WEBINAR: Bias and Randomization 1980 – 2020 – 2060|FEB, 11, 2021

Answers by Jay Herson, Feb 12, 2021

QUESTIONS

1. These are important issues and difficult to integrate into traditional RCTs. Could we have the first of 2 adequate and well-controlled trials be a rigorous and resource-intensive RCT for Efficacy? And the second of 2 trials could be a large simple trial for demonstrating overall Effectiveness and consistency of effect? These important issues that you raise can be better integrated into these more pragmatic trials.

   Yes this is a good idea but we must not neglect safety data. Large simple trials are most often conducted for already approved drugs. This allows them to collect minimum safety data. The LST is likely to be too clumsy to collect safety data according to pre-market standards.

2. What about small "unpowered" randomized trials sometimes preferred by some stakeholders instead of single-arm trials? False security?

   I usually tell sponsors that they are either doing clinical research or they are not. To do clinical research costs money. Underpowered trials waste money.

3. How large of a bias is introduced by inclusion criteria, and is this a serious concern?

   It is recognized that clinical trials are conducted on patients that do not resemble those seen in practice. This is not a bias because these trials are a construct for drug approval not proof that the drug works for all. In my home state people applying for a driver license must drive a car with an inspector through an obstacle course that does not represent the real world. An applicant would likely be issued a driver license on this basis but this test is also just a construct that the authorities have found useful to license drivers. A person passing this test could very well cause an accident the next day. As for clinical trial bias it is through post market trials and clinical experience that we reduce the inherent bias of the construct.

4. Would you concur that pragmatic trials with randomization is the most persuasive tool to generate robust RWE?

   Yes, this is better than using data from insurance claims. Good point.

5. Do you think that all the technology evolution described towards 2060 could allow to using more adaptive randomization phase III trials in a reasonably near future (e.g. 2030)?

   Yes, most trials that are called "adaptive" today are sample size re-estimation during an interim analysis. There is a demand for a broader definition of allowable adaptive designs and I think that is coming. I wish pharma companies would design a trial that doesn't involve drug efficacy—like comparing two ways of providing patient education for an approved drug. This trial can be done adaptively without any regulator interference. Publish what is learned from this trial.

6. Why do we wait 2060 to use the "cogent" coefficient to terminate clinical trials early?

   I didn't mean to imply that we will wait until 2060 for the coefficient of cogency. I mentioned it because it is a logical consequence of the huge swarm of data that will continuously flow in to a sponsor. It could take place earlier.

7. Do you believe that the GDPR (European Data Protection Regulation) will be overthrown before 2060? ;)

   The reg may exist but it will be much less or even zero labor intensive. Computers processing data will automatically follow the regs and use advanced encryption methods. No need for human intervention.

8. Do people SUPPLEMENT the RCT placebo dataset with RWE natural history for FDA approval? In this case, can we call the trial "placebo RCT", if some of the controls were truly randomized to placebo and some data also came from RWE?

   This practice is used rarely for FDA submission—limited to orphan drugs and cases like post-market commitment for accelerated approval. No I would not call the trial placebo RCT, more like hybrid control group.

9. What do you think of "AI generated" "virtual subjects"?

   This is OK for internal research, perhaps a go/no go decision but little else.

10. Last week, the FDA held a seminar on their current perspective for trials in Fatty Liver Disease. There are currently no treatments approved, so both the agency and sponsors are still feeling things out (to put it politely). Phase 4 trials are needed because marketing authorization is done on accelerated approval after a successful Phase 3. Several academic statistics groups have suggested seamless Phase 3 designs where the subjects in Phase 3 move directly into the Phase 4 trial. The FDA shot down this approach in the seminar saying it was unethical - separate randomizations (even if they begin simultaneously) would be required for Phase 3 and Phase 4 trials.

    I am not surprised that FDA said this. It is consistent with what they have said before in similar situations. If phase 3 patients pass into phase 4 they are selective, those well enough to move to phase 4 and willing to consent.

11. Can you explain why the seamless design is unethical?

    I think the seamless design is ethical. I am not familiar with an argument that it is unethical.

12. Can a randomized trial combined with an open label synthetic arm be acceptable to be used for submission?

    It is not up to me, but I don't think such a trial would be acceptable in the current climate. Pharma companies should gain further experience with this type of trial by doing a Phase 4 trial just for their own benefit, even a seeding trial. What is learned from this exercise could advance the state of the art.

13. Can you talk a little about ITT in the era of COVID19?

    Even without COVID19 ITT has come under fire. During COVID19 the anti-ITT wing will argue that there are so many missed appointments, missing data etc. that this will not represent the post-covid world where the drug will be used. One must use methods of causal inference that divide the intercurrent events by those that occur due to covid—such as missed appointment due to transportation issues and those that would occur anyway like forgetting to take the drug according to protocol. A composite endpoint definition would much of this into account.

14. What will be the patient's role in the design and choice of endpoints in future studies?

    We need different reports for different stakeholders. Patient defined endpoints would certainly be of interest to physician and patients.

15. The question was whether randomization was necessary, not if it was best practice.

    Randomization is necessary necessary but not sufficient for persuasive evidence.

16. If in the future response to treatment will become predictable based on genetic etc. data, will we need clinical trials in the first place ?

    Clinical trials will always be used to answer questions still not resolved by artificial intelligence/machine learning. The robotics will not only tell us we need a trial, it will design the trial and the analysis plan.