# Adaptive Health Interventions and Causal Inference

### with Daniel Almirall

### Dr. Daniel Almirall and Aaron Wagner

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Host [Aaron Wagner](http://methodology.psu.edu/people/awagner) interviews [Daniel Almirall](http://methodology.psu.edu/people/dalmirall), Faculty Research Fellow at the University of Michigan's Institute for Social Research and Investigator at The Methodology Center. The discussion focuses on [sequential, multiple-assignment, randomized trials (SMARTs](http://methodology.psu.edu/ra/adap-treat-strat)), which allow scientists to develop adaptive interventions. Danny works with [Susan Murphy](http://methodology.psu.edu/people/smurphy), the creator of SMART, to develop and promote this new methodological tool. Danny's work on causal inference is also discussed.

**Podcast Timeline:**

00:00 - introduction and Danny's background

02:38 - SMART designs for adaptive interventions

08:31 - SMART pilot studies

13:51 - an application of SMART

19:33 - causal inference

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Speaker 1: Methodology Minutes is brought to you by the Methodology Center at Penn State, your source for cutting edge research methodology in the social, behavioral and health sciences.

Aaron: Hello and welcome to Methodology Minutes. I'm your host, Aaron Wagner and with me today is Dr. Daniel Almirall. Danny is a faculty research fellow at the Institute for Social Research at the University of Michigan and is also a methodology center research investigator.

 He is here to discuss his research interests, specifically adaptive health interventions and causal inference. Danny received his Ph.D. in Statistics from the University of Michigan in 2007.

 Since that time, he has continued his association with his degree advisor Susan Murphy, with the University of Michigan, and with the Methodology Center. Clearly, once people get their hands on Danny, they don't want to let him go.

 Danny, thank you very much for taking the time to talk with us and welcome to Methodology Minutes.

Danny: Thank you, I'm very happy to be here.

Aaron: To start with, can you tell us a little bit about your background? How did you end up working as a methodologist in Michigan?

Danny: My interest in statistics started in college when I realized that mathematics can actually be useful with real data to answer real word questions. I think that's how most people get into statistics.

 You know we call statistics the quintessential interdisciplinary science.

Aaron: Sure.

Danny: That's always gotten me pretty excited. The fact that it plays such an important role in every step of the scientific process basically, both in the study design, study execution, all the way through data analysis.

 That's always gotten me really excited about statistics and that's how I came into this world of methodology and statistics.

Aaron: How does that lead into your work today on causal inference and on adaptive health interventions?

Danny: I was, as so many of us are in this center, I was really fortunate to meet Susan Murphy as a graduate student. We hit it off pretty quickly and she basically invited me to her lab meetings and she invited me to become involved in this thing called the Quantitative Methodology Program in the Institute for Social Research.

 There I got to see quantitative social science in action. Of course Susan at the time was working on causal inference, this was right when she was beginning to get into adaptive interventions, and so I found a niche within that umbrella, that research umbrella, I found a niche on developing models for examining the causal effect of time bearing treatments of time bearing predictors, and I got really interested in that and that's how it all started right there.

Aaron: Since then, you have been working with Susan Murphy on developing SMART, which stands for the Sequential Multiple Assignment Randomized Trial.

Danny: Right.

Aaron: Can you tell us a little bit about what that is?

Danny: Let me back up just a little bit.

Aaron: Sure.

Danny: Actually, so my graduate school experience did not involve SMART at all. My dissertation, my thesis was devoted to these models where we were examining how to assess the causal effect of time bearing treatments, and in particular how we do causal effect moderation. How do we do moderators analysis or subgroups analysis when both the treatment and the moderator is time bearing.

 That was the topic of my thesis. While I was working on that, Susan started working on the SMART designs. Using experimental design principles we get to examine the impact of sequences of treatments. That became an attractive alternative to what we were doing in my dissertation, which was examining the effect of time bearing treatments from observational study data.

 Actually these two areas obviously complement each other quite a bit.

