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so, what I was going to talk about today is cluster randomized clinical trials mainly the ethics but it's hard to

separate the ethics and science from these so exactly what are cluster

randomized trials they're a trial where the unit of randomization is not an

individual but it's rather a group that individuals may belong to and these

groups can be defined in many ways often they're defined by political boundaries

or by school classrooms or by clinics

specific clinics or hospitals there's many ways to define a cluster reading

the literature you may see these referred to not only as cluster randomized trials but as group

randomized trials or place randomized trials but one of the places you

commonly see these sorts of trials being done is in developing countries and so I

just in you know looking through the literature on the ethics of this I came across this quote which I thought was

particularly germane by Malawi and African by an ethicist says I am because

we are and because we are I am a person is not separated and isolated as an

individual but is a community of related individuals however despite that an

individual still has the right to self-determination and authorization so

I mean it's sort of an extension of Lee it takes a village approach that is common in especially in Africa but

probably other developing countries also um just comparing individual randomized

trials which is the common one that most of us here in the US

our familiar with it versus cluster randomized trials starting with

individual on the left-hand side as our seven randomization is at the individual

level whereas a cluster trial randomization at the group level and

then a major distinction and this is mainly a scientific issue is that in an

individual trial the randomization process is presumed to render the

subjects independent but in a cluster randomized trial because the individuals

are member of the same cluster they're inherently correlated the individual

trials usually have inclusion and exclusion criteria that are characteristics of each individual in

the trial whereas in cluster trials any

inclusion and exclusion criteria that there are are applied at the group level

so for instance in a study that I'll come back back and forth to in Africa my

my study we're looking at the epidemiology of perinatal mortality so

one of our inclusion exclusion criteria is how many births occur in our cluster

we want it to be somewhere around three hundred births per year so it cluster

not even a much bigger much longing that was excluded based on that characteristic in individual randomized

trials it's very clear who the subject is if you got randomized in cluster

randomized trials it's often fairly unclear who the subject is and this is

partly because a lot of clustered trial cluster randomized trials belong in the

implementation science royal day and you know sometimes the actual intervention is being done on health workers whereas

the outcome of studying on subjects or people that are in the care of the health workers so it can be a bit

clearer who exactly is the subject in an individual trial individuals can either

accept or decline to be involved in the trial and accept or decline the

randomization any more intervention in cluster trials because the randomization

or the intervention is applied to a group it's often very difficult for an

individual to decline the randomization

individual trials are excellent for determining the effect of an intervention especially a drug on

individuals but they may be whereas

cluster trials may be fairly poor and determining the effect of the

intervention and an individual level but

on the other hand individual trials may well they're good for effects of

individuals they may not be optimal for determining population level effects and

cluster randomized trials often are superior at determining population level

effects and then on the individual side strict inclusion exclusion criteria

while they make it easier to get to a statistically significant result they

may need to for generalizability of the trial because many subjects many in the

real world many people that might be ought to be eligible to receive the drug

as treatment don't have the same inclusion exclusion criteria on the

cluster side however all members of the group are subjects and so you know it's

a beta inherently a population level study so there's generally better

generalizability and then individual randomized trials are much better at the

discovery science side of translation on the search

whereas cluster trials are much better for looking at implementation science so

why would somebody choose to do a cluster randomized Chuck trial probably

one of the main reasons is that you're trying to capture a population level effect that would apply to intervention

so you know for instance many of our studies in Africa we're trying to see

what are you addiction what effect it has on perinatal mortality well

perinatal mortality is a population level statistic and so you have to look

at the entire population and another

reason would be the intervention by it's simple nature has to be applied to an

entire population so you know a classic one would be water fluoridation at

fluoridate a water supply to a city and then a people teaser or not choose to

have the intervention but there's many other situations - such as it is an

intervention directed to how educational initiatives are implemented because the

whole classroom is going to get whatever the intervention is so I need a visual student if they're in the classroom

they're automatically going to get that intervention another reason might be

that the aim is to effect change in a very low event rate outcome especially

like I said into mortality which is a low event rate and as a population level

statistic and then finally to avoid contamination between subjects if on the

individual if it's an individual trial if subjects are randomized to different worms so you know you may have two

subjects that are our neighbors or occasionally even failing them family members well as they once randomized

