WEBVTT
1 00:00:00.060 --> 00:00:02.670 <v Presenter>Okay, there we go. Okay.</v>
2 00:00:02.670 --> 00:00:03.503 All right.
3 00:00:03.503 --> 00:00:05.430 And this is where I wanted to start talking right here.
4 00:00:05.430 --> 00:00:07.849 So, to put...
5 00:00:07.849 --> 00:00:11.880 To put implementation science in sort of the context
6 00:00:11.880 --> 00:00:15.234 of the whole kind of public health scientific
7 00:00:15.234 --> 00:00:20.234 research pipeline, we think about efficacy trials,
8 00:00:21.420 --> 00:00:25.470 effectiveness, pragmatic and cost-effectiveness trials,
9 00:00:25.470 --> 00:00:29.310 So things don’t always work this way,
10 00:00:29.310 --> 00:00:33.210 but this is the idealized sort of research pipeline.
11 00:00:33.210 --> 00:00:36.689 And they established the biological efficacy
12 00:00:36.689 --> 00:00:40.080 of a particular drug or device.
13 00:00:40.080 --> 00:00:42.990 what happens is they’re usually kind of phase
14 00:00:42.990 --> 00:00:46.139 three individually randomized clinical trials
15 00:00:46.139 --> 00:00:49.740 of investigational drugs and devices.
16 00:00:49.740 --> 00:00:54.690 And they’re usually done in very relatively high budget
17 00:00:54.690 --> 00:00:57.690 research settings with lots of exclusion
18 00:00:57.690 --> 00:01:01.560 criteria and academic researchers and so forth.
19 00:01:01.560 --> 00:01:04.590 And they established the biological efficacy
20 00:01:04.590 --> 00:01:07.860 of a particular drug or device.
21 00:01:07.860 --> 00:01:10.553 Should that be found efficacious,
22 00:01:10.553 --> 00:01:13.230 then we might move on to
23 00:01:13.230 --> 00:01:16.080 what’s now called an effectiveness trial,
24 00:01:16.080 --> 00:01:18.870 an often a somewhat synonym
25 00:01:18.870 --> 00:01:23.100 is a pragmatic trial and sometimes cost-effectiveness,
26 00:01:23.100 --> 00:01:25.830 it is also studied at the same time,
and in effectiveness trials we might take that same drug and device, but now we’re kind of interested in how well it works at the community level. So oftentimes effectiveness trials and pragmatic trials are cluster-randomized, say, by providers, provider practices, clinics or facilities, villages, neighborhoods and so forth, and on the exclusion criteria, it’s encouraged that they be as minimal as possible to exclude as many people who might be eligible for this treatment should it be shown to be effective and cost-effective. And they tend to be larger and maybe run for a longer amount of time. Then should a particular intervention, now I’ve moved from the word drug or device to intervention because oftentimes a drug or device may be embedded within a much more complex program at the effectiveness stage, where we’d be looking at not just sort of biological impact or health impact, but also it’s how well it can be delivered. In this classic pipeline, should a programmer intervention be shown to be effective and cost-effective, then we move,
might move on to an implementation study. And there we might be taking the program that was the multi-level program that may have been shown to be effective and cost-effective at this second level of research and be adapting it contextually, tweaking, adapting,

modifying the program for new contexts such as from one country to another, from urban to rural, say, in the United States, from the North to the South and so forth. And then also experimenting potentially with cost-effective ways of implementing it to kind of streamline the delivery.

Also at the implementation phase, we’d be looking at scale up and scale out, and these things could be done without, with primary endpoints not even being health outcomes at this point.

They might purely be things such as adoption, reach and so forth. And then finally in the last stage, dissemination, that’s all again about the scale up stage, making it more available in the particular context that was studied, but to everybody within that context and everybody.
like those who were in that context.

And then scale out meaning to everybody, to other places.

And again, there could be further adaptation needed at that point.

Okay, so what is implementation science?

A number of definitions have been posed.

And maybe the one at the bottom is the simplest

implementation science is about determining what works

in real-life, full-scale settings.

It can also, say, the blue boxed definition of systematic,

scientific approach to ask and answer questions about how to get what works

to people who need it with greater speed, fidelity,

efficiency, quality and relevant coverage.

And then the middle definition I think is the one

that’s used by the NIH in the dissemination

and implementation science study section

that’s recently been closed down

and Bree issued in with some greater specializations,

that’s been defined,

implementation and prevention science

that was defined as the scientific study

of programs and interventions which promote

the systematic uptake of clinical research findings,
so here it’s hearkening to the pipeline I was just discussing, and other evidence-based approaches into routine clinical practice and public health policy, hence improving the quality, effectiveness, reliability, safety, appropriateness, equity, efficiency of healthcare. So hopefully that gives you some sense of what we’re talking about here. It’s not that there’s a single uniform definition that’s kind of universally agreed on by everybody, but it’s definitely getting at not so much showing that interventions, programs and so forth are effective because that’s already been done in these pragmatic and effectiveness trials, but at getting them to the largest populations possible in an efficient way in making sure that quality is maintained. So very practical, but also very challenging. So another piece of this in implementation science, since we’re studying evidence-based interventions is that implementation science studies, we call it the three Rs, Rigorous, Rapid and Relevant. So rigorous has to do with, even though we’re studying very practical things,
like implementation science in some ways is, you know, the outgrowth of what had been previously called program evaluation, that we might, we still wanna use state-of-the-art methods. The studies use, you know, formal power calculations for cluster-randomized designs. They can take into account multiple outcomes and the methodologies can use causal inference methods and so forth. There’s no drop off in the rigor necessarily. And in fact it’s very challenging to be rigorous in these kinds of settings where the data may, are imperfect so when we get onto rapid, we also need to get these answers very quickly ‘cause we’re talking about urgent public health questions and we want to have our implementation science work be informative to policy development and formulation and promulgation, not coming afterwards. So in order to be rapid, we wanna make use of existing data, electronic health records, other sorts of records and move things along quite rapidly even though we’re trying to maintain the rigor just as we would in a phase III randomized clinical trial.
in an academic setting. And then relevant, we wanna be answering the most important public health questions of the day. And those would be decided by public health leaders, policy directors and ministry of health officials at the different country, district and even community levels as well as the community itself. So it’s different than in the case of, say, academia where somebody is a research oncologist and they’re working on breast cancer and trying to figure out some new treatments to cure and prolong the life and quality of life of people with breast cancer. Implementation scientists wouldn’t necessarily be choosing the topical area of interest. They would let the public health community make those choices. And then where we might come in is, okay, this is an important policy question, how are we gonna study this and get you some answers, rigorously and rapidly. So given all of what I’ve said, it might be evident that implementation science is somewhat different from epidemiology, clinical research and so forth.
And at the study design level we have these sorts of considerations. So the first one is that implementation science is guided by implementation science theory models and frameworks. What I mean by that are, there are social science theories of behavioral change such as CFIR, the consolidated framework for implementation research or RE-AIM. There’s a number of them. And they guide the work in the sense that they help determine where we are in the pipeline of identifying barriers to full uptake at high quality. And then figuring out how to expand it, how to adapt it in a new setting and so forth. And many of these things in involve behavioral change and other sorts of human factors that are not typically the objects of study of clinical researchers, epidemiologists and biostatisticians. So implementation science brings in some new team members, namely social scientists, who might be psychologists, medical anthropologists, and social workers.
and then also economists because we still tend to be looking at cost from the sustainability point of view.

So I think I’ve already mentioned that implementation science tends to intrinsically be multilevel, because in terms of developing and sustaining successful interventions to address important public health programs, we need to engage often the healthcare system policymakers, organizational leaders, healthcare providers, clients and their families and social networks.

