Highlights and Summary of Part 7 Webinar:

Imagining the Future State of Clinical Research

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The COVID-19 pandemic has altered the course of clinical trials, but many of the changes we're starting to see have been percolating for decades.

"I think it's important and comforting to know that many of the imaginings that I'll touch on have actually been unfolding for decades. But for a variety of reasons, most … have remained on the periphery of mainstream clinical research until now," explained **Ken Getz, MBA.**

This quote comes from the seventh in a series of WCG webinars that address the coronavirus-related challenges facing the clinical trial industry.

Featured speaker:

Ken Getz, MBA
Deputy Director and Professor, CSDD, Tufts University School of Medicine; Founder and Board chair, CISCRP, and a Member of WCG's Board of Advisors

Lindsay McNair, MD, MPH, MSB, *Chief Medical Officer, WCG,* moderated.

You can find links to this webinar and an array of COVID-19 resources on our **WCG Insights Program page.**

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An Overview of 2019 and Q1 2020

Four key themes drive the 2019 and Q1 2020 clinical trial conditions.

1. Highly complex designs and execution
2. Fragmentation and poor coordination
3. High risk aversion; limited regulatory clarity
4. Mixed but improving public and patient engagement

The first two relate to a high degree of scientific and operating customization that drives inefficiency, cost and poor performance.

Protocol Design and Execution Complexity

Complexity is inversely related to performance: The more complex our protocols, the worse they perform from a speed standpoint and a recruitment effectiveness standpoint.

Complexity is also associated with a higher number of protocol amendments. The typical amendment adds three months of additional time. For a Phase 3 study, that's about a half a million dollars in direct cost to implement.

Several trends from over the past 10 years characterize complexity.

- **Exceptionally high growth in the number of endpoints:** The number of primary and key secondary endpoints has not risen dramatically. It's all the additional tertiary and exploratory and miscellaneous endpoints that we support by conducting more procedures and collecting more data that have really expanded the scope of our studies.
- **Dramatic increase in amount of data collected:** We're collecting twice as much data today, well in excess of a million data points for a Phase 3 study, but the growth has primarily come from all the procedures that collect data in support of the nonessential activities, those tertiary and miscellaneous and exploratory endpoints.

Fragmentation

The fragmentation is quite remarkable, and it cuts across so many different domains. Many functions that operate within sponsor companies are siloed, of course. But even more so, the landscape of providers supporting the clinical research enterprise is largely fragmented and siloed.

- **A vast community of global intermediaries:** Those primary groups are CRO service and investigative site providers. Today, the amount that pharma

spends on global development activity that is directed to outside providers far exceeds the amount that is spent on internal infrastructure and personnel.

Consider the incredible number of intermediaries that support clinical research at a global level:

- Roughly 3,000-plus contract service providers, both niche as well as full-service,
- More than 40,000 unique study conduct service providers,
- About 1,700 technology service providers and other service providers supporting the research enterprise.

- **Investigator inexperience, turnover:** Globally, the proportion of investigators who are first-timers hovers around 35% to 40% globally. The highest turnover rates come from the least experienced investigative sites.

Risk Aversion

Ours is a highly risk-averse culture that has--arguably--received only limited clarity from regulatory agencies.

Mixed Public and Patient Engagement

We see very high public and patient willingness to participate in clinical research, but that does not translate into participation. In fact, patient recruitment and retention rates are the lowest they have been in our history as an enterprise.

The research points to some contributing factors:

- There are wide disparities in study volunteer diversity with highest under-representation among black participants.
- Following informed consent review of those who choose not to enroll, nearly 60% indicated their decision was due to the expected burden of participation--number of procedures, scheduled visits, etc.

(Sources: CISCRP 2019 and Tufts CSDD 2018/2019)

Another factor: failing to engage healthcare providers as facilitators. We see typically very, very high levels of comfort among physicians and nurses in clinical care environments to discuss clinical research information with their patients, but the actual referral rates are remarkably low.

Looking at the Big Picture

All of the above factors help characterize and explain some of these macro-level findings:

High and rising level of development risk that companies are facing today. In fact, our failure rates have been the highest in our history. When you look across all therapeutic areas, one in every 10 drugs that enters human testing makes it into the marketplace, and of those, historically, only about 30% recoup their full development investment.

