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Agile Drug Development Required in a New Age of Urgency

Dealing with aggressive global pandemics

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Cognizant

It’s time to reconsider the current paradigm of drug development, clinical trials and regulatory approvals.

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Introduction

Encouraging faster and agile drug development paradigms in dealing with aggressive global pandemics

In light of the current circumstances of a global pandemic, it's time to reconsider the current paradigm of drug development, clinical trials and regulatory approvals.

The medical community, life sciences industry, health institutions, government, and regulatory bodies must act with a sense of urgency to examine any and all recommendations that bear a promise to delay or stop the spread of global pandemics.

Experts believe it's time to ask some probing questions:

1. Are prevailing industry norms, processes, and regulations — largely unchanged for decades — adept and agile enough to deal with accelerating global pandemics such as COVID-19?
2. What aspects of drug development and regulatory approval need to be nuanced or should be fundamentally revisited in the face of increasing pandemics to ensure critically needed therapies?
3. How can we leverage modern digital sciences and technologies to accelerate development of new therapies in epidemics and pandemics, while also enabling the earliest possible access of promising, potentially life-saving, new treatments to those afflicted?
4. Are there best practices of providing rapid access to novel treatments to patients in need during epidemics in other countries we can learn from?

Three industry leaders, representing life sciences and technology, attempt to answer these questions and explore thoughtful and perhaps even provocative approaches to drug development:

- **Srinivas (Srini) Shankar**
  Senior VP, Global Head of Life Sciences, Cognizant
- **Ulo Palm, M.D., Ph.D.**
  Senior VP of Digital Sciences, Allergan; Corporate Secretary, TransCelerate BioPharma, Inc.
- **Thomas A. Bock, M.D., MBA**
  Founder, HeritX; Chairman, Healthcare Advisory Board, Columbia Business School; former Senior VP, Global Head of Medical Affairs, Alexion Pharmaceuticals

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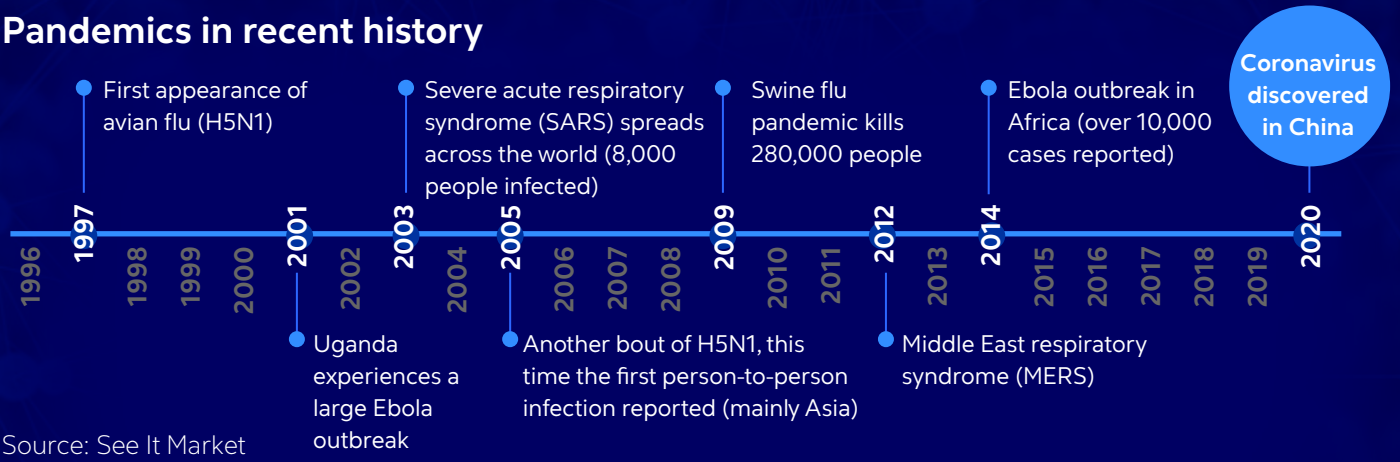
The urgency to act, challenge conventional norms and think outside the box

Per Worldometer reports, as of March 24, the number of reported cases of COVID-19 has surpassed 2 million reported cases and more than 145,000 deaths across almost 200 countries.