And social networks, I’d like to just say a word about, it’s a little throw in here, but actually it’s an area of research for my group and maybe other people who are participating in this discussion that on the provider and client level, at least, it’s quite possible and it’s starting to become increasingly documented that interventions that not everybody, not all providers and not all clients necessarily need to receive an intervention in order for an intervention to spread throughout a health system or throughout a community because people have social relationships and can influence one another.
in terms of the adoption of new practices at the provider level or the uptake of new interventions at the client and family, neighborhood, workforce and so forth level. So we're interested in leveraging these networks to perhaps make certain types of public health interventions be more cost-effective and have wider reach and sustainability. Another piece is that implementation science studies tend to be dynamic in that many of you, if you've worked in HIV, it's very well known, say, the HIV treatment cascade, the TB treatment cascade and so forth. And then to say prevent, say, HIV or to ensure the highest quality of life of people who are HIV positive, there are all these different steps along the way that involve different types of treatments, interventions, actors at different levels. And one of the things we do in implementation science is we might map those cascades and think, figure out where the weak points are and then figure out what interventions can we bring in to strengthen
the success of the entire cascade by targeting its weakest points.
So the timing of delivery of intervention components, can be, along the cascade,
can be as important as the delivery itself. And then as I mentioned, just as an effectiveness trials,
you know, I can’t say for sure there would never be an implementation study that wasn’t individually randomized. But in general the implication for design of these sorts of studies is that they tend to be group level assignments to study intervention components and they could be at the district, hospital, facility, practice, provider or community levels and even clients themselves can be group level. If you think that every client is a member of a social network and that by including them we’re actually indirectly including their entire social network as well. Okay. I’m now trying to go on to the next slide.
It’s not behaving. Let me try again.
Oh, there we go. So... So there’s many study design options in implementation science and they depend on a wide range of factors.
The factors are listed here what the research question is,
the type of clinical or public health intervention,
the type of implementation strategy, feasibility,
cost in personnel, the setting, who are the stakeholders,
what are the logistics, the target population,
timeline, ethical issues come up and they in fact can
be very different than those that we’re used
in randomized clinical trials of investigated drugs and devices.
And that’s an area of active development
that I’m quite interested in and there might be
other people here who are interested in being involved
in this as well.
And then funding opportunities.
So we have a number of to study design options
in implementation science and the rest of this talk
is actually gonna be focusing on this aspect
of what I, in the first part I kind of set the stage
by kind of talking about some of the key issues
in implementation science and then that of course
informs what the study design options are.
And Ike, I’m not monitoring the chat and I do welcome questions and comments. So if any are coming up, Ike, it would be great if you could throw them in because I’m just not seeing them at the same time I’m seeing my slides. So we talked about experimental study design, so those are usually the highest form of study design. Randomization is considered the highest form of, the highest type, allowing causal inference in the simplest ways, with the simplest types of designs, ensuring balance between the two groups.
that imbalances might not lead to, under the null would not lead to incorrect inferences, and on average will give us valid estimates, it will control for various sorts of selection bias and we don’t have any measurement error because we know who we gave who or what groups we gave the intervention to or not. So like we have many, several types of these experimental designs, some of which most people in this symposium would be familiar with randomized clinical trials which are individually randomized. And then that we use the acronym CRT or cluster-randomized trial, they’re also group randomized trials, very common in implementation science. And then there’s another type of cluster-randomized trial that’s become increasingly popular. The stepped wedge design and I’m gonna be talking in some detail about that and our group has here at Yale at the Center for Methods in Implementation and Prevention Science, we’ve done quite a bit of work on extending study design, CRTs and stepped wedge designs.
There’s a very useful design called the MOST design that is becoming increasingly popular in implementation science that I’ll talk about. And then there’s the LAGO design, learn as you go design, which has been developed by our group that I’ll also talk about briefly. And then, in the interest of rapid in implementation science, there are also quasi experimental designs. So these designs take advantage of certain features of the data in order to get sort of inference that’s almost as strong as that in the randomized designs without having to randomize, and randomization is an expensive and slow process and often may not be, I’m starting to increasingly think myself, the very best way to get the answers that we need in public health rigorously and rapidly. So in the group of quasi-experimental designs, we have pre-post designs,
difference in difference designs, interrupted time series designs and controlled interrupted time series designs. And I'll talk a little bit about those as well. And then finally there's observational research which in my view has been underappreciated and underutilized in implementation science because there's such a big emphasis on, I think, causal inference without having to make a lot of assumptions. So there's been a strong emphasis on experimental designs and so far very much less use of observational design such as the classic cohort cross-sectional and case-control studies that can be embedded in the ongoing practice of implementing public health programs and simultaneously evaluating them using observational data methods, in particular, causal inference methods. And then finally there are some other designs that you may have heard about that have come up in implementation science, hybrid designs and mixed methods designs, which I'll also mention as we go along. So, quite a lot of options, actually, as we can see.
So, okay. All right, there we go.

Here, this slide refers to these two citations that I have down here at the bottom and it's called the PRECIS, Pragmatic-Explanatory Continuum Indicator Summary.

And it's a way of evaluating how pragmatic your trial is. And in some cases in the United States we have this pretty important funding mechanism called PCORI and they explicitly fund pragmatic trials.

And if your trial is pragmatic, it isn't pragmatic enough, it's very unlikely to be accepted for PCORI funding mechanism.

And what the PCORI, this pragmatic trial, there are these various criteria, I've mentioned some of them already, so eligibility, these all are on Likert scales, so the idea is, again, the fewer eligibility requirements, the better, the recruitment, the more general and open the recruitment is, the better, the setting, the more community-based population based the setting, the better, the organization and so forth.
if you’re designing a study and you’re really wanting it to be in the effectiveness, you know, implementation part of the continuum, you can get access to these papers and literally rank your design and experiment with different possible designs and try to get your study to be more and more pragmatic. And I highly recommend it because that’s what we need in public health. We need pragmatic trials that will really tell us how well our interventions will work at broad scale in the full population in the community. So, and experimental designs can be pragmatic. That’s why I showed the pragmatic slide first. Even a randomized controlled trial, an RCT, can be rated on the precise scale and be made more pragmatic. And then, as I mentioned, cluster-randomized trials and then stepped wedge designs. And here’s a paper that was published in the Annual Review of Public Health if you wanted to, I’ll read a little bit more of an overview of the study design options for dissemination and implementation science.
So now I'm gonna talk about cluster-randomized trials and I'm gonna give an example of a trial that I worked on myself. I went a little too far. I think I did again, sorry.

No, no. Okay, there we go. So cluster-randomized trials, this is like a graphic, it gives a graphical view of the difference between cluster-randomized and individually randomized trials. So over here on the left hand side we have a individually randomized trial and on the right hand side we have an individually randomized trial and on the right hand side we have a cluster-randomized trial. You can see that they can have the same amount of people. So each one of these smiley phases is a participant in the study.

But in a cluster-randomized trial, we randomized by groups. So there were four groups here. And then two of them became part of the intervention group and then two of the groups became part of the control group. And then of course every group member within each of those groups became part of the intervention group and so forth for the control group. And so that's the idea.
And then when that is done, and oftentimes it has to be done because the intervention is actually applied at the group level. And even when it doesn’t have to be done pragmatically and in terms of rapidity, for example, it might make sense to have a study design that’s cluster-randomized anyway, that’s the way we would go and that’s usually what I see.

And the study design calculations and so forth are all, and the analysis are somewhat different when we have this. So now I’m gonna go over a case study that I was involved with when I was at the Harvard School of Public Health that was in collaboration with Management Development for Health in Dar es Salaam, Tanzania, an NGO, that’s the PEPFAR, implementing partner in the greater Dar es Salaam Region.

And together we conducted the study called Familia Salama and it was a 2x2 cluster-randomized trial. So 2x2 factorial means, it’s another design feature that can be used in any ones of these types of studies. But where it’s a very old idea but it allows us to study multiple interventions.
or implementation strategies components at the same

time in one single study.

And there’s no kind of statistical limit.

You don’t lose power.

You could do a 2x2x2 or a 2x2x2x2 and so forth.

The main limitation to how many things we can study

at one time using this factorial approach is actually

just logistics and feasibility.

It gets very complicated and confusing

when you’re trying to run a study at scale

at a population level and like every group like

this one is doing this, this and this,

and then the next one is doing some other combination,

it can start to become unmanageable.

But I also would like to bring it up and encourage

people like at least if you are conducting a study

and you’re going and you have like, say, you know,

if you have a well-funded study, you know,

a population-based effectiveness or implementation

trial with for very little, for no increased sample size,

you can basically add another factor and study two things,

and it’s like why not?

So just throwing that out ’cause it’s underutilized
as a design approach. But here we did this where we compared, we were looking at an enhanced community health worker versus standard of care to increase uptake of the World Health Organization’s recommendation that all pregnant women should have at least four ANC visits. And then that was crossed with option A versus option B, which are two approaches to prevention of mother to child transmission of HIV. Now option B has been universally adopted among HIV positive mothers. So we had these two things crossed in this trial. And here is the name of the paper that’s actually been submitted, just actually just publishing on one of the two factors, “The impact of community health worker intervention on uptake of antenatal care: a cluster-randomized, pragmatic trial...” And see, very, very large trial, almost 250,000 women in Dar es Salaam, Tanzania who reported to ANC at least once and were found to be pregnant.
And you can see that these kinds of big population based effectiveness and implementation trials are often highly collaborative and they involve a big team, if we’re working together in an international partnership, you can see that there are people you know from different, both from, say, the host country as well as, say, the part technical support partners and so forth.

In our case we had people involved from Norway, Germany, the United States and Tanzania involved in this trial and here’s all the different institutions that we all came from. And so here’s a schematic of the design.