Danon: Sure.

Danny: I got excited about SMART right after graduation now and then I've been working in that area ever since.

 SMART stands for Sequential Multiple Assignment Randomized Trial. I'm very lucky to have mentors like Susan Murphy and Linda Collins who are pioneers in this area.

 SMARTs are basically multi-stage experimental trials, all right, where at each stage corresponds to a critical decision point in the care process for an individual.

 These critical decision points might be for example, what should I do as first-line treatment for a child with anxiety disorders, and then given an earlier response or an early non-response, what should I do as second line treatment.

 How do I adapt treatment over time to a child with anxiety disorders?

 SMARTs allow us to develop these adaptive interventions to treat and manage the disease over time. That's what they allow us to do. They allow us to learn what are the best strategies, what are the best tailoring variables and what are the best treatment options at these different critical decision points.

 The way the SMART works is we basically re-randomize individuals at each of these critical decision points to different treatment options. That's intuitively how it works.

Aaron: You mentioned tailoring variables. For listeners who might not be familiar, can you talk about the role that tailoring variables play in the development of an adaptive treatment strategy?

Danny: Absolutely. It might be useful if I give a very simple example of what an adaptive intervention is. Let's do that first.

 Here's a simple example of an adaptive intervention for children with anxiety disorders, let's just say.

 Right after the child is diagnosed the first question is well what's the first line treatment. The first line treatment, let's pretend its CBT, cognitive behavioral therapy.

Aaron: Mm-hmm

Danny: Say after 8 or 12 weeks I assess the child for early response to CBT. If I see the child is responding to CBT, I might continue with CBT or CBT boosters. Whereas if I see that the child is not responding to CBT I might augment CBT with medication.

 That's an example of one adaptive treatment strategy or an adaptive intervention. Where I start with CBT, if responding, continue with CBT, if non-responding, augment with medications.

 In that example, adaptive intervention, the tailoring variable is that intermediate assessment of early response status, because what that does is it allows us to pinpoint what the next treatment ought to be so the tailoring variable helps us tailor the next treatment in the sequence of care. That's what a tailoring variable is.

 Of course we can have a lot more elaborate tailoring variables, they don't have to be that simple. We might have a tailoring variable up front at baseline, so maybe depending on the age of the child, first line treatment could be something different because they might be a different developmental processes.

Aaron: Yeah, sure.

Danny: Maybe depending on different comorbidities at baseline, the first line treatment might differ, so the tailoring variable could be both baseline variables as well as intermediate variables that occur during treatment.

Aaron: At all the decision points as you move along.

Danny: That's right, at each decision point as I move along.

Aaron: All right. I think that should give our listeners a general overview of what a SMART is. Can we talk for a second about what a SMART is not? For example, can I send away for a SMART and implement it when it shows up in my mailbox?

Danny: Right. Let me just take another quick step back and say there's an important distinction between a SMART and an adaptive intervention. This is actually pretty critical.

 SMART is the experimental design used to build an adaptive intervention. A SMART in and of itself might have various adaptive interventions embedded within it, so the SMART is the experimental design we use to at the end of the day, come up with a high quality adaptive intervention.

 Now back to your question, well no, you can't just get it in the mail and implement it. There's various ways to answer what a SMART is not. One thing it's not is it's not a typical randomize control trial, so in a typical randomized control trial we might have 2 arms where we have say medication A versus medication B, or we might be behavioral intervention A versus behavioral intervention B, and those interventions could be fixed for example, in a randomized control trial. SMART is not that.

 In a SMART we have multiple randomizations rather than one. That's one thing that distinguishes a SMART from a standard RCT.

 A SMART is also not an observational data analysis method. There's a little bit of confusion I think right now where for example someone might run a standard 2-arm RCT and then think that at the end of the day if stuff goes wrong in the standard 2 RCT, it might have become a SMART. That's another thing a SMART is not. It's not a way to salvage an RCT that might have gone wrong, for example.