control of one to intervention there's likely to be

contamination whereas on a cluster level it's a little easier to avoid

contamination because you can choose your clusters to be geographically

distant from each other this slide just

goes over the basic ethical issues that need to be looked at for any human

subject research comes from the Belmont report most people are familiar with

this and so I'm not going to go through point-by-point but clearly respect for

persons or autonomy and beneficence or do not harm and then justice which is a

little bit sometimes very defined but they're all ethical points that should

be considered whenever you're designing a any kind of study whether its

individual randomized or cluster randomized but the unique ethical

considerations in cluster randomization they fall in those same points but for

instance beneficence in a cluster

there's a whole spectrum of problems to whatever your baseline is and so your

risk benefit ratio may be vastly different from one individual to another

and so here you may have some individuals that are assuming that the

intervention is beneficial are much more likely to benefit from it than other

individuals that may have different based on characteristics autonomy

clearly is a major issue in cluster trials because as we already went

through consents given at the group level rather than individual level most

cluster trials will have what's called gatekeeper which will learn to who sort

of makes a a parental time decision on whether the cluster

will participate or not in the study but the problem is the gatekeeper may have

either real or potential conflicts of interest in terms of whether they agree

to or don't agree to be in the study you know again just go into our studies of

Africa you know our gatekeepers often a village elder as well village elders may

have some other relationships that we

may or may not understand that determine or affect how they decide whether to

give consent for their village to be in a given study and then I'll finally

justice and justices in this instance is closely related to the Nephilim because

as I said you may include be including subjects who have little or no chance to

benefit from the intervention now if the intervention is totally benign that's

not an issue but on the other hand if there is potential harm to the

intervention and you're including subjects who have virtually no chance of

benefiting there may be a just position there and then of course there's fairness and clusters selection and

randomization um so the key questions

when you're looking to design a and ethical cluster randomized trial first

of all decide who is the research subject and then once you've decided the

subject from whom how and when must inform consent be obtained is simple

cluster level concept adequate generally not generally you need at least not only

group consent from the gatekeeper but also consent from the individuals to at

least collect their data even if they can't decline the intervention they

still have the right to decline data collection this clinical equipoise

apply because of the issue with

including subjects that may not be may not benefit or likely the benefit

usually a cluster randomized trial is looking at interventions where there's

fairly good data already existing from individual trials that the intervention

is likely to be beneficial or at least unlikely to be mindful how vulnerable

groups be protected us course a very difficult question in all states but

it's especially difficult in cluster trials because they're just going to be

part of the population and may not actually have somebody looking out for

them individually as you generally do in an individual trial and then finally

determining who are the gatekeepers and what are their responsibilities okay

kind of look through that already but I just going through gatekeepers on so the

gatekeeper is someone who possesses legitimate and legitimate is important

here authority to make decisions on the cluster or organizations we have so in

in our studies and Africa is generally a community leader such as a village elder if you're doing the study in a school it

may well be the principal and superintendent if you're doing the study

in that health clinic it's likely to be the CMO or CEO of learner is in charge

of that particular health clinic and so the researcher has to obtain the

gatekeepers permission to enroll the cluster or the organization

but this permission does not replace the need to tain individual informed consent

when it's required and like I said before this most often is simply a

couple permission for data collection the scope of the gatekeepers Authority

has to encompass the interventions of the type in question so for instance if

you're doing an actual health intervention in a school it's possible

that you might not be satisfied simply with the principal's permission but you

might also need full health nurse or you know some other person who whose skills

are commensurate with the intervention it's being stained and then the

gatekeeper of course might choose to consult a wider group of community

representatives or advisors before taking the decision to commit the study

subject autonomy had kind of alluded to before that this is a major ethical

consideration in our skin would

comparing a cluster to an individual or CT because the gatekeepers deciding for

the community and individuals basically most the time really only are able to

consent for their own data collection but they do need to be approached given

the same sort of informed consent statement and then ask for consent for

their data question even if they're likely to receive the intervention on your guardians but occasionally

meta-study where the board is possible to separate at least part of the

intervention from the intervention as a whole and as an example of this we

recently completed in in Kenya a study where we devised the

whole implementation science procedure to identify women in clusters who were

at risk for future delivery and then if they are at risk for future delivery

attempt to have been get antenatal

corticosteroids so the intervention really had two parts in the

implementation part to identify women that really people couldn't consent for

individually because you know we had enumerators going out and finding people at risk but once a woman was found they