And so this sort of an intervention was implemented and rolled out at the ward level. So in Dar es Salaam there were two, at that time there were three districts for the whole greater Dar es Salaam region and we included two of the three districts. And as many of you may know, Dar es Salaam is one of the largest cities in Sub-Saharan Africa. And within those two districts there were 60 political wards and we randomized them to one of, you could say, four arms,
where first the 60 wards were randomly assigned to either the community health worker intervention or not. And 36 were assigned to the community health ward intervention, 24 to standard of care. And then of those 36, 22 went to option B, 14 to option A, and then among and so forth. So you can see how that’s divided up. And then you might be wondering, well, it’s kind of imbalanced by ward, and why was that? This is a tricky aspect of balanced design in a cluster-randomized trial because the wards did not have the same populations, and the same expected populations of pregnant women who would be delivering during the study period. So we were trading off both kind of having a sufficient number of wards with having a sufficient number of women within the wards. And so you can see that what ended up happening was we expected to have around, in the first intervention we expected to have a certain number of pregnant women in option A versus option B. And what we observed was quite different. And then similarly for the community health
worker intervention, we did our best to try to balance the number of women, pregnant women who would be in the community health worker intervention versus standard of care. And then what happened was we saw something very different. And then in addition you might notice something else which some of you who have actually run studies may have also seen that it can be quite challenging to specify what some of these input parameters are before a study is conducted. So one thing that happened was you can see that what we expected and then what we observed was we observed, you know, quite a few more pregnancies during the study period than were expected. We underestimated the fertility rate in this area, based on the population level data we had. And then you’ll also see a little later we also overestimated the HIV transmission rate. Or actually what we really overestimated was the proportion of pregnant women who are gonna be HIV positive. So as many of you know,
the various programs that have been implemented to kind
of end the AIDS epidemic have been quite successful.
We're not completely there,
but there were huge improvements that were made.
And even during the study period,
from the time we designed the study to the time
the study was actually conducted,
the HIV positivity rate went down substantially.
I think we predicted that it would be around 12% based
on data existing at the time when we designed and submitted it for funding.
And when we actually ran the study I think it had dropped to 6%.
So when those kinds of things happen,
they can really detract from the power of your study unless other types of adaptive study
designs are brought to bear.
But luckily, in our case,
we also had a higher pregnancy rate,
so we compensated for the lower HIV rate,
which of course is a wonderful thing,
with a higher pregnancy rate,
so we ended up maybe with around the power
that we might have hoped to have had at the start
with these input parameters being quite different
than what happened in the reality.
So the results here, intervention significantly increased the likelihood
of attending four or more ANC visits by around 42%.
And the intervention also had a modest beneficial
effect on the total number of ANC visits. It increased them by 8%.
It wasn’t successful in improving the timing of the first visit.
'Cause another kind of secondary goal was to hope
that women might become aware of their pregnancies
earlier on and get an initial ANC visit even in their first trimester.
And so what we concluded was that trained community
health workers can increase attendance of ANC visits
in Dar es Salaam in similar settings.
However, earlier additional interventions would be necessary to promote early initiation of ANC.
And then the study also demonstrates that routine
health systems data can be leveraged for outcome assessment in trials and program evaluation.
I neglected to dimension that among these 250,000 pregnancies in these 60 wards at that time there really wasn’t electronic health records in the facilities. So what was there were log books where people, intake healthcare providers would be entering certain data elements at the different types of clinics that women were going to. And what we did was at the end of the day we had study staff coming in and we had like a database set up that looked just like the log book and they would come in and they’d enter all the data from the log book for that day. And we did that for all of those pregnancies. Now, ideally, as more and more healthcare systems around the world become reliant on electronic health records, that wouldn’t even be necessary. In a study like this, you know, at full-scale, 250,000 pregnancies over a period of around two years could be conducted rapidly and rigorously with no additional research data collection, which is kind of the goal. So that’s an example of a cluster-randomized trial,
and that’s sort of an effectiveness implementation trial. And maybe I could say something about that, that the endpoint of, say, women having, say, four or more ANC visits during their pregnancies, there’s no health outcome there. It’s a pure implementation outcome where there’s an evidence-based intervention, the WHO has reviewed the data very carefully, they’ve made this recommendation and presumably the idea would be by having four or more ANC visits and of course receiving quality care at those visits, that we would be able to increasingly bring down the maternal mortality rate, which has also happened all around the world, as well as the sort of under five perinatal and neonatal mortality rates. But we weren’t even measuring those as primary outcomes in the study, that’s already been established through effectiveness and efficacy trials. And the implementation science we’re all about studying can we successfully implement a proven intervention, and in this case, at scale, that’s the purpose of the study. So that’s actually, it’s, you know, when I first started doing this,
having a biostatistics and epidemiology background,

it’s kind of shocking to think that you could propose a big study like this and not even have a health outcome.

just be studying an implementation outcome. But you come to realize that’s really what we need for the most part.

And if it’s possible to also look at the health outcome without slowing down the trial, increasing the expenses greatly, it’s a great thing to do.

And later on I’ll talk about hybrid designs.

So stepped wedge designs are popular for a number of reasons.

So let me just explain what this schematic diagram means.

So what happens in this particular case is the rows are clusters, so we have, or they could be groups of clusters, actually.

And here there are five groups of clusters.

The columns are time points.

So what happens, let’s just look at this first row.

So this row, this group one, so there could be one village,

say, that’s in this group or there could be five villages in this group,
but they were randomly assigned to pattern one. And what that means is that those villages assigned to pattern one, we take baseline data for everybody, but then at time two, which could be in six months, a year, two years, it’s often, in my experience, something like four months, six months, all the clusters randomly assigned to pattern one transition to the intervention. And then for the next 1, 2, 3, 5 periods, they’re in the intervention group. Then those clusters assigned to pattern two, they stay on control for two time periods and then it’s at time three, at time step three they go onto the intervention group. And so what you notice is we have baseline data on everybody and at the end of the study we also have, every cluster and every individual within those clusters are assigned to the intervention. So two things happen. One is that oftentimes in implementation science, we’re studying evidence-based interventions. So you could say, how could we withhold having well-trained community
health workers from anybody?

Well, you know, that’s not necessarily an optimal thing to do, but a sort of compromise is that by the end of this study, all women living in all of the wards, if it had been a stepped wedge design, which it wasn’t, would have access to this enhanced community health worker intervention, all the facilities would be trained to this new evidence-based intervention. So it addresses some of the ethical issues that might come up in implementation science when we’re studying evidence-based interventions. What’s in equipoise is not whether the intervention works or not, what’s in equipoise is whether this implementation of the evidence-based intervention will work. So it’s a little bit of a subtle difference from an ethical point of view and it’s also why people are discussing and writing about new ethics for public health. And then the other thing that I wanna point out about stepped wedge designs that make it very, make them very rigorous from a causal inference point
of view is that at each time point, which clusters and then which individuals within the clusters are in the intervention group or not, is completely randomly assigned. So when you contrast time two, these four to this one, it’s a random contrast. And then time three, these three to these two is a random contrast and so forth. So between clusters at any given time point we have this fully randomized design. And then what we also have is this element of pre-post, because, say, we could, even with just this first row, we could estimate and test the effect of the intervention because we have at time one all of the villages or clusters assigned to time one are not in the intervention group and then we have five periods where they were and the before/after can be compared. And so what we worry about with the before/after design is because there’s one other thing that’s changing, if it’s the same villages clusters and people or comparable people
in this one row of all the clusters assigned to this row at this one time, they should be the same with respect to all time and variant confounders. But time is happening here, so there could be no intervention effect, let’s say between time one and time two, something else happened in the background like the government instituted a new program or some new drug became widely available or there is a natural disaster. So then comparing the before/after within the same clusters will be biased by these time varying effects. And so without these contemporaneous clusters happening at the same time, we can’t control for those effects. So it’s almost like an enhanced pre-post design where we’re controlling for time varying effects through randomized contrasts. So it’s a very strong design, and here’s a good paper to read if you wanna learn about it a little bit more. Now I’m gonna give an example of a study I worked on that was a stepped wedge design. It was called early access or it studied early access. }
to ART in what’s now called Eswatini, Swaziland.

Its primary funder was the Clinton Health Access Initiative. Other funding sources were brought in, the Dutch Lottery and some other sources. And what we were looking at here was the impact of early initiation of ART versus national standard of care not be initiated to ART until later on in the development of their disease, when they started to develop different types of symptoms, which I know many people on this call would be familiar with.

And it’s called the MaxART study. So what made this study a little bit different than the studies of the other big trials was that we were looking at the impact not of controlling community HIV incidents, but we were actually looking at the impact of early access to ART on the clients themselves.

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changed to 500 and so forth or certain symptoms and AIDS-defining conditions developed, that was the standard for many, many years until early access to ART happened. And it really wasn’t known what the impact would be of early access on HIV positive people themselves, both in terms of their health outcomes as well as even more implementation type outcomes such as retention in care and this issue of, say, developing resistance if people are being initiated very early on when they’re not showing any signs of illness and so forth. So again, because I think partially both for logistical reasons, which is another reason why we like stepped wedge designs, it was as Swaziland, Eswatini didn’t have early access to ART when the study started. And so to train the providers to do this, to get the medications in at the scale and volume that was needed, to have the testing facilities scaled up and so forth, it wasn’t possible to do that all and be ready on August 14th when the study started here. So by phasing it in, it made it possible.
We randomly, in this case there were 14 facilities included, so two in each one of these clusters and we were, randomly rolled them in to early access, giving us time to properly set up each pair of facilities to be able to implement early access in a high quality manner. And then, of course, at the end, all the facilities were in early access. And in fact, what I didn’t mention, I mentioned this early on about like this was a high grade, research quality study, there were extra resources put in and so forth, and somewhere in the middle of this, WHO decided everybody should have early access and Eswatini immediately adopted that recommendation and that was the end of the standard of care we were studying. So our power was compromised, not fully, luckily, but that’s, this issue that I’m mentioning, that rapid is just such an important aspect in implementation science, I think it’s an area of, you know, sort of research. We need good examples as well as possibly new methodologies of moving these studies along so that the policy, when policies are being made,
the policymakers would actually have data from studies like this to inform their decision making, which wasn’t the case here.

So here is a published paper on the protocol if you wanted to learn a little bit more about the design of this study.

And then the results.

So this study was conducted between 2014 and 2017, 3,405 participants were enrolled. And the 12 month HIV care retention rates were 80% and 86%.

So there was a, you know, it was an improvement.

6% retention means alive and remaining in care.

So it’s a comprehensive outcome that both includes sort of the implementation aspect of not losing people for coming in, getting their medications, being checked to make sure their disease isn’t advancing and then also their health outcome, making sure they’re still alive.

So again, 80% to 86%, it’s not huge, but it’s still, you know, a nice improvement.

And then the 12 month combined retention and viral suppression endpoint rates were 44% versus 80%.