 As with RCT's, a SMART is an experimental design that you have to plan and be proactive and think through in the design stages just like you would any experimental trial.

Aaron: You recently worked on a project about how to design a SMART pilot project for the purpose of creating an adaptive intervention, and for interested readers, Danny's tech report on this topic is available at methodology.psu.edu.

 In this article you make the case for pilot studies before launching a full smart. What can we learn from a pilot project that we couldn't learn by going straight to a full scale trial?

Danny: Let me just tell you a little bit about the motivation for that manuscript. One of the initial reactions that both Susan Murphy and I and Linda get when we talk about SMART designs at conferences is because it's a deviation from the standard 2-arm clinical trial, in other words because it's a deviation from the way we typically think about randomized trials, a slight deviation, I would add, people get nervous. It's something different, and when people are first exposed to it, it looks complicated. The SMART appears complicated.

 Because of that, review committees and other stakeholders are often worried about the feasibility of carrying out such a design because of its apparent complexity. When Susan and I got to talking about this we thought, well, it would be useful to write a manuscript that is entirely devoted to how you would pilot a SMART trial to address acceptability and feasibility concerns in preparation for doing the full scale SMART trial. That was the motivation for that manuscript.

 What that manuscript does is it's kind of both a tutorial on SMARTs in a sense as well as a paper about things to look out for, acceptability and feasibility things to look for in the conduct of a SMART that are best taken care of in a small scale pilot before you go on and launch a full scale SMART.

 An example of feasibility concerns might be is the investigative team capable of doing multiple randomizations at different critical decision points.

 Another acceptability and feasibility concern is are participants willing to receive sequences of treatment. If there's going to be a change in treatment are the participants willing, are there any issues in that transition between say CBT as first stage treatment and then moving to combination therapy at second stage treatment among non-responders. Are there any issues with that?

 The SMART pilot tries to address these acceptability and feasibility concerns. What that'll do is when a scientist presents the results of a SMART pilot to a review committee, for example, you'll show a certain level of maturity, you'll show that you've actually gone through a SMART, you'll show that you've addressed some of those feasibility concerns and that you are capable of carrying out a SMART and that you understand what some of the challenges and obstacles are.

 Basically you've learned from the SMART pilot experience. Not only that, but the actual SMART itself might change. The actual design might change as a result of what you learn in the pilot. We thought this manuscript was going to be useful from that perspective.

Aaron: It might be expected that you, as one of the people who's been working on SMART from its inception, are working on SMART trials, but are other researchers? Are you seeing an uptake of SMART in high quality experiments?

Danny: Absolutely. The notion of adaptive interventions

Aaron: Mm-hmm

Danny: In and of itself, that idea is incredibly attractive to scientists because in fact, in clinical practice, that's what happens.

Aaron: Sure.

Danny: Treatments are adapted over time. We rarely in clinical practice implement a fixed treatment for an infinite duration of time. We adapt treatment to the changing course of the participant, of the patient, in clinical practice that's what we do.

 The notion of adaptive interventions are really attractive, and it's gaining steam. Because this is a hot area, there are a number of methodologists now working in the area of adaptive interventions.

 Really from my perspective it splits off into 2 different worlds. One group of scientists are working on observational study methods for developing adaptive interventions, that is given an observational study data set, how do we learn about the best adaptive intervention from an observational study data set.

 Then we have others who are working on SMART trials, which is an experimental way to learn about the best adaptive intervention.

 I would say that from there's a numerous number of methodologists working in both of these areas, and the interest is astonishing at this point. There's a lot of interest in this area.

 Many clinicians are taken with the idea of using an experimental design that explicitly informs how to develop an adaptive intervention, which is what they're doing in clinical practice anyway.