High and rising development cost: We've seen more than a doubling in that capitalized cost with, today, an estimated $2.6 billion spent to develop a single successful drug:

- 26% of that capitalized cost is associated with the direct expense, direct out of pocket expense, to develop that individual drug.
- 18% is associated with the time that investment is tied up in the development time horizon.
- 56% is due to the high rate of failures that have to be supported by every successful drug.

Additionally, we see a roughly 6% to 7% annual growth in what is spent by pharmaceutical companies to support global R&D activity.

Long and highly variable cycle times that are associated primarily with supporting randomized controlled clinical trials. Those timelines have continued to increase over the last several decades. The total time has increased from IND filing to NDA submission. But even more notable is the variation around the mean time; that coefficient of variation is rising, which suggests it's getting more and more difficult to even predict our cycle time.

Perpetual piloting and proof of concept: "They primarily pilot solutions, as many of my colleagues like to say; they're sort of in perpetual proof of concept mode given that industry-wide aversion to risk, particularly in the absence of regulatory insight and clarity."

A very high percentage of companies report relying heavily on the use of pilots to guide their adoption decisions. But the same percentage essentially indicated it was difficult to even generalize their pilot experience to actual portfolio activity. And as a result, that has been a major barrier to adoption of a number of approaches that have really been available for some time.

For example, 40% of sponsors and CROs were piloting and implementing the use of home nursing services. Thirty-seven percent and 34% respectively were reporting planning and piloting and implementing the use of wearable devices and concierge services.

(Source 2018 Tufts Center study conducted in collaboration with the DIA)

Where We Are Today: The COVID-19 Era

Let's shift gears and look at where we are now. The drug development community, like so many communities in all sectors of the global economy, was essentially caught flat-footed, if you will, when COVID-19 first hit.

But as we settled into a new normal and we began to show our resilience, we started to see that there's much to draw on from these past experiences.

The FDA guidance and communication on trial designs and execution during COVID-19 have been uncharacteristically strong. And that has really helped us as we've looked to navigate these three areas.

Planning and Design

- **Dramatic increase in internal activity:** This is one place where teams can interact effectively while they're operating remotely from home-based settings.
- **Growth in design collaborations:** We see the extremely high level of collaboration between companies that are now engaged in co-development relationships. We see public-private partnerships, emphasis on the use of master protocols to support concurrent studies that might involve a variety of different patient subgroups.
- **Increased use of simulations and modeling**, and data-driven approaches to support design decisions.
- **Growth in regulatory advisory interactions to really inform deviations** that might be made to protocol designs, or to inform new designs that are being considered.
- **Dramatic increase in submissions / resubmissions for ethical review** as designs continue to adapt and change in response to those trials that are now either supporting the development of COVID-19 treatments or those ongoing studies that continue to support patients in active trials during COVID-19.

Clinical Trial Execution

The clinical trial execution area has perhaps been the most negatively affected.

- Major disruptions:
  - Halting new trial initiations globally
  - Delaying enrollment for most ongoing clinical trials
  - Impact on sites and CROs: We're seeing some site closures as well as some layoffs now, as a lot of the smaller and inexperienced sites are encountering cash flow challenges. The same can be said for a lot of the small CROs that are starting to consolidate as well. It's those organizations that have typically seen

very low volume, that rely so heavily on new trial initiations to support their cash flow. Organizations that do not have a lot of diversity or diversification in their portfolios have been hit particularly hard.

- Broad adoption of digital support, remote and virtual solutions
- Increased interest in supplementing data that's coming from randomized controlled clinical trials with real-world data
- Clinical supply disruptions, most notably the shipping and the delivery of supplies to investigative sites

Data Analysis and Reporting

- **Data lock delays:** Sponsors and CROs report data lock delays partly as a result of delayed enrollment, and the longer time it's taking to clean, compile and curate data.
- **Growth in collaborations:** We're also seeing a lot of shared data, and open collaborative platforms where more professionals than usual have operated externally. They're being invited to assist and support the analysis of data.
- **Increased efforts to use real-world data and real-world evidence** to supplement clinical research data.
- **Growth in application of machine learning and associated AI.**
- **Increase in regulatory advisory interactions,** in particular, getting feedback on statistical analysis plans that have changed as a result of new data collection activity during COVID-19.

Let's now shift gears and assume that this pandemic has been a springboard for adoption.