So that’s very, very big. And you know, as we all know,
getting people in ART really improves viral suppression rates. So that was shown to be very beneficial and highly significant. So we’ve considered this to be good news in terms of early access to ART also being strongly beneficial to the clients themselves, not just society as a whole. And at the same time we noticed that there were significant gaps in the healthcare system’s ability to provide viral load monitoring with 80% participants in standard of care and 60% in early access each having a missing viral load. So that’s an example of a stepped-wedge cluster-randomized design that both was looking at kind of a combined implementation health outcome as its primary outcome. Okay, I think I’m gonna, well, all right, so a little bit about, I wonder, I’m sorry, I just thought maybe I can get rid of this. Oh, okay, now I got rid of all these drawings, sorry, there were all these colored pencil things on here. Stepped wedge designs, when are they useful? When there’s evidence to support of the intervention or resistance to a parallel design where only...
half received the treatment.

Another aspect of stepped wedge designs it’s often believed, and this is on the ethical side,

that the treatment is service delivery or policy change.

And that it’s often believed that when what’s being studied is a service delivery issue or policy change,

we don’t need individual informed consent.

And then when the intra-cluster correlation is high.

So I haven’t talked about the inter-cluster correlation,

but that’s a very important input parameter when we look at cluster-randomized designs. And what that measures, we obviously call it the ICC or sometimes you’ll see it indicated by the Greek letter rho is that it tells us how highly correlated the outcome is, particularly the primary outcome.

So, let’s say, if we were, let’s say, in the MaxART study in Eswatini, if certain facilities, let’s say, had very high mortality rates and then

other facilities, you know at baseline had low mortality rates, that would suggest a high ICC.
And when you have a high ICC, a lot of variability in the event rate between clusters, you lose power, in a standard cluster-randomized trial, you lose a lot of power. It’s dramatic. In fact, the ICC like any other correlation coefficient ranges from zero to one and when it’s one that means that the only variation is between facilities, there’s a, you know, no variation between individuals within a facility, then your sample, your effective sample size is essentially the number of facilities, say, in MaxART, compared to, say, which would be the effective sample size if there was no variation in the event rates between facilities and all the variation was just between clients. So when the ICC is high, you’re gonna need a lot of clusters to get power in a cluster-randomized trial. Whereas in a stepped wedge design, because of the feature that I showed you, that stepped wedge designs completely exploit the within facility contrast, the pre-post contrast within facilities,
you lose very little power when you have a high ICC.

So it's a feasible way of running

a cluster-randomized trial when there's a lot of heterogeneity between the groups.

And then of course because of that it can be more efficient over the parallel design.

I'm gonna skip this point about why there might be caution,

but one caution is this piece about clusters not being able to follow the randomization schedule.

So, you know, we can say okay, you start at time two and you start at time three and so forth.

But, you know, we're talking about pragmatic trials embedded often within public health systems,

and there's other things that come up, maybe some issues have come up, some people have left,

it's just not possible to start at time two,

they have to start at time three and that sort of thing.

And then once the random patterns start to be violated,

then you no longer have the strength of the causal inference from the randomization.

and it becomes more like an observational study,
where the facilities just chose when they were gonna start the intervention.

Okay. So how are we doing on time, Ike?

We would like to just have what you have prepared for us. I'm sure...

We still, that's, go on. Please, go on. I'm sure we'll be okay.

We're happy to have you. We're enjoying this.

'Cause I tend to underestimate how quickly I can get through a talk and I like to, you know, enrich it with things that aren’t necessarily on the slides and then it goes a lot more slowly.

But just let me know if you feel like I need to wrap up, otherwise I'll just keep talking about everything I've prepared to discuss today.

So now we’re gonna move from experimental studies to quasi-experimental and non-experimental studies. Next. So observational.

Okay. Observational study designs.

So for those of you who have studied biostatistics and epidemiology, we know about these very well.
We’re studying and assessing phenomena as they occur naturally. We can look at policy initiatives. It’s hard to think about randomizing a policy initiative.

We’re not manipulating. Cohort studies can be conducted within electronic health records as well as cross-sectional studies. And of course we don’t necessarily need electronic health records, but they sure do make it easy to do very quick evaluations of interventions and implementation strategies as they’re occurring in the health system in a completely pragmatic manner. And then here’s a bunch of papers in the implementation science literature about the use of observational studies. And then there’s quasi-experimental study designs.

I listed those out earlier, the before/after design. So when we, I just wanted to see what I’m gonna do next here. Oh yeah, okay. The before after design, that would be, as I illustrated with the stepped wedge design, if we just had one of these rows,
we could just compare a facility or group of facilities,
what their outcome rates were at baseline compared
to what their outcome rates were after a certain lag,
after the intervention was delivered. And because we’re comparing clusters to themselves,
we’re controlling for all known and measured risk factors,
which could be potential confounders that are,
time and variant through this pre-post design.
That’s why it’s called quasi-experimental because there’s full control of confounding for time
and variant characteristics in a pre-post design.
And you know, the individual level analog of a pre-post design would be an individual, you know,
match pair study where we use, say, the paired t test
to evaluate the results and assess the impact of a individually applied intervention.
And then there are cluster analogs
to the paired t test
when we conduct a pre-post or before after design
in a clustered setting.
And then the controlled before after design,
which you might have also heard is the difference.
in difference design is a pre-post design enhanced by having other clusters or groups for which there’s no intervention is applied. And so by subtracting the change in the groups where no intervention was applied from the change in the groups where the intervention was applied, we can subtract out all the time invariant characteristics as well as the time varying characteristics. So that’s a very nice design, and again, doesn’t require randomization. Then there’s interrupted time series designs where we look at multiple assessments prior to and following introduction of an intervention and it’s kind of like an interrupted time series design where time actually becomes a continuous variable, instead of before/after we’ve got the whole time sequence. And I’m gonna illustrate that shortly. And then finally there’s another quasi-experimental design that’s been used, again, to evaluate public health interventions.
and implementation strategies without having to randomize the regression discontinuity design where individuals and groups can be considered to assign to intervention or control based on some a priori score or metric that’s kind of independent of their outcomes. And then it’s sort of in a causal inference perspective, it’s an can be treated as an instrumental variable and causal inference can be made. And for those of you who are health economists on this call or have exposure to this, these quasi-experimental designs have been put forward, I think they’re, putting them forward has been led by health economists as opposed to, say, biostatisticians and clinical researchers. And so it’s a way that I think stepped wedge designs and cluster-randomized trials kind of gain traction. And many of the methodologies were worked out in the health sciences, and then these quasi-experimental study designs. A lot of the literature arose in health economics
and now has kind of crossed over into clinical research and biostatistics and so forth. And then here’s an article that I can recommend that would talk about these quasi-experimental designs sort of from a way that’s very accessible, I think, to a large audience. So the interrupted time series design is a way that you can look at it through the schematic graphic. It’s considered one of the strongest quasi-experimental designs and it’s increasingly advocated for use in the evaluation of health system quality improvement interventions, when randomization is impossible, it can also be used to evaluate other like population level changes in health policies. So here what we do is we observe an outcome rate. You know, it could be, say, HIV incidents rates, it could be, say, suicide rates, any sort of health outcome, maternal mortality, under five mortality, you know, any sort of health outcome. You know, ideally, usually that’s measured at kind of more of a population level or even measured...
And it doesn’t have to be measured by everybody like say using DSS survey data, it can be monitored through sampling techniques before the intervention.

And so we might expect, in this idealized situation, we’re seeing that before the intervention, this outcome rate is stable, there’s not getting worse, it’s not getting better.

But you could also have, it doesn’t have to be a flat kind of slope. It could be getting worse or better, it could go in either direction.

And then the idea is that when, if the intervention didn’t happen, it would just trot along at the same rate that it had prior to the intervention.

And then when the intervention happens, we might think that the rate drops, let’s say if this was an adverse health effect, this would be around the time of the intervention.

And people can also hypothesize lag. Maybe it wouldn’t be immediate, maybe it would be six months later or a year later, you’d see a drop in the rate if this was something to improve health.
And then you also might see in addition to the drop we might see a change in the slopes so that it might continue to improve slowly over time. So there could be a trend change. It could also happen that there’s no drop, but that we just see the trend change, or there could be a drop and then no further trend change. And an interrupted time series design at the analysis stage would allow any of these possibilities. And then with the controlled interrupted time series design, we would have other groups that we might be observing before the intervention, they could be at the same level or a different level ’cause what we really care about is around the time that the intervention happened, we would hope to not, if we see any change in them of a drop in the level or a change in the slope, that we’d subtract that out and not attribute that in the group that had the intervention, we could attribute that to part of the drop and that part of the change in slope to these background time effects. And so that’s why we like the control group.
And here’s an article about if you wanted to learn more about interrupted time series in public health.

So a few examples.

So here, this was a project that I worked on in Mexico, and we were thinking about a learning healthcare system in Mexico for evaluating the performance. In Mexico, there’s something like, I think, 34 states, just like the United States we have 50 states, so they have 34, and these are the acronyms for each state.

And then we use the electronic medical records, they’re trying to use them for chronic disease prevention, screening and care.

So here there was almost 2 million patients included who had at least one clinic visit that included a chronic disease diagnosis, a chronic disease was defined here as hypertension, diabetes, dyslipidemia, or obesity, among over 12,000 healthcare facilities.

And then there was a implementation outcome developed that was indexed the quality of care being used for the prevention, screening and treatment of diabetes that was called ICAD.
And then that was able, through the health records, we were able to score each facility at every month during the study period as to how well they were doing between June, 2016 and July, 2018 on their quality of care for the prevention, screening and treatment of diabetes. 