couldn't decline the drug intervention and so for this study we had a 2-step

consent process so everyone in the cluster was approached for consent for

data collection but then if women actually were found to be at risk before

they got the steroids they were asked to sign a separate secondary consent form

for the drug intervention so thank you yeah you know the complexity of that

also for data analysis is it have a cluster randomized trial there if you

then do the sensitive penta tree you know since someone we can opt out and

can decide not to consent to the drug treatment with a neck lock so I mean

that's a great question and it really it really addresses when you do an

individual trial versus a foster problem because this what the point of our study

was not to determine whether it's Kara's work or not we already know anything

stewards work there's many individual randomized Casso in them they were what

our goal was to see if our implementation design would work and so

the intent to treat was at the cluster level not at the individual that we did of course keep track of whether how many

women opted out how many women deliver prematurely and we're never identified

in the first phase implement identification process etc those were

all useless process metrics to determine how all the implementation that makes

sense yes okay I can see it but it is very complex yeah but but but I think it

raises a good point in general you don't do a cluster randomized trial to prove

that on an individual level of drug desert doesn't work another major issue

between cluster randomized trials and individual has to do with subject

numbers that are needed and it comes back to this point I made earlier that

the major difference between our teams and CR T's is that in in CRT the

subjects are not independent but they're inherently correlated

now in some depending what you're looking at that correlation being small

or maybe quite large you know for instance if you're looking at trying to

implement something in a given physician's office and your outcome is

going to be half the client the physician is with certain guidelines

there's going to be some physicians that are at baseline much more compliant than others and so depending which are one or

the other plank falls into your correlation within

that health center cluster may be very very large

that any any of the end of the eventually applied but the outcome of

the fact that they're inherently correlated is that he almost always need a larger number of subjects in a cluster

randomized trial and you know the reasons are first of all baseline risk

of the outcomes of people that not near formed throughout the cluster population

the unit of randomization is the cluster so you knew some degree of freedom just

controlling for the cluster and then the data from the individuals in the cluster will be correlated and there's a

statistic called the intraclass correlation often referred to as li isis

lead you should whatever you read a study on that were they used cluster in

in my studies i they should tell you what i see they used when they

calculate their power because the ICC has a big effect on how much power

or how many subjects it takes to achieve a certain power and generally you get

better power with more clusters and fewer subjects for closer so yeah you

know a set number of subjects you're better off down a lot of clusters

with not mating subjects in each cluster than in vice versa I've got a slide to illustrate that so

this is primarily a scientific and sort

of economic issue but it does have ethical considerations because still

coming back to personal justice you want to limit the sample size and exposure to

some unknown risk benefit ratio to the minimum number of subjects to achieve

valid results and so you know in general if you can do an

individual randomized trial it's better because you don't expose as many subjects to the intervention so

calculate power for these sorts of trials it depends on a number of

variables first of all number of clusters the size of each cluster and

then the outcome risk in the underlying population of course that yeah and the

effect size outcome risk and effect size are not their inherent to power both for

IR T's FC artis and then this intraclass correlation which only applies to

cluster randomized trials and this just that shows graphically the effect of

number of clusters and number of individuals in a cluster this was done

for one of our studies in Africa where we're looking at trying to reduce or

neonatal mortality so the underlying risk of neonatal mortality is

approximately 50 per thousand so it's a fairly low low incidence or low event

outcome we estimated the intraclass correlation again fairly low in this

situation and we were hoping for a 30% reduction which is a fairly large

reduction in that sort of study but even given that sort of reduction you can see

how many subjects it takes and you know going from the top line to the bottom

it's just decreasing numbers of clusters so this was 50 up here and the red is 25

mm ones in between are 30 40 etc. so

there's a couple important points to pay first of all as I've already said the more clusters you have the better

is but the other thing to remember is that so this is number of subjects per

cluster on the x-axis and you really get to a point where adding more subjects

per cluster has almost no effect on our

and that's whether you have a small number of clusters or large number of

clusters so let's assume that you play the role 6,000 subjects if you have 50

clusters that's 120 subjects per cluster you get to the power of proximal 90% if

you'll I have 25 clusters to have 6,000 subjects you need 240 subjects per

cluster and your power is only 80% so you know you're much better off as you

know to add more clusters than to add more subjects in each cluster and then

just you know comparing to an IRT for a

34-7 risk reduction at that same level of incidence you get an 80% power with

approximately 3,000 subjects so you know the cluster randomization takes you know