"There's an urgency to act and to challenge conventional norms," Mr. Shankar says. "For example, given the exponential magnitude of what's happening today, the number of deaths that are being reported, no approved antiviral or vaccine for the coronavirus, and the resulting economic chaos means we need to think outside the box."

The progression of the virus shows no sign of abating, and there is no approved antiviral treatment or vaccine yet. At the face of this global pandemic crisis, it is unethical not to explore unconventional wisdom and outside-the-box thinking. Let us examine the use of experimental — not approved yet — therapies.

Pandemics in recent history



Source: See It Market

Figure 1

"When I say outside the box, I'm talking about doing a risk-benefit analysis of experimental therapies that are not approved for a viral indication," Mr. Shankar explains. For example, Remdesivir, developed by Gilead for Ebola, was never submitted for approval because other Ebola treatments turned out to be more effective. However, large-scale GMP manufacturing for Remdesivir has been built up, and in 2018 there were 18,000 doses of Remdesivir available.

Dose-finding studies have been completed and the safety profile has been established. It has been shown in cell cultures and animal models that Remdesivir can block the replication of a variety of coronaviruses, including MERS and SARS.

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The urgency to act, challenge conventional norms and think outside the box

“Viruses don’t care about our regulations or the methodologies we apply. They relentlessly replicate. We have to take the appropriate actions to deal with this global menace.”

Mr. Shankar says in addition to reassessing the value of experimental therapies, the whole concept of resorting to randomized clinical trials (RCTs) in situations of a pandemic need to be re-evaluated. “Relying only on RCTs in situations such as this is not acceptable.”

The NIH and Gilead have started RCTs to study the safety and effectiveness of Remdesivir in COVID-19 patients.

Unfortunately RCT studies are slow because of difficulties recruiting patients. This is not surprising as RCTs, which were invented in the 1940s, are notoriously slow and are, in our view, inadequate for dealing with the current global health crisis. “Recruiting patients is always a challenge in traditional approaches,” Mr. Shankar says. “There are many ways in which we can accelerate the analysis of efficacy and safety of specific drugs that have demonstrative potential, whether an antiviral or a vaccine, by looking at real-world evidence data.”

Dr. Palm adds that there are additional ways — such as big data computation, cloud computing, and real-time data access — based on the technological opportunities that are now available that are a no-brainer, especially in a pandemic when time is of the essence to accelerate the process. “We have to think and act at the speed of viral replication,” Dr. Palm says. “The time is now. Viruses don’t care about our regulations or the methodologies we apply. They relentlessly replicate. We have to take the appropriate actions to deal with this global menace.”

When faced with global pandemics of the scale of COVID-19 that exact a human toll in the thousands — and rapidly counting each day — the medical community, life sciences industry, regulatory bodies, and governments cannot afford to resort to conventional approaches for treatment or prevention. They must develop mechanisms to rapidly deploy, at scale, experimental therapies that have demonstrated efficacy in a preclinical setting and are known to have an acceptable safety profile.

The urgency to act, challenge conventional norms and think outside the box

“If we always have the patient in focus and simultaneously ensure business continuation, we are moving in the right direction.”

“When testing new therapies in a massive and ultra-rapidly expanding pandemic situation, we have to particularly focus on what is best for patients, which includes fast patient access to prospective therapies,” Dr. Bock says. “To advance in the fastest way possible, this is where technology comes in. And for swift execution, we have to anticipate and quickly elevate critical decisions to the ultimate decision-makers so momentum never stops. Therefore, we need to redesign processes for emergencies as the crisis warrants at a speed that standard protocols often do not provide.”

Dr. Bock says the need to quickly reprioritize resources is another reason to elevate decisions quickly, which may require organizations to rethink their traditional ways of operating. “If we always have the patient in focus and simultaneously ensure business continuation, we are moving in the right direction,” he says.

Regulatory bodies have an important role to play here, such as providing regulatory guidelines for the widespread use of investigational compounds in large epidemics or a pandemic.

