that ignoring that if you're

going to get that information you probably shouldn't ignore it even if it doesn't preclude them from participating the protocol when I think about human

subjects protection and thinking that individual drop dead I've been in my a

month later and come back to find that they participated in this research protocol and here's the kitchen says

probable cause at the very least we

ought to feel bad about that but I think we also ought to do more to protect it and maybe the better way to protect them

is to bury your heads and you know not use that modality to assess the heart

rate if all you really need is an artery so my garden will tell me what my heart

rate is once they have bigeminy that's usually right so you know really

thinking about what is the data you need and restricting your focus to that data particularly in a non clinical context

weird there are people running around with the expertise to tell you how to interpret that's all I'm going to say about

incidental findings so stay tuned for later

I just work for kind but when I think

about especially that last protocol with the EKG machine as we discuss these in

these issues I'm thinking to a casual observer goes into a lab to participate in this research protocol and there are

people walking around with white coats and there's an EKG machine there and there's a guarantee there and there's a

stethoscope and a blood pressure cuff that looks for all the world like these people know what they're doing in a

clinical sentence and so you know we worry a lot about therapeutic

misconception in terms of is there therapeutic benefit to participating in

research and trying to you know disabuse people for that notion but also just in

the way that we present ourselves it may create an expectation for a level of

expertise around clinical matters that frankly doesn't exist so what are the

safeguards and so these are the elements they think we need to be at nf2 in

clinical research in outside of the clinical context where we need to make

sure that there has been careful consideration of those but I also think

it's a it's important to think about it as if we're the humans that they're

coming to participate in this and what expectations have created in our mind by

the very way this is presented and maybe that needs to be an explicit part

of the consent process this looks very much like the doctor's office it's kind of like our model patient program this

looks very much like a doctor's visit but it's not this is a medical student he's learning to get doctor doctors hood

so how do we set the stage for then encounter in in a way that at least does as best

we can to ensure that the expectations of the research subject match what the

output of this will be and what kinds of expertise they can expect to encounter

to what extent does that promote the protection of human subjects so I'm you

know stop there I just wanted to kind of plant those seeds but really want to hear your thoughts about what are the

challenges associated with these types of clinical research there any cases

where you'd be worried about having the wrong type of questions so you talked about brain imaging and cardiovascular

issues there'd be an issue where Commission says oh yeah I know about the medical basics and so they're

overconfident say yeah that's a great

question and I certainly don't think it's unique to these non clinical

contexts so yeah good print Magnussen need an ecologist who was brought in to

consult for the IRB around a community colleges protocol because there was no

one on the IRB I played with lots of lots of physicians and including

pediatricians but nobody who felt like they had kind of the physiological and

clinical expertise to address issues in that particular subject so I think

it's a risk here as much as it would be anywhere but I think part of what I

heard you say was you know and the risk of

either you know the clinician or particularly of someone else

overestimating the level of content expertise they have around particular

issues let's say you know why cause I'm

not a neurologist I have no particular expertise there I have no psychiatric expertise and so in doing the literature

reviews and saying you know what are the interesting thing is when my

literature review driven assessment at risk is very different than the PD I

repeat across the board at least to date they've underestimated risk compared to

my family literature and so navigating that discrepancy has been challenged and

it might be that somebody with more actual clinical expertise in that means yeah so so they might do better to have

someone with you know more sophisticated content expertise in again I think yes

one of the risks that I see kind of the operational level of the RV is you know

to lack of a better term to a casual observer it might look like yeah this

looks pretty complete so again back to the prior example if the if the PA reports

you know adverse events are you know vanishingly rare and they write a

consent form that conveys it that way

for a lot of our B's there's not going to be anyone to counter that order for it to question them and I think that's a

potential points at the same time you don't want to induce hysteria because

you know everything could you phlebotomy you know I always ask med students to

spin out the scenario in which patient died from routine because it certainly

can happen from infection or bleeding disorder or from some of the developing

syncope and hitting their head traumatic brain injury so I can spend at least

three scenarios right there probably more so you don't want to end up

hysteria but I think you need to be at least reasonably prepared both for the

kinds of adverse experience adverse events that could arise and the

perspective research subjects need to be aware of that and be aware of how you're

prepared to respond but I think finding that finding the right match for those

things again it's more likely to happen in a large academic center where you have lots of different kinds of national

concern

an institution okay so I'm going to try

to summarize a little bit of nervousness in additional questions so summarizing I think what you're saying it's a clinical

interaction going on screening procedures address that was by a

clinician should be involved in the planning and evaluation so really we

should find ways to get the finishes and

the mistake that might be made Picchu not and I was focusing when I asked you

I think it's what we do space but the

question was when is it providers have to be present in the room during the clinical trial how close which clinician

kudos wonderful I love the Eclat broader to plastic vibration IRB how about that

that very hour pushes own serious

nothing the clinician it's not too serious maybe it's really serious get a license mention you may need to stay

that sort of area actually in the room something's happening so to say that

you'd have to have a clinician in the room to do it shut down a lot of

researchers probably unnecessarily so I think the risks are

so I think that I would like to see the clinician involved on the front end with

in terms of you know the development of the screening process and development of you know robust procedures for

responding to untoward events again if it's a seizure if a seizure is a

foreseeable risk then the undergraduate research assistant needs to have

something that they can rely on how should I respond you know after I know

so what are the outcomes between these

because I thought about the screening

questions is it excellent I guess wagons for co-op not at all and I agreed 100% that in