And so what we see here is, and I apologize 'cause this work was done in Mexico, so the graph is in Spanish, but I think what you can see graphically is what is the point estimate, the black vertical lines is the mean quality of care ICAT index for the state, and then the 95% confidence intervals for how it varied over the study period. And so here actually what happened was that these, there were two, only two states that actually ended up doing worse. And then there were two states that significantly worse because the 95% confidence intervals aren’t touching the null value, which means no change. And then there were two states that, two additional states or three additional states that did worse but not significantly so.
And then you can see these, you know, these are sorted by how well they did on this ICAD score. And you can see that there was a huge variation in Mexico among these 34 states. So then, in addition to seeing like who needs help, we can also see that, you know, there’s big, oftentimes in the United States we talk a lot about disparities, but in many other countries there are big disparities as well. And here’s, you know, sort of a graphical illustration of how big a disparity might be between some of the wealthier, more urban, higher SES states and some of the poorer, rural states. So this is a starting point in terms of documenting what are the issues and then we might wanna go on and figure out the next steps, which we would’ve liked to have gotten to would be, let’s say, let’s take the top five highest performing states, understand what’s working there at the facility and client and system level that they’re able to achieve these very high ICAD scores. And then what are the barriers to those sorts
of implementation strategies that are happening in some of these states where there’s either no improvement or things have actually gotten worse. And then how can we adapt these implementation strategies to create a new intervention that might improve chronic disease prevention, screening and care in some of these states for which these disparities exist.

And then another example here of a paper that I along with others recently published that gives an example of a controlled interrupted time series looking at the causal impact of the Affordable Care Act on colorectal cancer incidence and mortality.

So colorectal cancer incidence and mortality are one of the biggest causes of cancer cases and deaths in the United States. And with the changing nutrition epidemiologic transition, I think colorectal cancer is understudied. Around the world, but it only stands to reason, just as we’ve seen the increase in rates of breast cancer and so forth.
we’ll be seeing soon increases in the incidence of colorectal cancer.

And it’s known we have an efficacious evidence-based intervention for colorectal cancer.

It’s called colonoscopy and it involves an examination of the colon for polyps and removal of polyps before they have an opportunity to develop into pre-cancerous and cancerous lesions. And it’s been found to be at least 50% efficacious in randomized trials.

It’s also expensive, in the United States it costs at least $3,000 per colonoscopy screening. So many Americans were not able to afford colonoscopy screening.

And when President Obama brought in the Affordable Care Act, it’s also called Obamacare, one of the main tenets that it brought in, which people in the public health community really liked is that it guaranteed funding for evidence-based preventive interventions. And colonoscopy was among those and maybe among the most important.

So here’s a perfect example where we can study the impact of the Affordable Care Act on colorectal cancer incidence and mortality.
Well, we know from these trials that if people manage to get colonoscopies, their rates, you know, on the population level will go down by around 50% or more, but can, by just simply changing the law, if you think of the cascade, there’s so many steps that have to happen before people might actually get these colonoscopies and get them on the recommended schedule and then see the impact on reduction in colorectal cancer and incidence. So what we did was we were able to, through, we have a very big health system in the western part of the United States called the Kaiser Permanente system, and then they’re divided into kind of subgroups. So I had colleagues at Kaiser Permanente in Northern California. It’s an integrated healthcare delivery system. It’s a private system with over 4 million members who are representative of the regional population. And so we used an open cohort of Kaiser Permanente of Northern California members who were 50 years or older between January 1st, 2000 and December 31st, 2017.
So there were over 1 million such individuals who were part of the study population at some points in time over this period. And with around 220 million person months of follow up.

And during that time, there were almost 20,000 colorectal cancer cases occurred, and over 2,600 people died of colorectal cancer.

So that’s basically the study population here. And then here is our interrupted time series design. So it wasn’t a controlled time series design, but what we saw is, so this is colorectal cancer incidence

And, on the Y axis, so it’s how many cases per hundred thousand were occurring in the study population.

And then here’s the red line. That’s when the ACA, the Affordable Care Act was rolled into public policy.

And then here’s the after data. And what we’re seeing, and then these, the very jagged lines are the natural variation in the monthly rates, which is the kind of thing we see, statistical random variation. We don’t see smooth curves when we look at rates.
on a very fine scale like this, they’re kind of going up and down. And then the red line kind of smooths these curves without testing any particular hypothesis. But we see that, you know, the rate before the Affordable Care Act came in, it was kind of fluctuating up and down a little bit. It’s not that, when I showed you that earlier slide of the sort of schematic of an interrupted time series design, there was just a straight line going through here, it’s not quite that, this is real-life data, but that we do see after the AC came in, even just, you know, not imposing any structure on the model that we see that the colorectal cancer incidence went down fairly quickly. And you might wonder why. Well, they take out these polyps that are pre-cancerous and you don’t get cancer. So it can happen very quickly. And then what we did was then we fit that classic interrupted time series model to the data. And so what we saw, that’s this line here where you can see what was happening was colorectal cancer actually
in the background is slowly going up a little bit in this part of the country and probably everywhere in the United States. But then ACA came in, we actually, I mean we couldn’t believe it, you know, there was this, we saw this drop and then just like in the classic design, this was significant and then we saw this continued slower decrease in trend. So right, it was at this point that everyone in Kaiser Permanente was able to get access to colonoscopies, and so it lowered the rates right away and then the rates continued to decline. So that’s an example of an interrupted time series design to study the implementation of an evidence-based intervention at the policy level, namely through the Affordable Care Act. And here are the co-authors, and then here’s the publication. So now I’m gonna talk a little bit more about some more innovative designs, because really everything I’ve talked about so far, the stepped wedge design, cluster-randomized trial, interrupted time series
and so forth, those have been around for quite some time. But now we can go into a little bit more of some model, I mean some novel designs that are just starting to be considered in implementation science. In particular MOST, SMART and LAGO. So the MOST design is one design that’s very well suited for complex, multi-level, multi-component interventions. That can be a very hard thing to set up at the start. So in the MOST design, which was developed and promoted by a researcher named Linda Collins, these different features at different levels to know exactly how to constitute your intervention package, both what’s in it and what’s not in it, and at what kind of dose or strength of implementation should each one of these components be. So in the MOST design, which was developed and promoted by a researcher named Linda Collins, and here’s two of the key citations to this design down here, there are three phases. So what the first one is preparation, and that’s where things would be done, such as developing the conceptual model for what the implementation strategy might be,
to identify sets of candidate components and to conduct pilot tests and identify optimization criteria.

And so what we mean by this is is this might be done largely through qualitative research.

This is the first time I’ve mentioned qualitative research in this talk. It’s a very important part of implementation science.

Because what would happen in a MOST design, for example, and even often informally in all of these other designs we’ve talked about or many of them, is that qualitative researchers, social scientists will conduct focus groups and individual interviews of stakeholders and network members to find out both what are the facilitators and barriers to them taking advantage of or utilizing and promoting this evidence-based intervention.

And then also what their views might be about different components of an intervention strategy or an implementation strategy that would make this evidence-based intervention be adopted,
be more acceptable, be used with fidelity, be sustainable and so forth.
And so with that kind of information at the preparation phase, you wouldn’t really determine definitively what the package would be, but you would get some ideas of what should and shouldn’t be in the package, it could be a much larger set than what you ultimately will study.
And then at the optimization phase, you would conduct a factorial design that would take as many kind of combinations of these implementation strategies and components as possible and test them for response for some sort of very short term implementation outcome, which could be maybe even acceptability, appropriateness and feasibility, and there are five item scales that have been developed by implementation scientists that can be used in that way.
And then based on, say, the responses, you can then pare down what the implementation strategy, what the intervention package should be to roll out in a formal either stepped-wedge design or cluster-randomized trial.
So what MOST does is it adds
on to these randomized designs that we had talked about earlier these two phases, the preparation phase, which can often be largely qualitative, and then the optimization phase, which involves a very short term pilot high level factorial design to weed out the less promising intervention package components. And there’s some examples of using the MOST design and it definitely could be used a lot more often. And hopefully people can see that this is like, you know, sort of a more scientific and rigorous way to use data, not just quantitative data, but also qualitative data to, sort of rigorously design a complex intervention package before it’s rolled out. And then there’s the question of adaptation versus fidelity, and then that’s gonna come up for these next two designs. So even after, say, using a MOST structure, which would maximize the chances that you would kind of get it right at baseline, I’m sure everybody here who’s actually rolled out any kind of complex public health program of any sort.
knows that the realistic scenario is that this program is gonna be adapted as we go along, providers are gonna learn, the system is gonna learn, clients are gonna learn, we’re gonna learn like what isn’t working, what we can improve and so forth...

And so it’s just basically impossible usually for researchers to say, and maybe even unethical for researchers to say, no, you know, this is a randomized trial and you must stick with this intervention that we set at baseline no matter what.

Obviously that’s what we do in a phase III individually randomized clinical trial. People either get the new drug or the placebo and we don’t change the new drug after baseline, even if it’s, people are getting the feeling somehow that it’s not doing what it’s supposed to do, all we can do is like early stopping for overwhelming evidence of benefit or harm.

So this very busy slide is taken from this article down here and it’s a framework for reporting adaptations and modifications to evidence-based interventions.

So the reason, it’s complicated,
but that’s because what these researchers are trying to do is think of every possible kind of category of adaptation that could take place after an intervention is started to help people record the adaptations.

Because those of us who kind of want implementation science to be relevant, one of the three Rs, realize that we should not only allow adaptations, we should embrace adaptations because they’re only gonna likely improve the success of these evidence-based interventions.

But the only way to learn in a rigorous way, what aspects of adaptation are actually working, is to be able to record them.