Drug discovery and development pipeline

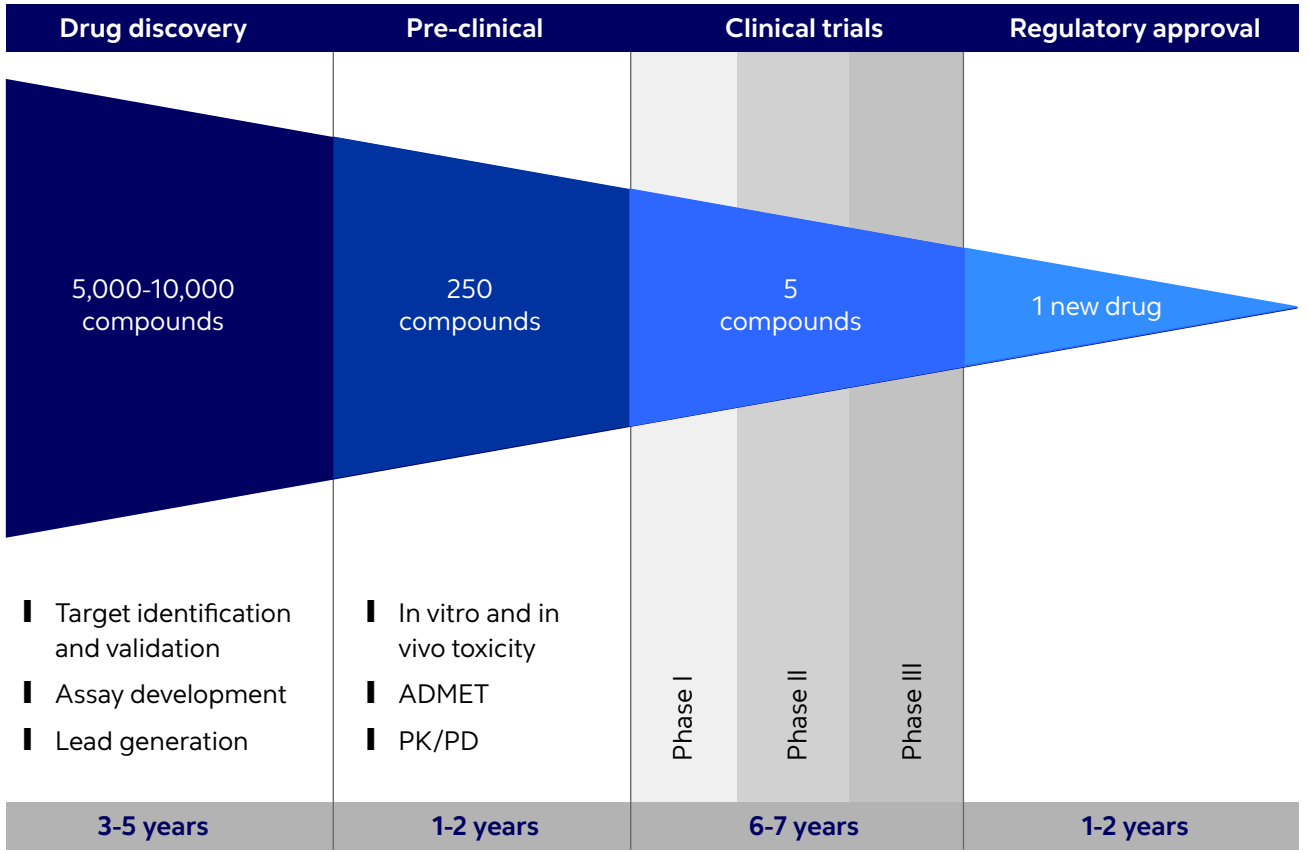

Figure 2

Source: PhRMA

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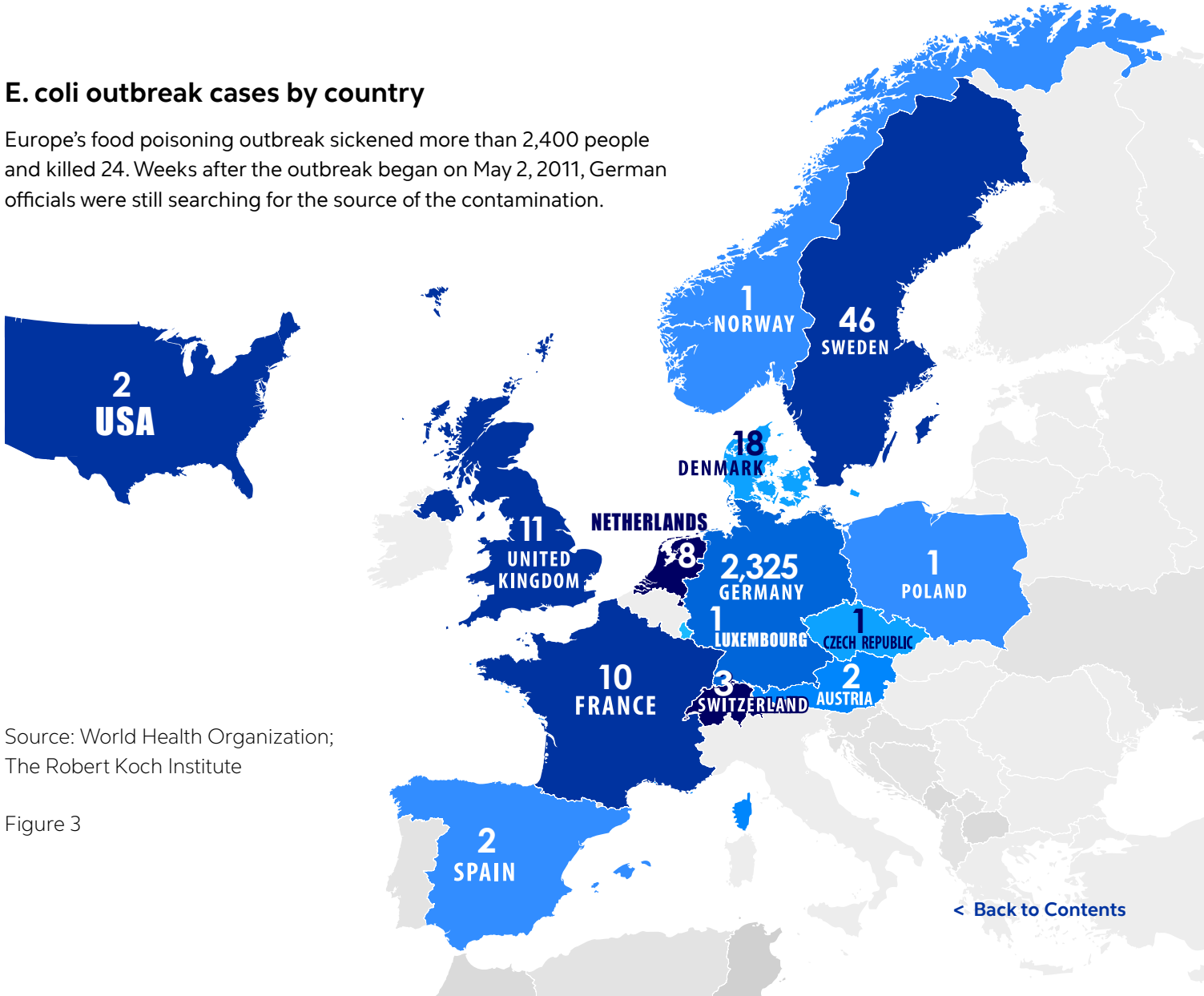
The urgency to act, challenge conventional norms and think outside the box

An example of the decisive use of investigational therapies to save lives was a rapid access program during an E. coli epidemic in 2011 in Germany. Thanks to the patient focus, courage, and collaboration between leaders of Alexion, the medical community, and government, Alexion was able to deploy an investigational therapy across the German hospital system on a large scale and within days, and to help address a life-threatening health crisis while real-world data was collected.

Dr. Bock explains the epidemic in Germany involved almost 3,000 thousand people infected by E. coli, an infection that typically affects clusters of 15 to 20 people at a time. However, with so many people infected and hundreds needing hospital care, emergency rooms were quickly overwhelmed and the healthcare system was challenged to manage patients with E. coli-induced life-threatening complications of the kidney, brain, and heart and the detrimental impact on ICU, dialysis, and overall care capacity. "This type of situation could become imminent in the current coronavirus environment," he says.