again its women can easily be missed then I could hope spider both asking

with romance and depressive they're all types of medications that might be classified assess each have their own

risk profiles and push the right way to do this I'm a script mother given our study but it's a script where are

questions hospital all and different answers these different follow-up

questions you're going to have a RA who is up maybe just graduated from college or

students maybe they are going to know those follow-up questions position has

to be all up your example again with wonderful uterine is a great example of

my which a lot of additions with no Oh teachers now if you have position you probably just know the full FDA are

conservative which is 30 things but if you're fishing party with friends on location you know this actually happened

because you know somewhere some of these

P guys as I said train likely trained in

a place where there was a medical school and there were lots of clinicians right and they basically just replicated the

same protocol and so is it true that the same protocol implemented in

Indianapolis looks different than the same protocol implemented in Wabash

College you know where there's not in that school there are clinicians running around well you know so what is it

about that context that's different and is it that there are at least possibly

clinicians on their IRB that would say you probably need to be a little more

careful about that that might be the case in Indianapolis and that expertise

may not exist and is a

Dunning-Kruger effect that they were

confident about being able to translate a protocol from the neck and a medical

center to a non clinical setting so I

guess it's ETSI you could think should maybe does have the resources to say

you're a non clinician let's get you a couple of some clinicians help you our

season has done that and what's happened incredibly HD researchers guys gratis bail you don't

use me expert clinical specimens for patients you work with but also DSMBs

so dad sexy modern boys one of the services I find a lot of times people

running trials come to us and say there's a lot of risk in this time and

it's going to respect some very lazy I refuse to do work no because off what they need is actual clinical expertise

from yesterday like if it's a trial and bobbing say you know cardiac you need to

have a cardiologist specializing driven on that bgs and because I

I have nothing to say about Jessie I

don't know what's very interesting how much expertise do you expect against the pieces again the question of balancing

risk reduction and valuation against Valerie or significant research done very hard yeah that's that was a good

question because the DSMB you're right

issue is it's not in the first instance

an ethical issue it's a practical clinical expertise issue but it's really

is this clinical entity happening more than we would predict than it should

right so efficient so yeah I think you need a statistician informed by the

clinician more than and in fact him you know in one of these protocols where

there were a number of lightheaded college-age females and more than would

have more than a reasonably informed clinician would expect based on

literature reporters and more than we would expect based on general sense of

interacting with college-age females you know figure of the wind said yeah this

is more common than we would expect so is this a problem mistreating isn't

something

I'll commit murder game I guess I may be

an underlying questions people not see clinicians so yeah they don't want

to pay for it generally somehow have they had budget

for it they certainly don't want to pay for someone else's time you know the

clinicians running around at a Notre Dame we're the ones who run Student Health and who provides sports medicine

coverage for athletic teams who are pretty busy anyway they likely don't

have any particular expertise in some of these areas and so one of the things

that we've done is to try to direct them towards some clinicians who do have the

requisite expertise that can help them these have all been after the protocols

developed so how we how we improve it you have to return again that's where if

we if the med school itself and had a code of practice arm which we don't then

the expertise might be more nothing else we can play swizzle stick

function string connects but I also think there are some insurmountable that

but not insignificant at least perceived

liability issues so in fact research compliance is cotton Notre Dame legal

council involvement some things about what those Regents with either with

positions employed by another name what that looks like or with clinicians with

Anna peg Notre Dame has this really extensive national network of Notre Dame

alums who lead blue and gold who actually would volunteer all sorts of time probably to consult on protocols

even from distance just to keep that connection to you know they have so

simple kinds of steps like that and

that's where I think I think that's where a clinician could help say how far

back does it matter why doesn't matter how far back yeah we should the questioning start

with is great in getting us and what medicines are you doing

I was senior Karen I see if you count when he was saying that hello Ken would

head that off which is that from a

gentleman Dawkins everybody noticed by Tom we do work on cancer screening with

the GI and I am surprised often he adds

clinical expertise I do not have a rap it's wonderful he's part of the team and

so again it's that question who you bring this April but we may not expect

the value but it's going to show up interesting times now they were crazy

now you can also put our patient community setting me patients the tables

sometimes a minute little boy we got we assess the patient's I know what I'm going to do my other question is here

and then repeatedly I guess one common

response here you know medication history thing when I first became an

attending I was attending to a general medicine inpatient unit and I was on weekend

coverage so I had four resident teams and two nurse practitioner teams I was

covered so I was rambling on about 75 patients on a Saturday and so the

residents are random in your note I'm slogging through to powder 3:30 in the afternoon I get to this one dudes new

admission going through her chart and internet you know definitely documented

everything so you know how long have you had her

well how many beat meditation taking digoxin what about your depression so

grocery bag full of mess I went through every single one digoxin

well that Sparky the dogs the September crack was the sister-in-law so the

patient did when they were told they brought all their benefit they happen to bring a few other family the intern

dutifully documented and ordered all you know fortunately I caught that before

the order had been fulfilled so she didn't get into jock Sanders down but it's like you know in theory everyone

did what they were supposed to and probably if it had not been my first

month of inpatient defending I might just take one into the face value so med

reconciliation them you know if they'd said what medicine are you taking

instead of just filling out the grocery bag full of medicine just I think about

that how lucky I was