Assuming the New Normal Brings Real and Lasting Change

"Now, I know many would argue, and with evidence could suggest in fact, that a lot of these newer innovative approaches may be short-lived, and we may revert to our traditional or older ways. I tend to be more of an optimist, and I believe some of these changes will have a long-term impact."

Let's just assume that urgency and compassion have really pushed stakeholders in the drug development community to embrace being far more collaborative and flexible, and to recognize they can operate well and also protect their intellectual property under more of an open innovation model. That they can, in fact, push the boundaries of development speed with regulatory support behind it.

Let's take those four broad themes mentioned earlier again.

How might protocol designs look in 2021 and beyond?

- **Increased scientific and operational complexity:** We can expect our protocols to become even more complex, but they'll now be supported by scaled and flexible digital capabilities, and more machine-learning and analytical approaches that we'll apply under more collaborative models.
- **Companies will continue to test and challenge the traditional randomized, controlled clinical trial.** For example…

- **Increased use of collaborative designs and shared development risk.** We'll see more master protocols, and platform and umbrella trials that rely on these collaborative designs. With many more co-development partners that are sharing development risk, and also sharing resources to support faster-running clinical trial activity.
- **More pre-authorized and conditional-use trials;** they will enhance speed by relying increasingly on collecting data in real-world clinical care settings. We'll put treatments, investigational treatments that have known safety profiles into the hands of clinical care settings and select investigative sites where we can continuously monitor and adapt in real time. And these will be approaches we can build into our protocol designs that might support a far faster development timeline.
- **Infrastructure and capabilities to offer more options for study volunteers.** Look for broader use of remote and virtual approaches, and a variety of technologies, and approaches supporting participant convenience. We can expect to see interest on the part of sponsors and CROs to offer more options to study volunteers. This will create higher levels of customization.

How might our provider landscape and the coordination of all of these different parties look in 2021?

- **Consolidation:** Industry insiders and observers speculate that in 2021 we're going to be looking at a consolidated provider landscape. There are many small, lower-volume, poorly diversified sites and CROs I described earlier that we can expect will exit the enterprise. Those better-managed sites, the ones that are dedicated to clinical research, they've built their infrastructure, they have more of a diverse portfolio of services, these are the sites that will find themselves stronger moving into 2021.
- **Decentralization**, including increased use of remote monitoring.
- **Migration away from urban settings.** With a greater receptivity on the part of sponsors and CROs to remote and decentralized clinical trial models (and given residual risk that may exist in more densely populated areas), we can imagine that clinical trials will move to more rural and less congested areas and may become less dependent on the larger health systems.
- **Greater patient control of data, including patient-directed data aggregation.** Given the fragmented environment in which patient electronic health records sit today as well, where we see a lot of intermediary gatekeepers, we could also anticipate that sponsors and CROs may look to empower patients to have more control over the aggregation of their own electronic health and observational data (perhaps including self-administered procedures and diagnostic assessments).

How might our interactions with regulatory agencies and regulatory stakeholders look in 2021?

We like to think regulators have been pushed to challenge some of the legacy drug development practices, and they'll take a more mature and open-minded approach in the future.

That's very hopeful thinking, but certainly the FDA and the EMA have started down that path with improved communication and interaction, including their more transparent encouragement of patient engagement and more flexible clinical trial activity.

We anticipate the use of real-world data supported by continuous monitoring will also help support, augment and supplement--and in some cases even replace--data that will be acquired from the classic randomized, controlled clinical trial.

What might changes in public and patient attitudes look like in 2021 and beyond?

It may be too early to see whether the pandemic will have a lasting impact, but we're seeing:

- a higher **level of awareness about clinical research,**
- some indications of increased **trust in the pharmaceutical industry.**

What might changes be in workplace attitudes in 2021 and beyond?

- **Increased receptivity to working from home** and remote interaction.
- **Greater interest and awareness of colleagues,** including greater empathy toward colleagues and work-life balance.
- **Better meeting preparation and shorter meetings.** Many have noted people are better prepared when they attend virtual meetings. This could shorten the amount of time required to have our meetings and to make decisions.