E. coli outbreak cases by country

Europe's food poisoning outbreak sickened more than 2,400 people and killed 24. Weeks after the outbreak began on May 2, 2011, German officials were still searching for the source of the contamination.



Source: World Health Organization; The Robert Koch Institute

Figure 3

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Complementing traditional RCTs with accelerated RWE studies and real-time clinical analysis

In urgent situations, large population-wide digital studies should be set up.

The time associated with executing RCTs requires rethinking the conventional drug development model when nations are faced with a quickly evolving health crisis. In these situations, it can be very effective to set up large population-wide digital studies that can analyze real-world evidence (RWE) data in real time while providing patients with the most promising treatment options available.

It is no secret that the process of executing a clinical trial hasn't materially changed in decades. It takes months to author and approve a protocol and additional time to set up studies, including preparing control and placebo arms. Do we really have time for all this in the face of a global pandemic? Is the use of a placebo arm even ethical in situations such as this?

Real-world data (RWD) and evidence (RWE)

Sources of real-world data: Electronic health records, insurance claims, patient registries, digital health applications.

Real-world evidence: Clinical evidence regarding the use and potential benefits or risks of a medical product derived from analysis of real-world data.

Real-world data: Data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of sources.

Source: FDA Voice blog by Dr. Scott Gottlieb

Figure 4

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Complementing traditional RCTs with accelerated RWE studies and real-time clinical analysis

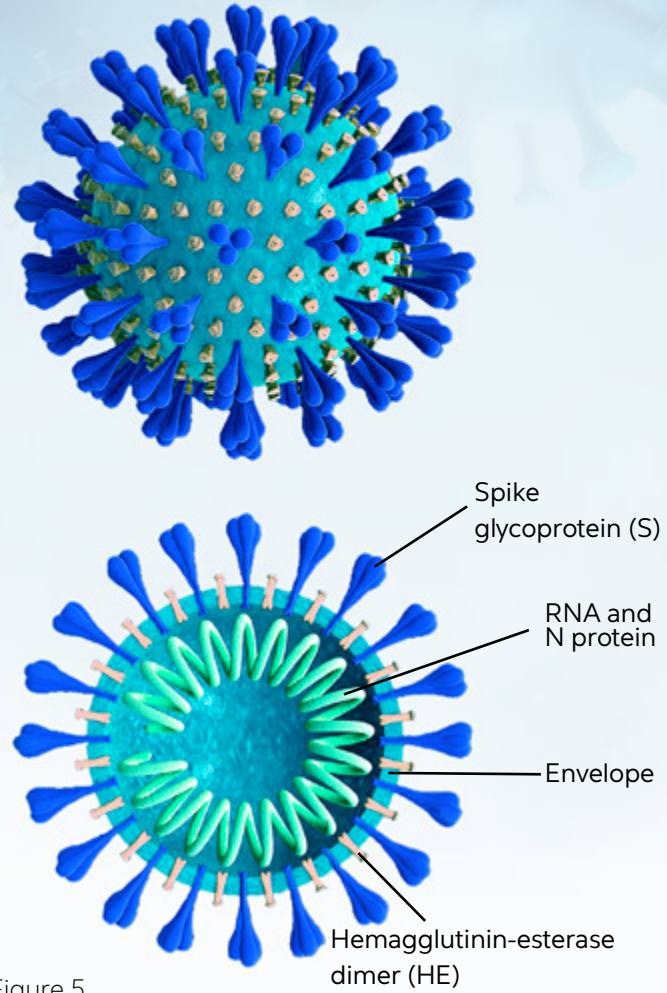


Figure 5

"Our rules for drug development have evolved for treatments such as psoriasis, hyperlipidemia — in essence all slowly evolving diseases," Dr. Palm says. "We need to have a regulatory framework that is specific for pandemic situations because of the globalization of the world. We all know it. Viruses now travel quickly across the world. In order to protect us — humanity – from the next pandemic and the next pandemic and the next pandemic, we need to have a new regulatory framework that allows us to develop, study, and apply new promising compounds in a matter of weeks rather than in months or years."