a lot more subjects to achieve the same power as you would if you could do the

same study as an individual randomized trial now this this graph shows

basically the same thing except now instead of 20% of fact or 3% of fact

we're looking at a 20% effect and you can see here with 25 questions you

basically never going to get much above around 5055 percent power so you not

only need a lot of clusters you need a

fairly good effect size to be able to use cluster randomized trials

um has got to mention a few alternative style zones that can also be considered

and generally these would be useful when it would be considered unethical to

randomize or withhold the proposed intervention so for instance a also in

Africa we did a study where we wanted to see whether what's called me an in

resuscitation which is standard of care in the United States but rarely

practiced in Africa we wanted to implement with training and providing equipment and serve in health centers

whether we can improve up them with an

implementation of being able to susat ation we thought that sense of standard

of care in the United States and wouldn't be ethical to randomize some health centers to receive the

implementation and others to not and so what we ended up doing was a pre post

intervention where we took years data before the implementation and then did

the implementation and then looked at outcomes in the year after the

implementation and compared the two so in a pretty post all your clusters begin

the intervention simultaneously they're fairly easy to design and conduct and

then consent courses for data collection only the problem is they fail to control

for any temporal trends that are occurring matches

so if infant mortality is naturally declining and you do a pre post exam

study design your baseline is going to be higher during the pre the post

regardless of interventions so you need one thing please you know you do this when you did

this study obviously you don't have internet right so even if you do it as a

pre post cluster randomized or Tequesta not random cluster design there

inevitably going to be places where you can't implement right the intervention

but you might have resources to be able to track those other places and track

infant mortality pleasing so would that be unethical because you can't again you

can't if this was in Kenya and I assume that you implement of the study who you obviously can't implement it everywhere

right no I mean I yeah I see what you mean I mean so at least oh look there's

broad trends yeah I mean that's not the other option it's just simply doing

observational try because I think basically right we'll do a combination pre-post with with you know

observational where you just get kind of group data in order to branch off in order to take a look at what the

historical transmen yeah I mean I

think that's a that's another sort of enough yeah we're did that same pretty

posted regression type study design at tracking the subjects that just never

are exposed to the intervention I think that's what you're saying yes yeah yeah

yeah so we having when I was reviewing a grant recently where they wanted to it's

in a country where the incidence of hepatitis B in mother's pregnant women

is relatively high in the US the common

procedure for that is to give the mother

or give the baby at birth the hepatitis B vaccine and in addition and give

appetites B immunoglobulin well there have been some people who show that that

some of the anti retrovirals if you give them to the mother they reduce the viral load of the mother low amount you may

not even need the certainly not the Indian globulin and the area of London

is incredibly expensive and there's coal chain issues etcetera that make it difficult to use in developing country

and so what they wanted to do was in motors that are getting the

antiretroviral intervention so everybody will give you and in retroviral

intervention all the babies and get the vaccine then they wanted to randomize where the Gators got the immunoglobulin

or not the problem is it's considered standard of care by not only the US with

my demo to give a given so you know our IRB so to approve randomization to you

to get or not definitive but an alternative would be just to simply do

an observational trial in those situations where the motors are getting

the antiretroviral the babies are getting the vaccine and then if some babies may or may not get the immune

globulin just based on whether it happens to be in available in that hospital run so that would then be

another alternative design a second

alternative designs what's called stepped wedge and this is where it's similar to pre post but rather than

beginning all your implementation or interventions on Casely you randomized

clusters to the order in which the intervention is begun and in the main

advantage of a stepped wedge is because the RET of the intervention occurs at

different time points age cluster you can get some idea whether there's

some long-term temporal trend that's contributing to any change that you see

breathe close but of course even this

design is still susceptible to short-term externalities them for

instance in Kenya during one of our studies the health care system we're

totally on strike many of our health centers just closed and so even with a staff wedge design you can't control for

that so the others there's problems of eatables this just graphically shows a

stepped wedge with in this case just with six clusters so you're free here

then gradually introduce more more clusters to the intervention and then

you'll find some other alternative study designs on these can be useful when

you're looking at two interventions either of which could be considered standard of care so you like on all two

over two days or over the weeks do interim standard of care a or standard

of care P or maybe even an odd Hospital numbers the problem with these of course

is that it can be difficult to avoid bias in your group assignments because

you you know subjects are either going to be born when we could next there's

not an inclusion exclusion criteria and

that's where so many questions it's very

interesting and helpful and then so and part of the reason I wanted to come here

is because I've been involved in both like surprised although mostly in

individual because within research I chose health messaging decision to get back to David