And then once they’re recorded, later on in secondary analysis, we can go back and analyze the data because all these adaptations are just like exposure variables in a complex epidemiologic study, and using causal inference methods to control for confounding, we can look at which adaptations actually improved outcomes, which made outcomes worse, which didn’t do anything.
we can evaluate their cost-effectiveness and so forth,
but if they’re not recorded, we’re stuck.
So that’s why I have this very busy slide here.
It’s a very, very important one in terms of ensuring
that implementation science produces relevant results.
In a rigorous manner.
Now we can talk about the learn as you go design.
So that’s a design that’s very dear to my heart
because as you can see here to the left hand side,
I’m one of the people who’s developed this design,
and it’s a very new design, we just published it last year.
We are in the process of using it in a study going on.
Some of you might be part of the HLB-SIMPLe consortium that’s supported
by the United States National Heart, Lung, and Blood Institute.
It’s a series of,
I think maybe six or more studies taking place
in sub-Saharan Africa where what’s being looked
at is different ways of integrating
hypertension prevention, screening and treatment.
into HIV clinics with the idea that, as we all know, the AIDS epidemic has, AIDS has become a chronic disease everywhere in the world. And we have aging HIV AIDS patients and they’re getting chronic diseases just like those of us who are HIV negative. The idea, the concept of integration of care, I think, is a very important one in global health and US domestic health. And this consortium is playing a role in making this happen. So I’m the statistician for one of the projects, it’s called Police and it’s taking place in two districts in Uganda where we’re integrating two types of intervention packages into HIV clinics, hypertension basic and hypertension plus to try to increase hypertension screening and treatment and prevention in the clinics there. And we’re gonna be using this LAGO design. So what is LAGO? Well first of all, the intervention is a package consisting of multiple components. We’ve both basically been talking about multiple component interventions throughout this talk.
And it can include combinations with treatments, a device, care organization, multiple stakeholders, and similar stepped wedge design in a LAGO design the data analyzed after each stage. And then what makes it like radically different in a way from other prior study designs is it’s actually possible in this design to reconfigure the intervention package and not just do it sort of in a more ad hoc way, as we were talking about with the previous slide on how to adapt interventions. But you do it in a formal way where we have a computer algorithm that will take all the data up to the current stage, analyze it, and then the data itself recommend what’s the optimal combination of the intervention for the next stage. And optimality would be determined by both trying to guarantee that we have adequate statistical power to test the overall intervention effect at the end of the study. And that it might be that we’re trying to achieve also a certain outcome goal.
So like in the Police study I was just talking about,
we think that about 20% of people,
20% of adults over,
HIV positive adults in the clinics might
be hypertensive and be in hypertension control.
And then we’re hoping to improve that to,
say, 40%.
So the goal of the study is to get to 40%
through the intervention.
You might think that’s modest,
but another thing that I’ve seen is sometimes
with these kinds of studies,
persons are overly ambitious and they might
say,
we wanna get like 80% or 90% of hypertension control
by the end of the study.
But you know, if we’re starting from 5%,
10% or 20%
to get all the way to like, say,
80%, we’re starting to talk about relative risks of 160.
Those are like, you know,
huge intervention effects that maybe we’re being too
hard on ourselves when we try to achieve goals like that,
even though that’s what where we might ultimately
might wanna get to.
So back to the LAGO design, we can, using the data,
we can recommend the optimal intervention package for the next stage.

We can also use qualitative data and we don’t have to just use the quantitative data, we can reconfigure the intervention package, then we roll it out again and then we repeat that up to as many times as was preplanned.

And then we can, at the end of the study, ideally, we would have a final outcome assessment, we test the null hypothesis that the intervention had no effect. We could assess the cost-effectiveness of the different intervention components. We have a model that we can use, that could predict for different intervention component combinations, what level of the outcome we might expect to have and so forth.

So that’s the LAGO design, we’ll see how it works in Police and hopefully some other studies.

There’s some other projects under consideration for funding that have also proposed to use LAGO.

And I’ll give an example of LAGO here.

This is a post-hoc design.
So it’s an illustrative example that we used in our paper in this Annals of Statistics paper that was published in 2021. And by the way, not to kind of toot my horn, but just to emphasize the rigor of this design because it is, you know, very different for people to accept that you can actually change your intervention after you start the study and still have a valid P value. You know, the mathematics to prove this were quite high level. And the journal where this paper was published, the Annals of Statistics, is kind of considered one of the top and most theoretical journals in statistics. So this design is like really okay, it just, it’s okay theoretically, but it does need to kind of be fleshed out in terms of being used and working at the kinks on a practical level. And as we start to use it, I’m sure we’ll start to learn a lot of things and be able to further improve it. But anyway, we took the BetterBirth study as our example in this Annals of Statistics paper.
It was a multicenter study that was conducted in Uttar Pradesh, India, which is a poor state in Northern India. And its purpose was to test multiple component intervention package to improve process and health outcomes for mothers and newborns, that is to lower maternal mortality and neonatal mortality in the state where the rates were unacceptably high. The components involved: launching the intervention, how many coaching visits, how often, the frequency, the duration, there's audit and feedback loops, which is a very popular method in implementation where it can be through direct observation or through electronic health records, providers are audited as to what extent they're actually implementing the intervention and they're given feedback as to how well they're doing, and oftentimes there can be group discussions where people talk about, you know,
what were the barriers to why they didn’t do it more
and how could they do it more often and so forth,
and that’s been shown to be a proven way to improve
the uptake of a evidence-based intervention program
at the provider and system level.
And then of course, stakeholder engagement is increasingly taken to be
an important part of successful sustainable interventions conducted at high fidelity.
And so engaging the district and facility leaders
was another important part of this package.
And there were three stages of the study.
In stage one, they piloted this intervention in two centers, then through, you know, non-rigorously,
not using LAGO, they then adapted the intervention package and they piloted it in four more centers.
And then in stage three they rolled out a full trial
in 30 centers where the intervention was fixed
and they couldn’t change it any more.
And in stages one and two,
they used both quantitative and qualitative data
to guide the adaptation.
And so this is again, a very big ambitious trial.
There were 120 sites in 24 districts and it involved almost 160,000 pregnancies.

And the intervention, the primary outcome was an implementation outcome and it was use of the WHO safe childbirth checklist with many of you might be familiar with, there are 27 different things that are supposed to be done at different stages when a woman comes in to give birth with the different stages of pregnancy and right after and so forth.

And the WHO recommends that this safe childbirth checklist, which is a means of trying to ensure that these 27 evidence-based, you know, components be used, that it should be used at least 90% of the time. So that was the goal of the study.

Again, they were, I think in this study it was at something like 5% where it was happening. So extremely ambitious and probably unrealistic.

And then we could look at different outcomes. So one outcome is, that we looked at, just, this is, again, an illustrative example of the LAGO design was adherence to oxytocin administration after birth.

or after delivery.
And then we could also look at, say, seven day mortality of the mother and or the child.

And then there were also costs, say, the costs per coaching session.

Okay. So that’s an example of the LAGO design.

And in fact, just to say that this study was published in the New England Journal of Medicine in 2015.

And then the outcome was the, in the New England Journal of Medicine.

And in fact, the trial was not successful in achieving its goals.

And probably what happened was, you could say that’s why we said, well, if LAGO could have been used at stage three when there were all 30 centers, there could have been more feedback figuring out what aspects of this is working, what aspects of these components are working and not working.

And then maybe some other things need to be brought in.

Oh, somebody else who’s maybe unmuted. They failed to increase the use of the safe childbirth checklist to 90%, but they did improve it.
But they also, I don’t think, failed to see significant differences in, say, health outcomes of mother and or child. So it’s an example of how unfortunate it could be to have a very big study like this with a very complex intervention following, attempting to implement WHO standards and then being hard-coded in like this. So there’s no way to adapt and improve the intervention when it starts to look like it’s not achieving its goals.

So now I’m gonna talk about effectiveness implementing-<v>Donna?</v> <v>Yes.</v>

Yeah, it’s been a wonderful time.<v>Yeah, it’s been a wonderful time.</v>

I don’t know, how many slides do you have left?<v>Yeah, I’m not even sure myself. Let me see.</v>

So, because, you know,<v>And it’s late, right? Yeah, okay.</v>

this is Nigeria and it’s about... And it’s late, right? Yeah, okay.<v>Oh, I was almost there actually.</v>

Almost there. Okay.<v>Oh good, good. Okay.</v>

Oh good, good. Okay. <v>Yes.</v>

So, sorry everybody, you know, I’m very excited,
have weeded it down a little bit more, but I really appreciate you all hanging in there with me. I can see we've lost very few people there.

We're happy with you too. And the lecture is quite illuminating.

So I’ll just quickly say that because of an implementation science, I’ve been mostly talking about the interventions in the design point of view, but there’s also this hybrid design framework where we can think of combined outcomes or differently emphasizing the health outcome versus the implementation outcome. So there are three types, type 1, type 2, type 3.

And the goal here in using these hybrid designs is to accelerate transition from effectiveness trials to implementation trials. And this is a very unique design. Here is the reference for it in implementation science.