The three experts believe the United States has a leadership role to play. "If we get it going in the U.S., the rest of the world will follow," Dr. Palm says. "We need to be better prepared from a regulatory perspective and from a government perspective with how to deal and contain — and not just contain — but stop a virus from spreading to become a pandemic with the modern medical tools available."

To counter the speed of viral replication that is happening at a relentless speed, accelerated studies should happen under the umbrella of a simplified pragmatic RWE study. Data should be collected and continuously monitored and analyzed, almost in real time, through existing EHR/EMR networks, with statistical approaches different from RCTs. Digital technology and sciences have evolved to the point where, in a global health crisis like this, they allow us to react quickly on a large scale, balancing the vital needs of individual patients with the need to collect scientific data about efficacy and safety.

Dr. Bock, as well as Mr. Shankar and Dr. Palm, believe it's important to rethink how to repurpose drugs that are already approved and that have an established safety profile. They say if there is a biological rationale of efficacy, no predicted safety concern, as well as data in support of an approved drug's application in terms of RWE based on technologies that weren't available years ago, we could advance treatments quickly and test and monitor a situation in real time.

“In a situation, such as coronavirus, where the virus is so infectious, having remote access to data and patient reported outcomes is exceptionally beneficial.”

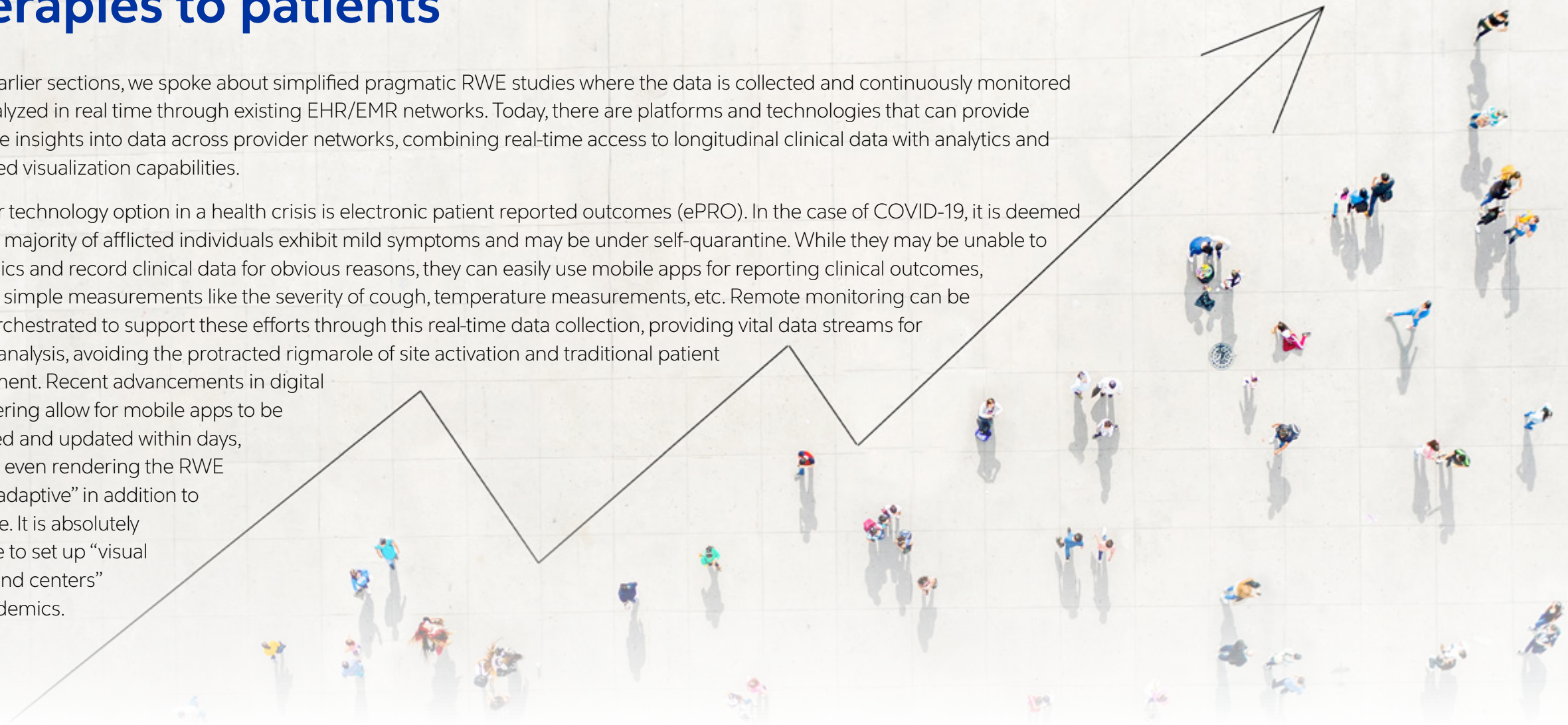
“Simply stated, time is running out,” Dr. Bock says. “It’s is a matter of a risk-benefit trade off, which is different in emergencies and pandemics due to the extreme downside of not acting, and therefore, any and all options must be considered. It is simply unethical not to do so. In a situation, such as coronavirus, where the virus is so infectious, having remote access to data and patient reported outcomes is exceptionally beneficial. We want to avoid sending people into infectious areas.”