but more recently I've been working speed down some projects using the chica

surprise really interesting cluster randomized approach so it violates some

of the part of the partner issues so we did we've done a couple of interventions

which were reminder prompts to healthcare providers where the

healthcare provider is requesting and their patients then are the patients are the clustered within each healthcare

provider so yes clustered by provider which is which is an odd way of thinking about it

but it actually works some of the chica studies they randomly the cluster has been with two clusters

within one set of clinics which is another site of crime but it's constrained by its constrained in that

case because there's the world in this case are the clinics of utilize people

so there's not there's not a 500 schools where we can use it

select out maybe 200 to minimize 100 to one and not one or to another we have 29

health care providers and that that sort

of that's the universe and McDavid healthcare providers we had a three on one of the first studies of 300 study

which is just finished minister for expression Tony mind but as a sort of

interesting because there's also - there are other constraints that come to bear when you have that limited number

of clusters that you can select from right on yeah I mean I actually I was

thinking of the chica studies with some of my comments it hadn't I had talked to

one of the fellows don't remember which one that they were

going to do some sort of an intervention where basically was the computer prompt

future right and you know what in talking to the fellow the issues that in

my mind came up first of all I think in those studies in class correlation is

going to be variable because there's certainly physicians that are very

scrupulous about those prompts and others that may not ever you know they

may not even just grab random dick and so I think he has a provider level if

you're randomizing your clusters to provider yeah I think your intraclass correlation for if it even if it's the

health center if that particular position well it probably helps the problem the health center Assessor

define an overlooked by plenty right so if you have a few armed intervention

prompt let's say it's prompt nor conferred in our case we had no protein usual care prompt and elaborated prompt

and you have to buy it you can't relieve them do much of a

cluster randomized trial because so few clusters yeah I mean we we so as

empathic as we we use our own destiny equations basically to control for that issue of the audible hi contribute

intraclass correlation coefficient and it was interesting this is simple you

know if you looked at the difference in that this is for HPV vaccines you look at the different vaccination rate so the

simple prompt it was about 14 or 15

percent higher than the usual care and the elaborated prompt those of that time

under her 17% higher giving like 59-42

for the elaborated comprehensive percent first steps the simple prompted was this so much

moral it still is like 14 or 15 percentage point difference both if you

don't use give both of those words statistical significance for that mm-hmm

lesson from the old one but when you apply to UE the simple prompt

disappeared as an effect entirely which ensures because we just happen to have some kind of some of the providers in

one of the groups right you know but the

library prompt even which we still showed it is a significant effect so

it's a sort of interesting because the effect sizes know the elaborated pump is

at a higher effect size but not hugely higher but I think we've encountered

some of that difficulty with intraclass correlation Danny might have thought of

match with that fella was it just seemed I was skeptical and you have enough

clusters to actually be able to get out of Alice's yeah so I mean that

they're issues with it it's it's a wonderful laboratory for testing these

kinds of interventions but yeah but there are certain limitations mmm and

clearly we needed a fairly large effects on right good to go from 42 percent 9

percent in terms of rates of first vaccine delivery is pretty sizable

increase yeah and this is interesting

seeing this because it's a really it there's these additional problems that come into play with with the kind of

constraints that's examples but I mean you're thinking that vaccines and you

can imagine sorry where some physicians just as far as their bedside manner

ever are much better at talking to a family about a vaccine than other

physicians well Q how do you randomize the physician was good at it to also get

in the crowd right you're going to get a higher effect size when some is just an

intro class correlation right absolutely yeah and particularly for vaccines so

you know the Sun beckons every because they're going to require two spoilers so if you need that the meningococcal vaccine

everyone's good at that because everyone wants the parents want to get it you know the kid wants but it's with these

vaccines like HPV or influenza vaccine where those kinds of issues for someone

who's you know really good delivering those vaccines in that communication typically if you have a few of those in

the closet right yeah we could even have in maybe one clinic has a high

population of people who are anti HPV vaccine right I'm going to do it no

matter what yeah that's sort of that issue or you know finding you know that that you want

the clusters in the intervention versus control group but there there ought to

be a similar distribution right which means you like with an individual trial you might stratify these are the

characteristic yeah good thank you yeah