And so the type 1, 2, and 3, I’ll show you on the next slide. So the type 1, the focus is the clinical intervention. So that would be, say, in, let’s say, the clinical intervention, none of the examples
I've given actually were a type 1 design, 'cause the clinical, let's say with BetterBirth, which we were just talking about, the clinical intervention would be, I think actually they were powered for combined endpoint of maternal and neonatal morbidity and mortality, that would make it a type 1 design. But then they were also measuring the implementation outcome of the extent to which the Safe Childbirth Checklist was used. That's an implementation outcome that wasn't their primary outcome. So that makes it a hybrid type 1 design. A hybrid type 2 design, which a lot of people are very interested in, would mean that we jointly think we power the study both to ensure that we have the power to detect a meaningful difference in the clinical outcome, but also in the implementation strategy and their co-primary endpoints. And then the hybrid types 3 would be, focusing exclusively on the implementation endpoint. But we're still measuring the health outcome just to get some idea that maybe in this new context, we're at this greater scale,
maybe we might see a difference, good or bad,
in the health endpoint.
So those hybrid designs I think are very useful
in implementation science and I’d encourage you all.
So this is my last slide.
These are a few textbooks on implementation science
that I encourage people to take a look at, if you can.
Implementation studies require consideration of context,
multiple levels, multiple components, timing matters.
When you’re thinking about conducting an implementation science study,
you can identify and rank potential study designs
then decide, and I’ve gone through a number of the most important ones and discuss some of their pros and cons.
We’ll consider randomization and real world rollouts when possible to increase rigor.
But also I’m mentioning if randomization is not possible,
there are quasi-experimental and observational designs available for which causal inference methods can be applied.
And consider some of these innovative approaches if they're relevant to your study.

So thank you all very much. I'm sorry for keeping you up so late tonight. It's been a pleasure to talking with you all and sharing this information.

Wow, wow, wow, wow. Donna, you are fantastic.

We're very, very greatful.

Thank you so much, Ike.

Everyone...

We're all still listening to you since you started the lecture, that shows that we really appreciate you and actually no other person could have delivered this lecture but you,

the expertise cannot be underestimated.

We are very, very grateful, and if you look at the chat,

oh, it’s something that is quite encouraging,

I wish, I’ve saved the chat, so I will send this to you.

Wonderful time,

highly appreciated lecture, stimulating lecture...

It’s still coming. Wow, great.

Thanks to the lecturer. So you can imagine.

So we’re really very, very happy and really I’m sure I’m going to be bombarded with requests for you to come.
Well, Erica Saracho who’s assisting me with this.

Because we should capture the chat, a number of people are asking for the slides and we can get back to everybody with these slides.

Good. Yes, Donna.

I saved the chats.

Thank you so much, Erica. Thank you very much, Erica.

And so let us have some questions.

I’m sure some of us would want to clarify whatever gray areas they have.

So I’ve asked them to send in their questions but I’ve not seen one.

What we are just seeing is email addresses, send me lectures.

So our colleagues there,

could you please send in your questions because she’s here now,
she can clarify things and also give you some better understanding of the slides that you are requesting for.

Please... I know.

but maybe it’s so late, Ike, maybe people, it’s too late to actually take questions now.

I mean I’m fine but I understand it is quite late for people and I understand if people would like to just say goodbye at this time.
Let me just wait, maybe let’s, can you unmute?

Erica, can you unmute and let’s see anyone raising up his hand, anyone raising up?

I think there are two questions earlier

if you scroll up.

Yeah, there is one I actually, okay,

there is one here that says how do we balance between rigor and relevance in implementation size?

Yeah, so that’s a great question.

Do you have—Absolutely.

Yeah, that’s a great question.

And you know,

my view is there’s no right answer to that.

That, you know, it’s really, you have to say it depends,

but, you know, in my opinion I feel that implementation science so far has overemphasized rigor over readiness and relevance

and therefore many of these big studies, including these examples that I’ve given,

have missed the boat in terms of policy.

So I might say, maybe we need to, if we have to choose,

and I’ve also given examples of studies and designs

that can maybe be used that could still be rigorous
and rapid, that if we have to choose, maybe we need to go over to the other, that the rigorous needs to be, let’s say, especially randomization needs to be softened up a little bit so we can get, we can contribute to policy decisions. Okay, thank you very much.

There is another question. What is the difference, if any, between implementation science study and implementation research? Yeah, I don’t think there is a difference in my opinion. You know, an implementation science study is a type of implementation research, but there’s a lot of terminology floating around. So sometimes people say implementation research, sometimes they say implementation science, in the United States, a lot of people say dissemination and implementation research because they wanna emphasize the dissemination piece more. They feel like there’s still inadequate uptake and scale up and scale out of a lot of evidence-based interventions for whom, you know, acceptable implementation packages have been developed.
So these words, these various words are, from my point of view, more or less synonymous.

Oh, thank you very much.

Another question is is there a difference between clinical and implementation outcomes?

So I probably should have actually had one or two slides about that, 'cause that’s actually an important concept in implementation science.

So in, and it’s related even to the cascade on my very first slide, where we go from efficacy research,

has clinical endpoints, that’s it.

Effectiveness research usually has clinical endpoints, that’s it.

Then we get to implementation research, we start to have implementation outcomes where we’re not actually even looking at the impact of the intervention on the health endpoints.

We’re looking at the impact of the intervention on how the evidence-based intervention is being implemented with the idea that the actual public health barrier at this point in time is not like discovering a new intervention,
it’s rolling out an existing intervention that’s useful,
and that’s where the type 1, 2 and 3 hybrid designs
come in, where in a type 3 hybrid design you
would just look at, is the safe childbirth,
is the uptake of the safe childbirth checklist,
has that increased?
We’re not looking to see, did fewer mothers die?
Did fewer babies die?
We know, if these 27 things have been done,
fewer mothers and fewer babies are gonna die.
So we just wanna get more providers using
these 27 things.
So that’s pure implementation outcome.
Well, thank you very much.
I think the last one here or there’s one about how do
we calculate the sample size for these designs.
I wonder how that will be addressed,
but that’s the question. Okay.
So that could be another like one or two hour talk
or even a whole class in itself.
But I can say a few basic principles is if you know
how to calculate, say, a study,
let’s say, I’ll just say
for a cluster-randomized trial compared
to an individually randomized trial,
you can do the sample size calculation for the individually randomized trial. And there’s even like, you know, in most statistics textbooks, you know even basic statistics 101 type courses, you’ll see the formula for power or sample size for a test for the difference between two sample means or two proportions in two groups. You can do that sample size or power calculation and then adjust it by what’s called the design factor, which takes clustering into account. And the design factor also is a very simple, it’s like one plus the number of clusters minus one times the intraclass correlation coefficient and you multiply the sample size by that, I don’t remember the exact details actually, I’m sorry, I don’t wanna give a wrong formula and I don’t remember it off the top of my head. But you can modify, without a computer, just using a hand calculation, you can modify a sample size calculation for an individually randomized trial with this design factor that only takes, that all it needs to calculate it is the number
of clusters and the intraclass correlation coefficient.

And then you get your new sample size or your new power for your cluster-randomized trial.

There are also, in R, there are R packages for doing these kinds of calculations for stepped wedge designs and for cluster-randomized trials.

In fact we have an R package that calculates sample size and power for a whole bunch of different variations of step wedge designs with continuous outcomes and binary outcomes and repeated measures.

It's called SWD_PWR, stepped wedge design power and it's an R package that's freely available to everybody.

So that's just a little bit about how to do this and what's involved.

Yeah, thank you. I think I'll just take two more questions. There's one that is quite important and I think would also help Donna to see how she can help us.

The comment says, there is generally poor knowledge
of implementation research among low to medium income countries researchers as evidenced especially by the number of publications in Africa. Where can one get specific training opportunities in implementation science research. Yeah, so that is an extremely important point, The first one is, I'm pretty sure that there's a West African Implementation Science Society. Is there anybody on this call who's a part of this society? Yeah, CAWISA, there's CAWISA and there's NISA in Nigeria also. Yeah, so I don't know, would you like to say something about that and what the society is doing, at least in the West African context, in terms of promoting implementation science, supporting new researchers at implementation science and so forth? I know that NISA holds an annual conference on implementation science in Abuja, I've been, I've attended that before.
I’m very aware that CAWISA is Central and West Africa and they currently are expanding. I think they have six countries in their court and they’re currently expanding. I could send to, the details of, you know, the two organizations who do training, therefore they have NIH grant I think to support... Yes, they do have one or two NIH grants to support implementation. They just received a grant to do it. Wow. Wonderful. Thank you very much. Okay. So that’s one thing. In the chat. Yeah, can I get the link? Maybe give the others hint on this. Thank you. In the chat. Okay. So that’s one thing. In the chat. Yeah, so, go on. And I know that the World Health Organization has an implementation science academy that’s focused on,
there's one that's more focused on infectious disease
and then there's one that's focused on chronic disease.
But I don't have the links for either of those.
I'm not sure if there's anybody on this call who's participated in either one and they're,
I know the chronic disease one, I'm pretty sure,
is done in the summer and I don't remember
if before COVID it might have been
that people had to apply and go to Geneva, but maybe
now it's done by Zoom and it can be more inclusive.
I'm not really sure but I'm wondering if there's anyone
on the call who is involved with either of those trainings
that are connected to WHO.
I guess please, let me advise our participants to actually use the Google.
You can type this in the Google and get some
of the resources.
There are some training programs too.
I know the NIH also have the implementation
science training program and we can,
I mean you can actually apply for it. It is online.
And then in December- Didn't you do that, Ike?
You join the group. Yeah, that one.
Didn’t you do that one?
Yes, I did. I did that.
Maybe you could say a little bit more.
The conference.
Yeah, maybe you could say a little bit more.
about what was involved because that was a pretty
in-depth training I think that you were able to access.
Yes, it was actually for about three months.
or so and we had the training online, and we had exercises, assignments and we had also facilitators
or resource courses for the different lectures, and a lot was given on the theories.
I mean they really went in depth so that they were
well grounded in the theory of implementation science.
And then the various examples.
And this was capped by a meeting in Washington and there, there was
a conference and we also had some sessions, small group sessions and I mean
just to experience
the different kinds of implementation research
that has been carried out and it was quite helpful.
So I guess with the emails we have, but like you said,
you can just Google and you can actually access all of this, and like Donna said, there is also this WHO implementation science training that’s also free.