This leads us to the next part — the availability of modern digital sciences and technologies to accelerate development of new therapies in epidemics and pandemics. Technology has evolved, but have drug development paradigms kept pace?

Leveraging disruptive technologies for accelerating therapies to patients

In the earlier sections, we spoke about simplified pragmatic RWE studies where the data is collected and continuously monitored and analyzed in real time through existing EHR/EMR networks. Today, there are platforms and technologies that can provide real-time insights into data across provider networks, combining real-time access to longitudinal clinical data with analytics and advanced visualization capabilities.

Another technology option in a health crisis is electronic patient reported outcomes (ePRO). In the case of COVID-19, it is deemed that the majority of afflicted individuals exhibit mild symptoms and may be under self-quarantine. While they may be unable to visit clinics and record clinical data for obvious reasons, they can easily use mobile apps for reporting clinical outcomes, such as simple measurements like the severity of cough, temperature measurements, etc. Remote monitoring can be easily orchestrated to support these efforts through this real-time data collection, providing vital data streams for clinical analysis, avoiding the protracted rigmarole of site activation and traditional patient recruitment. Recent advancements in digital engineering allow for mobile apps to be deployed and updated within days, thereby even rendering the RWE study "adaptive" in addition to real time. It is absolutely possible to set up "visual command centers" for pandemics.



Leveraging disruptive technologies for accelerating therapies to patients

For example, at the CDC, data streams from EMR systems and eCOA apps could come together from across the nation to provide a daily/weekly snapshot of how the infected patient population is reacting to Remdesivir or any other treatment. The whole system could be set up as an integrated research platform using umbrella designs where new treatments are seamlessly added while ineffective ones are removed, determining safety and efficacy in real time and moving closer to successful treatments.

"We have the technology and the capability today to set up a call center in 24 hours," Mr. Shankar says. "Nurses can be employed remotely — in a multilingual context — to call physicians and register patients. In the event that we have patients in self-quarantine who are not able to visit a physician, the challenge is getting data into an EMR/EHR type of a system, but there are technologies that can derive patient-reported outcomes."

Mr. Shankar adds there are apps that can be built very quickly to collect basic patient clinical metrics, such as coughing, registering a fever, etc. "We're not talking about 300 clinical metrics around a complicated protocol that require a lot of diagnosis," he says. "Technologies such as eSource, ePRO, etc., all exist today and can measure basic metrics."

