

How Do You Design Trials That Are Fit for Purpose?

Lesley Curtis:

I want to talk about how we actually design trials that are pragmatic trials, and talk through the PRECIS-2 tool as a way to really help us design trials that are fit for purpose.

There are a few things that I want to really underscore. The first is that that line between explanatory and pragmatic, it's a continuum, there are arrows on either end of the line. To me, that reinforces that trials are not either explanatory or pragmatic, but they are on the continuum between those two. Too often I hear us talk about pragmatic trials as though it's some sort of magical dichotomous definition or binary pragmatic yes or no, and the PRECIS tool really underscores the many different considerations that go into the underlying pragmatism of a trial.

Just to orient everyone, the most pragmatic along each of these axes, the most pragmatic would be at five. So, one could imagine visually a very pragmatic trial looking like the circle, the big circle. Whereas as there are less pragmatic elements of the trial along these axes, you get something that begins to look like, well, not a deflated balloon, but maybe a tire that has some flat spots.

So at the top, the question is, who's actually going to be in this trial? Who's selected to participate? A really pragmatic approach might be to include anyone in the trial who would ever be a candidate for that intervention in clinical practice in usual care, right? Almost no restrictions, all in. Now, we can think of all sorts of situations where we'd want to maybe restrict the population, the eligible participants a little bit, and that would bring us in from that outer edge.

In terms of recruitment, for those of us who've been involved in explanatory trials, we know that recruitment, sometimes we do a lot to recruit people into trials. The most pragmatic approach would be to say we take people who are coming into maybe a clinic for their usual care, and those are the people we approach, and we don't go to any special measures to recruit additional folks.

In terms of the setting, where are we doing this? Is the setting identical to the setting in which these results would be applied? That would be really pragmatic. We may need to put some boundaries around that, but the most pragmatic would be to say we're doing it right where these results would be applied. The organization element really gets at what do we actually need, that is in terms of expertise and resources to deliver the intervention? Now, if we need specialized skills to deliver the intervention, and those specialized skills don't exist in usual practice, that's not going to be very pragmatic. But if we have an intervention that can be delivered by people who usually take care of patients and the participants, then that's pragmatic.

Now, in terms of delivery, the question here is can we kind of slot whatever the intervention is into the usual care? So again, we're just using what already exists in that usual care setting, not inserting additional people, if you will, or additional expertise.

On the adherence axis, the question there is how much flexibility do we give? What measures do we put in place to make sure that the participants adhere to the intervention, right? In a highly pragmatic trial, we would just kind of allow for full flexibility and let the end user engage with the intervention and adhere as they would, or not, but not put special constraints around that. Now, we can imagine that where we end up on these different parameters will have implications for the results, and so I hope this underscores the importance of all of these factors coming together.

With respect to follow-up, the question there is how closely are we following them up? Or are we just following them up when they return for their usual care? Keep in mind that for any trial, complete follow-up is essential, and so even in the context of a pragmatic trial, we have to make sure we have some mechanism for accounting for everyone who started at the beginning or at some level.

In terms of the outcome, relevancy to the participants is really important, relevancy to the decision-makers, really important. Finally, the way we construct the primary analysis. So, the most pragmatic approach would certainly be to do the intent to treat analysis. That is, people or groups are randomized, and we do the analysis on the basis of that randomization or the intention to treat.

What's really important is to make sure that the approach that you select is the most appropriate for answering your question. There aren't any bonus points for going farther out on the wheel, right? It's not like when reviewers or anyone looks at your trial proposal, you get extra points for being more pragmatic than somebody else. It's really about what is your question and how do you answer that question using a pragmatic approach that best fits the question?

The real takeaway here is that it's a total balancing act. So if you want your results to be really relevant to real world decision-making, you'll probably be trading off some efficiency.

Trade-offs abound, they abound everywhere, and we make those trade-offs in the context of the question we are answering. With all of these embedded pragmatic trials, some have elements that are more pragmatic and some have elements that are more explanatory, and that just speaks to the underlying question.