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Tufts' Ken Getz: Onerous Clinical Trial Protocols Contribute to High Failure Rates

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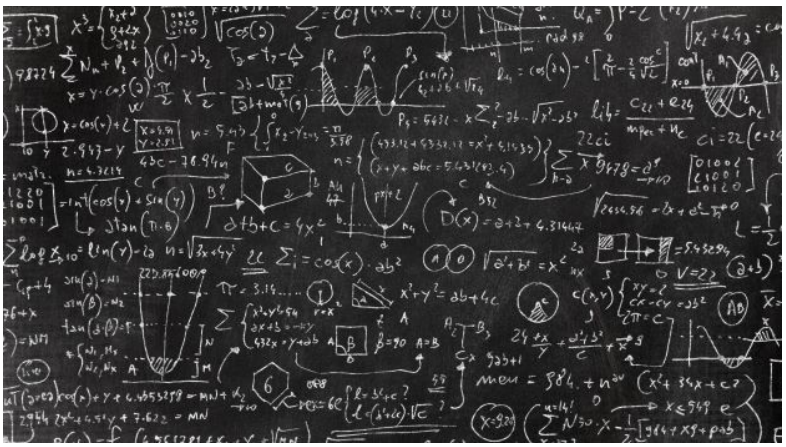

When industry executives talk about why so many clinical trials take so long to complete and often fail, they inevitably point out that the low-hanging fruit has been picked. That's true, but there's more to the issue than the increasing difficulty of drug development. **One study** showed a success rate – defined as advancing to the next stage or regulatory approval – for all therapeutic areas of just under 14%. Once therapeutics entered Phase III trials, the success improved from a low of nearly 36% for oncology to a high of more than 85% for vaccines.

BioSpace spoke with Ken Getz, executive director, **Tufts Center for the Study of Drug Development** and professor of public health and community medicine at Tufts University, about this issue.

BioSpace (BSP): So, what is behind the high failure rates in clinical trials today?

Ken Getz (KG): There is such a complex development process – and the level of scientific, operational and executional risk continues to rise – that we can't just point to difficulty in demonstrating safety and efficacy. It's true that the diseases we're studying are more difficult and you need larger amounts of data and more patients to demonstrate a therapeutic effect relative to a placebo or standard of care. But, we also must look at executional challenges. Studies today involve more intermediaries, more technologies and sites in more countries, all of which adds layers of complexity and inefficiency. We're collecting so much more data than before, and our protocol designs are so much more onerous for the investigative site and for the patients who participate.

BSP: How is it more onerous for the study coordinator, administrative professionals or others involved with the trials?

KG: They have to have the patients participate in more visits where more procedures are conducted per visit. They have to ensure the collected data is monitored properly and, if data falls outside the normal ranges, they have to be more active in curating and cleaning it. Often they have to use more virtual technologies, which also adds to their burden. Even the consent form is more complicated, so discussing the study with a prospective participant is more onerous because it is harder to describe and the requirements of the protocol are more elaborate. Therefore, convincing someone to participate becomes harder.

BSP: You suggested in the media recently that shoehorning personalized medicine trials into traditional R&D models may not be effective. Can you elaborate?

KG: Most of the clinical trial approaches we're using today have been around for more than 50 years. Traditional randomized controlled clinical trials consist of targeted cohorts that receive the investigational drug, and a comparison or control group. Typically, the patient presents at the research center or

clinic and may have to maintain a diary or do certain things at home during the study. Into this basic trial paradigm, we keep trying to fit more technologies, more intermediaries and more approaches.

BSP: Why is that a problem?

KG: We have found, time and again, that the more fragmentation, the more customization, the more moving parts you introduce, the longer the trial takes, the higher the levels of inefficiency and the greater the likelihood that you will encounter delays and perhaps even patient dropout.

BSP: What do you propose to minimize those issues?

KG: In some recent discussions, we've pointed towards more agile and synchronous activity, where we're doing more work in parallel as opposed to the classic sequential approach. There are inefficiencies with having to select and engage vendors at the site and inefficiencies between trial phases. Every area could involve more planning prior to executing the activity.

Look at everything that occurred during the pandemic. Its legacy will be the fact that we had regulatory agencies and organizations that provide oversight behaving proactively and

responsibly by mobilizing professionals within companies as well as external parties to meet more frequently, set better expectations, mobilize around plans, set coordination guidelines and not second guess other parties. There was a lot more trust, desire to delegate and reliance on collaborative partners, based on managing milestones and coordination time points. That creates an environment in which internal and external team members can collaborate at a much higher level than we've typically seen.

BSP: You've analyzed success rates of trials involving personalized medicine and, despite the use of biomarkers for patient selection, have said there have been no broad improvements. Why hasn't patient stratification improved trial successes?

KG: Success isn't a function of just the science alone, which biomarkers help us address. There are many factors at play, such as being able to attract and retain that highly-targeted patient community, and that relates to the design of the trial protocols. Most of our studies in personalized medicine collect so much data, including miscellaneous and tertiary endpoints, that there's a lot of noise that makes it even harder to demonstrate that

the biomarker has delivered a cleaner, more targeted therapy.

BSP: What is behind low retention rates?

KG: Retention rates are a major barrier and a major challenge. A lot of that is tied to the burden of participation, which not only manifests in the large number of people who choose not to participate in trials but also for those who are in the trial and realize after the second or third visit that they have 10 more scheduled over the next six months. A lot of people may question whether they're able to comply with the protocol. There also could be a halo or placebo effect, so patients feel they already are getting some benefit from the therapy and therefore don't need to continue or comply with the burdens that the protocol requires. There are many reasons why people drop out of trials prematurely.

Incorporating remote, virtual technology (to replace some medical appointments) can help relieve the burden of trial participation and improve access to trials in a more convenient way. We are hearing from patients that they like those options. That said, most patients want a balance between a purely virtual trial and human interaction with the study team.

BSP: What is the challenge for clinical trials, going forward?

KG: There's a paradoxical dilemma we face as we continue to develop highly personalized medicines: The closer we get to developing therapies for the individual patient, the more people, infrastructure and data we need, and the more complex the trials must be, to achieve the objective. So many of the benefits that can be added through the promise of personalized medicine – not only to patients but also to clinical research – are not being realized because we're struggling to manage that hyper-customization and complexity.

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