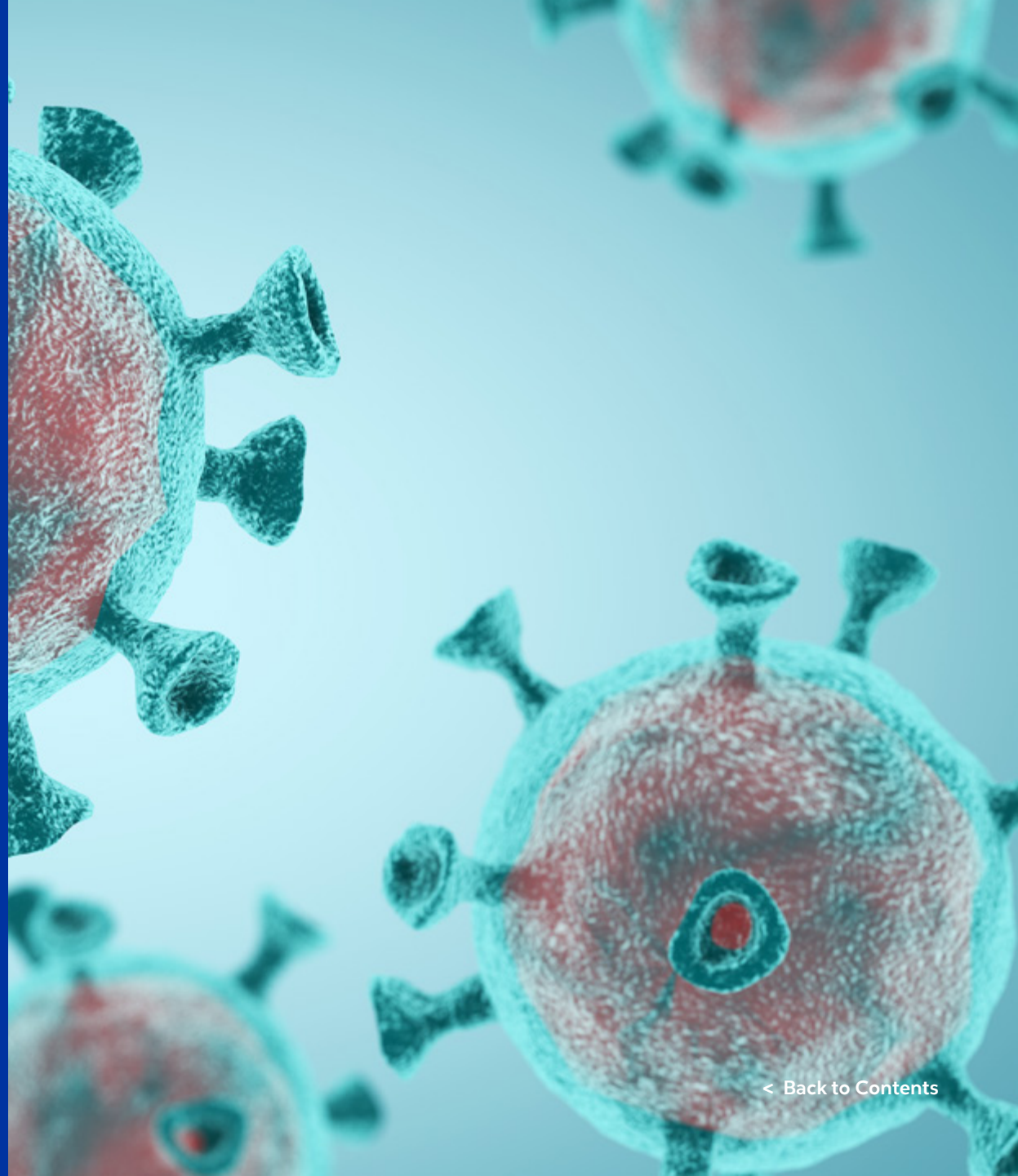
Conclusion

As an industry, we are nowhere near exhausting the art of the possible.

In conclusion, as an industry, we are nowhere near exhausting the art of the possible and the boundaries of human imagination in dealing with a crisis of the magnitude and velocity that is COVID-19. Answers are within our reach, and those who are in positions of responsibility, be it industry or regulatory leaders, have an obligation to humanity to act now to explore any and all avenues.

"We don't have directives or guidelines to deal with drug development during global pandemics, such as what we are experiencing with COVID-19," Mr. Shankar says. "The industry, including regulatory bodies, companies and others, haven't caught up with disruptive technologies that are amply available in a consumer context."

To learn more, visit Cognizant's YouTube channel by **clicking here**.



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