 From the novelty and innovation point of view, SMART's extremely attractive to clinical scientists. The main barrier that we confront then is this barrier of well it's different from the randomized clinical trial, and so there's a lot of interest in this area, and then it's a question of working with clinical scientists who continue to get their buy-in and to work with them on really fundamentally to work with clinical scientists on addressing the questions about adaptive interventions that they care about, and working to answer their questions using these SMART design principles.

 Both areas are extremely important from my point of view, both using observational study, sort of to generate hypotheses about adapting interventions as well as using the SMART experimental design to sort of build adaptive interventions using sound experimental design principles. Both areas are extremely important from my point of view.

Aaron: In the interest of encouraging adoption you also recently published a tech report of an example of a SMART design, SMART or discontinuation trials with application to the treatment of anxious youth and this type of report is also available at the methodology center website.

 First of all briefly, can you explain what a discontinuation trial is?

Danny: It's easiest to think about the discontinuation trial in the medication context, which is usually where it's taking place.

 In a discontinuation trial, the burning scientific question there has to do with duration of medication, how long do I treat the patient for.

 In a typical discontinuation trial, the burning question is at what point can I discontinue medication.

Aaron: Sure.

Danny: Right? Which is equivalent to thinking about who long do I need to medicate for. This is an especially important concern when we're using medications to treat children, for example.

Aaron: Yeah.

Danny: Which is one of the motivations for that manuscript because it discusses discontinuation trials in the context of pediatric anxiety.

 In a typical discontinuation trial, what ends up happening is let's just say we have 3 arms, and so what we would do is we would randomize children who have shown an acute response to medication treatment.

 In the typical discontinuation trial we take children who have shown that they respond to an initial duration of medication, let's just say.

Aaron: Mm-hmm

Danny: Then what investigators typically do is then they randomize these children to let's just say 3 different arms. One arm might be immediately discontinue medication. They've shown successful acute response to say an initial 12 weeks, and then we take all these responders and then we say well, let's randomize them to 3 arms.

 One arm might be immediately taper medication. A second arm might be, let's go an additional 12 weeks of medication, and then a third arm might be let's go an additional 24 weeks of decimation. That's the typical discontinuation trial.

 What they're trying to examine is how do outcomes look in the long term based on these different levels of treatment duration.

 Typically the primary outcome in these trials historically has been a survival outcome, so time to relapse, because remember these are kids, these are patients who have already shown an acute response. Then the question is if I taper you off of medication, how long is it going to take for you to relapse. Or if I taper you off of medication 12 weeks later, how long is it going to take for you to relapse, and if I taper you off medication 24 weeks later, how long? What are the impacts of that? That's the typical discontinuation trial.

 What we realized in thinking about this, and actually I was approached by a group of pediatric anxiety investigators to work on a discontinuation trial, we can design a SMART clinical trial, a SMART design to answer those questions about treatment discontinuation as well as answer other more exciting questions having to do with what we realize is we can use a SMART design and be able to still answer those questions, those primary questions about treatment discontinuation as well as be able to answer additional interesting questions about how we might adapt treatment over time in the context of treatment duration.

 What this managed group spent some time talking about, the smarter alternative to the discontinuation trial, so for example, take a child who was randomized to the arm for 12 additional weeks of medication and suppose this child relapses at week 13. Well in the typical discontinuation trial, that child has given us their survival outcome and that child is now removed from the study, because they've given us their primary outcome.

 Remember, primary outcome is survival.

Aaron: Mm-hmm

Danny: Is time until relapse. Well what we're arguing in this paper is what about addressing the question of what to do with the child who relapses, right? That's a question about adaptive interventions. I treated them for 12 weeks, they relapse, what do I do next?

 What we're arguing in this paper is we can still answer those very same questions about time to relapse on different treatment durations, but keep the child who relapses in the trial and maybe investigate what you might do next with that child.

 We make this argument that you might be able to learn those other exciting questions about what to do with a child who relapses.

Aaron: Is that much more resource intensive?