Questions from Audience

Questions for Getz

Ken Getz, MBA
Deputy Director and Professor, CSDD, Tufts University School of Medicine; Founder and Board chair, CISCRP, and a Member of WCG's Board of Advisors

Q **Do you expect the relationships between biopharma sponsors and their CROs to change much in the future?**

A **Getz:** It's a great question. The words "change much" are the ones that I get hung up on because I think that in general, the reliance on contract service providers, which has been strong for a very long time, will continue to exist along those lines. I think if anything, you're seeing sponsor reliance on CROs to help support and guide them in their transition from the traditional site- visit-based clinical trial to those that are more remote and decentralized. That reliance has really increased dramatically. So we see a lot of sponsors that are eager to support these relationships and eager to see their contract service providers play an even more active role in supporting the collaborations and guiding that transition and helping them build that capability.

Q **Do you think there may be greater efforts in the future to educate and train and bring in more physicians from more rural areas, smaller community hospitals, private practices, outside major academic areas to serve as research investigators, where there may be more limited access to healthcare or healthcare facilities?**

A **Getz:** I think that's a great question and also a great implied observation. I agree with it. I think in the short term, as I was mentioning, the highest risk areas, risk of exposure to the COVID-19 virus for example, will help stimulate interest and focus in those less densely populated lower risk and more rural areas. A lot of the major health systems in urban areas have also been diverting their attention to their frontline medical response. And so I think, in the short term in particular, you'll see a number of

companies looking to engage the more rural physicians and more rural investigators to help ramp up clinical activity, trial activity as we start to see the restrictions relaxed. So I think that's clearly going to be there.

I think the remote and decentralized technologies also favor our ability to engage a more remote community provided that the data access and that infrastructure oriented around the data exists. And there are certainly many physician networks that have very good electronic health and medical records systems within more rural communities that could play a part there. Clearly the training and the infrastructure that we can provide to strengthen that rural environment will further help us expand their involvement in clinical trial activity in the future.

Q **Do you expect that we might see biopharma companies start to trim down their development pipelines or reduce the number of products that they are developing, as has happened before in periods of economic downturn?**

A **Getz:** If you look historically at the impact that global economic downturns have on R&D, pharmaceutical R&D, the impact is very, very short-lived. And then we typically see a very strong rebound, especially as you start to see access to capital improve for a lot of the smaller companies. The major pharma and mid-sized pharma and biotech companies recognize that R&D is integral to their success. So, we rarely see companies start to reduce their investment in R&D. You will see them, as we've talked about, halting the initiation of new trials for a period of time, but once we move past the crisis we can expect to see a really rapid rebound. For those sites that can sort of weather the short-term decline, I think they can expect to see a busy period as we move past the pandemic.

Q **Where in the development process do most drugs fall out of development and for what reasons? Is it mostly safety, mostly efficacy?**

A **Getz:** The highest risk area is the transition between phase two and phase three. And it's a very interesting question. What is the primary reason for terminating a program at that point? It's in part because you have continued to expand your collection of safety data, but you're also now beginning to collect more data on the efficacy profile of the drug.

We also see a lot of organizations beginning to get a better handle on the market opportunity for the product as well as even other insights into how well received the molecule may be once it enters the marketplace. As a result, companies really try to make a go/no-go decision between phase two and three before entering the more expensive later stage of clinical trials.

Q **You talked about how one of the primary reasons people decline to participate in research is the anticipated burden of participation--the additional visits to the hospital, the additional requirements that they will have to face. And then you talked a little bit in your forward-looking slides about a shift toward remote and virtual tools and clinical trials. Do you think those two things might tie together? Is the shift toward possibly doing more remote and virtual participation tools going to help us get more people who are willing to participate in research as we start to think about decreasing that burden of participation for them?**

A **Getz:** I do. I think it's all about options. We have patient communities that have such wide variation in their preferences, and there are subsets that really prefer more of the remote or home-based participation, others that may still be looking for more frequent interactions with investigative site personnel. Our ability to offer those options and improve the perceived convenience and the actual participation experience I think will strengthen our ability to attract and retain volunteers in our studies.

Also, I think moving beyond that pilot mode, to where we can really scale and support more remote and decentralized clinical trials, is really a critical way to move forward to offer options now. And I think in the future you'll see an even larger number of patients who prefer to participate under that type of model.

And one other point: It's interesting, we've done some studies recently showing that minority communities are particularly receptive, significantly more receptive to having remote and decentralized participation options.