And we can, I mean you can access all of this at some point, but you can get back to me if you need further information on this.

And we have also heard about others who can help. So if we get that, the names of the society organizations, it’ll also help us to link a network amongst ourselves on this implementation science and implementation research across the continent and even the group.

So the lot of network is there for us. I have to keep raising up their hands. I have to allow them before we end this, Dr. William and I have... (indistinct) Dr. William, please let it be brief. Thank you.

Dr. William? I better tell Dr. Spigelman that too.</v> Pardon me. Donna?</p>

Let it be brief also. (laughs)
I'm just joking.

<v ->Hello?</v> <v ->Okay.</v>

<v Speaker>Hello. Good evening.</v>

<v Speaker>Hello Dr. Is that Dr. William? Yeah, thank you.</v>

<v Speaker>Hello. Good evening, ma'am.</v>

<v ->Yeah we are hearing you.</v> <v -Good evening, ma'am.</v>

<v Speaker>Yes, we're hearing you. Good evening. Hello.</v>

<v Speaker>Yeah, the lecture is awesome.</v>

I had a lot of new things that were,

was being taught but my question majorly is concerning

the hybrid research that you mentioned

that it is the same thing as mixed method research

and that since HIV is the chronic disease now,

would is it be better to do the research that you want

to do in East Africa, that's in Uganda, also

in West Africa also to see if there are changes in the,

though there are both flat,

but the different terrains and all that who also help

in managing the patient.

So those are the issues I have. So, thank you.

<v Presenter>Great.</v> 

So I'm glad you asked that question.
Hybrid designs and mixed methods are not the same thing. So hybrid designs are, well, let me say, mixed methods, which I didn’t really talk about. That’s another thing I could have actually included in this talk. But mixed methods involve the mixing of qualitative and quantitative research along the entire study process. And there’s different types of mixed methods designs depending on what’s considered to be more important, the qualitative or the quantitative. So like you could say, the MOST design, which I did talk about is a mixed method design, because phase one of the MOST design at least has a qualitative component. We use qualitative data to kind of narrow down the intervention package components. But then we’d use quantitative data in phase two in MOST to further weed them down to what we’re gonna use for the intervention we’re gonna roll out in the full trial. But it’s recommended, and even though I have really almost no social science training,
I’ve come to deeply appreciate and value the role of social scientists in implementation science. And I would say that we need qualitative research along with quantitative along the entire like pathway from qualitative and quantitative data about what is and isn’t working about the intervention if it’s been in place or what people think about a new kind of way of adapting the intervention to a new situation. And then you kind of roll out your trial, whatever kind of trial you have. And then while the trial’s going on, it’s really important to collect qualitative data because if it doesn’t work, we wanna know why. So like in the BetterBirth study that I mentioned, because it wasn’t a mixed method study, we have no idea why there was this failure to take up the Safe Childbirth Checklist. Was it that the turnover of staff was too high or the supply is not in the facilities? I mean there’s just so many reasons, we have no idea. So the qualitative piece while the study is going on is really important.
And then you do your quantitative evaluation of your endpoints. And then a lot of people advocate, after that, further qualitative data collection to find out what people thought of the intervention, what suggestions they have for improvement, what they think the next step might be in terms of scale up or scale out. And then also there’s also formal ways of doing mixed methods analysis where, when you evaluate outcomes, you actually integrate the qualitative and quantitative data in some formal ways that I know exist, I haven’t actually had the opportunity to do that yet. And so I’m looking forward to learning more. So that’s very different now I hope you can see from the hybrid design where we have a standard quantitative study design like a CRT or a stepped wedge design and the hybrid design is just more about, is the primary outcome, health outcome, a health outcome and an implementation outcome or an implementation outcome only?
Okay, thank you, Donna.

Yeah, thank you. Thank you very much.

One of the universities in Nigeria.

It’s all right. You’re welcome.

It’s all right. Thank you very much.

Professor Donna, Professor Ajayi and everybody here.

Thank you.

My network, I was on the road so my network was off and on.

I started hearing, listening to implementation science.

I think around 2016 at NIH and one the last speakers spoke about, showed up when they draw the map,

it was still new then,

you would just see a lot of studies on East Africa,

hardly anything in West Africa.

You know, I’m just trying to look at the gaps that we need to be filling.

I’m challenging those of us present here and our speaker,

what really causes that?

There’s not a balance.

You see a lot of studies on East African coast and very minimal...

That’s one thing I observed.
Secondly, each time I go for these meetings, you are talking about trials, you’re talking about these implementations, hospitals, everything. We hardly see those who handle these drugs. We hardly see, I mean I’d love multidisciplinary research, that’s why I’m here. I believe in it. But we hardly, it could be the fault of the, those drug handlers, the pharmacies, those that handle drugs. Because I was in another group with Harvard on malaria it’s the same thing. They were even shocked. They say you are the only pharmacist we’ve seen in this thing and you’re talking about medicines, and they’re not involved, in the hospitals, when I listen to them, they don’t even want to mention them. So we should really be looking at involving everybody in this healthcare sector for the implementation. In terms of community pharmacists, they do a lot in Africa. They really need to be brought on board. They do a whole lot. They’re the (indistinct) when they’re ill.
So we should look at those gaps and fill the skill sets in that area.
And then finally is that all these other websites and all that, it would be good for those of us here, maybe or Professor Ajayi to really do certification, social certification courses on these things so that we will be well trained. It’s obvious that you need a lot of statistics. Some of us may not be good as why multidisciplinary approach is very important.
Well, thank you very much for everything. Thank you. Oh thank you very much. I think it’ll be more interesting just ahead.
Okay. Donna, I’m with you.
Oh, okay.
Well, I think these comments are probably best discussed by the many participants on this call more than me, ’cause they have to do with, you know, the role of implementation science in West Africa and what are the questions, and some of them, the only thing I would just say one small observation that,
you know, it’s an unintended consequence of the fact that, you know,
I think, to some extent the issue you’re bringing up is because HIV rates were so much lower in West Africa than East Africa.
So there was so much funding being poured into East Africa in terms of mitigation of the HIV AIDS epidemic. And then now as the epidemic has lessened, it’s starting to evolve into some of these other topics. Whereas in West Africa there just wasn’t as much because luckily the AIDS epidemic was just so much less severe.
Yeah, thank you very much for that response.
And I think it is a challenge also to researchers in this part of the continent.
I know. And with this lecture we should start thinking of materials opportunities that are there for us to tap into.
So thank you very much, (indistinct) for that observation and I think we should try and bridge the gap and come up with...
(indistinct) (indistinct)
Please.
So I think we need to really round up, I want to mention that Donna actually moved from one lecture to ours. So we are really very grateful because we know by now you should be resting from the various assignments you had all morning.

So to Randolph, Donna, I’ve just observed we’re wearing the, our clothes are of the same color.

I know, I noticed it also. It’s kind of amazing.

Oh, what a coincidence. I’m so happy.

And that means I need to come back there soon.

Yeah, that’d be great. That would be wonderful.

Thank you very much.

So we have Dr. Kiemi who is going to do the vote of thanks on behalf of the Institute for Advanced Medical Research and Training.

Dr. Kiemi, are you there?

Yes, I am.

Okay, please,

The floor is yours now, thank you.

Right, thank you very much.

Professor Donna Spiegelman, for a very exciting illumination lecture on implementation science.
In this vote of thanks, I just like to say that this lecture is coming just at the heels of an African summit that we had just last week. And one of the strong takes of that summit was that we need implementation science to reduce burden of stroke in Africa. We discovered that in Africa only 7% of hypertensives are controlled. And that begs the question of the need of interpretation science to, you know, to improve awareness about hypertension and, you know, and other risk factors and to improve optic of hypertensives to enhance control of hypertension, and of course to our body.

So it’s very germane to the field of non-communicative diseases on the continent. And I’m sure you wouldn’t mind partnering with us in the years ahead, you know, to undertake implementation science research in reducing the burden of stroke in Africa. So on that note, I’d like to, on behalf of the director of the Institute for Advanced Medical Research and Training College of Medicine...
I’d like to say very big thank you for the time you have invested in sharing with us these deep thoughts from your profound wealth of experience and knowledge in the field of implementation science.

Director, the entire staff and indeed the purpose of the College of Medicine, and a time not about the community and including colleagues who have joined from other institutions in Nigeria, 201232.213 across the continent, but they be grateful. We trust, we hope to build on this foundational knowledge and share with us to advance the field.

Thank you very much and God bless.

2475 02:13:09.981 --> 02:13:11.564 <v - >Bye.</v> <v - >Bye, Donna.</v>
2476 02:13:12.894 --> 02:13:15.826 <v Student>Bye bye, thank you.</v>
2477 02:13:15.826 --> 02:13:18.743 <v - >Thank you, thank you.</v> <v - >Thank you.</v>
2478 02:13:21.231 --> 02:13:24.254 <v Speaker>Thank you, Donna. Thank you again.</v>
2479 02:13:24.254 --> 02:13:25.921 <v Speaker>So much.</v>