Danny: It is more resource intensive, and we spend some time talking about that in the manuscript. It is more resource intensive in the short run, but we argue that in the long run we're actually going to learn more from this trial, the smarter trial, and it's going to in the long run be more cost effective from a scientific point of view than for example, running another trial later where we take the non-responders to the 12 week medication and do another trial with them.

 These are the kind of things we talk about in this manuscript. We talk about the pros and cons of doing SMART versus discontinuation trial from a resource management point of view.

Aaron: Would you say that a SMART design is always the best choice for a discontinuation trial?

Danny: Well the way I would answer that question is it really depends on the scientific interests of the investigator. I would not say a SMART design is always the answer. If the investigator has an interest in adaptive interventions and an interest in for example, what to do after a relapse to a particular treatment duration, then a SMART might be an attractive option.

 Fundamentally as I said earlier, SMARTs are about developing adaptive interventions, and so there are cases, for example with acute disorders, disorders that are not chronic disorders, like a headache, for example, a SMART design might be overkill.

 A SMART design is not always the solution to all questions. The investigator has to be interested in sort of managing treatment over time in response to the patient's response to prior treatments. I would say that's the driving motivation for wanting to do SMART.

Aaron: Leaving SMART behind for a moment, you also work on causal inference. Though much of the audience will be familiar with causal inference, can you briefly tell us what causal inference is and what specifically you work on involving causal inference?

Danny: This is also quite a hot area right now, as you know. This whole area of causal inference from my point of view, it's kind of a two-fold kind of thing.

 Shedding light on what the assumptions are using traditional methods that we've been using for a long time that would allow us to make statements of causality.

Aaron: Mm-hmm

Danny: As well as of course developing new methods to address questions of causality. From my point of view, causal inference is really about clarifying what those assumptions are, and then my particular area of interest within the big umbrella of causal inference has been this issue of how do we develop models and estimation methods that would allow us to examine the impact of time bearing treatments, the causal effect of time bearing treatments.

 Let's pretend for the moment we have clients who are substance abusers and in an observational data set you observe that some clients in the first 3 months take on outpatient treatment followed by in-patient treatment versus other clients who are always in residential care versus other clients don't take treatment at all.

Aaron: Mm-hmm

Danny: The key is we observe clients under these different sequences of treatment, and then the question is now that I've observed that can I say something about the effect of these different sequences of treatment on substance use outcomes, for example.

 How do we go about doing those things? That's the area I work in in causal inference, and there's a lot of interesting subtle questions around there, not only the sequencing but what about time bearing effect moderation.

 We all know about moderation in a simple time point setting, meaning when we have a baseline moderator, say like gender or age. What about when the moderator gets updated or varies over time.

 Suppose I want to ask the question, what is the impact of an additional 3 months of treatment? Given how the participant has responded over the first 3 months of treatment.

 I might have observational data that assesses response during the first 3 months of treatment as well as outcomes at say the end of a year. How do we develop models to be able to answer the questions such as those, such as the impact of an additional 3 months of treatment given my response to date?

 We work on methods to answer questions such as those.

Aaron: It sounds like that ties together very neatly with your work on SMART and those new methodological questions that you were referring to just a minute ago.

Danny: That's right. I think the thread that ties it all together in both my work on causal inference and my work on adaptive interventions using SMART designs, which is this interest in time bearing treatment or time bearing predictors, and they both inform each other, you know we can generate hypotheses about what the best adaptive interventions might be from observational study data set, and so it's really exciting to be in both those areas.

Aaron: Danny I want to thank you for joining me today.

Danny: Thanks so much, Aaron.

Aaron: After this podcast was recorded, both of the papers that we discussed extensively were accepted for publication. The article, "Preparing for a Sequential Multiple Assignment Randomized Trial for Developing an Adaptive Treatment Strategy, Designing a SMART Pilot Study," will appear in a forthcoming issue of Statistics in Medicine.

 The article, "SMARTER Discontinuation Trials with Application to the Treatment of Anxious Youth," will appear in the Journal of Child and Adolescent Pharmacology.

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