Disruptive Changes for a Better Clinical Research Future

The SARS-CoV-2 pandemic highlighted that the industry could change in response to outside pressure. However, change can be volitional instead of reactionary, which could better the industry before the next crisis

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The biopharmaceutical industry, and particularly clinical research, is certainly one of the most regulated industries on the planet. Due to the high level of scrutiny it receives, the industry is slow to adapt to a changing world. However, even within these strictures, opportunities abound for beneficial disruptive changes.

COVID-19: Crisis and Opportunities for Clinical Research Reform

The COVID-19 crisis has pressured every biomedical system since 2020. During the height of the pandemic in 2020, private companies and regulators attempted to adapt to an ongoing crisis, which they were poorly prepared for by the current state of the industry. In fact, a multi-institution panel of leading physicians and scientists recommended a broad range of changes to infectious disease clinical research (1). While the industry is slow to change, at least some of these recommendations were adopted to facilitate the unprecedented speed of approvals for SARS-CoV-2 vaccines (2).

Though these feats were impressive, the industry must move beyond a reactionary stance. By proactively changing clinical research, the industry can improve as a whole for more than just infectious disease outbreaks or other emergent crises. In fact, an improved clinical trial ecosystem would benefit more stakeholders, while still creating a better environment to respond to new public health emergencies.

The most important changes to the biopharma industry in 2020 were those that were greatly disruptive – such as the liberal use of the FDA's Emergency Use Authorization to facilitate distribution of vaccines as quickly as possible. Similarly, clinical research can adopt such major changes to create a significantly better industry.

Disruption Has a History of Positive Results

Disruptive change has a long history of increasing humanity's welfare in the aggregate. The advent of agriculture created the prototype schema for the development of cities and the downstream technical advances. Computers created the modern economy, specifically providing the processing power for a logistics company to revolutionise retail. Notably, each has had negative consequences, such as the unpredicted negative impact of social media in computing, but overall, these major innovations have moved toward increasing human life span and productivity.

In biomedicine, germ theory revolutionised disease care, which has raised average longevity globally (3). Importantly, viruses and bacteria caused disease before these observations, meaning a forward-thinking physician could have made the same revelations centuries earlier.

A more recent example of disruptive thought with clinical relevance was the advent of the HIV/AIDS crisis. A dogmatic approach to disease, assuming that RNA could not be reverse transcribed into DNA, prevented a quick understanding of the virus (4). Recognising the capabilities of HIV disrupted clinical care, virological research, and social understandings of disease. Now the use of reverse transcriptase is commonplace throughout biological studies, even though a disruption of conventional thought was necessary to find and characterise it.

To the credit of the entire biomedical industry, stakeholders saw the potential of genetic information. Both private and public entities took a proactive step toward what was once considered an insurmountable goal – sequencing the

human genome. From the success of the Human Genome Project, what was once considered impossible is now commonplace (5). A researcher can find the consensus sequence for any human gene instantaneously in a massive, centralised database. In addition, other organisms have been sequenced, allowing for unprecedented evolutionary screenings.

Clinical research can choose to launch its own proactive changes. They will by nature be disruptive, which causes resistance. However, the history of disruptive change is positive – a better system will outcompete a less capable one, which is intuitive to a field familiar with evolutionary competition.

Seven Challenges in the Current Model of Clinical Research

When looking for areas for disruption, venture capitalists look for major 'pain points' or flaws in the system that new businesses seek to address. By looking at the major challenges in clinical research, stakeholders can similarly find opportunities for innovation:

1. Growing regulatory burdens are the bane of the clinical research industry. Despite evidence that cautious regulatory agencies are contributing to a decrease in efficient drug development, regulatory burdens continue to increase (6). Now, regulatory bodies, like the FDA, have created more onerous requirements on clinical trial sites, such as different licences and multiple versions of similar trainings (7).

Suggested Disruptive Change
Unsurprisingly, reducing the regulatory burden on clinical trial sites would greatly change the state of the industry. The FDA or other centralised organisations should assume exclusive responsibility for collecting licences and conducting annual mandatory trainings. In addition, this agency could audit these research sites to eliminate per-study requirements and reduce the number of site qualification visits. Collectively, such a scheme would significantly reduce redundant regulatory burdens and facilitate faster conventional trials.

The primary disadvantage of the system would be its inability to adapt quickly. A central agency may not be adaptive enough to deal with the unique attributes of a truly novel therapeutic approach.

2. Information access and distribution is slow. Clinicaltrials.gov is the de facto resource for clinical trial information (8). The interface is difficult to navigate and unfriendly to new users. Many do not understand the capabilities of the site. In addition, the site often fails to meet expectations of cross-compatibility with common electronic tools and reporting systems.

Suggested Disruptive Change
Clinicaltrials.gov is the centralised resource for clinical trial information. Despite this position, it is a haphazard resource that maintains its primacy because there is no real alternative. Its centrality makes it a place where even a small change could have an outsized impact on the industry. For example, a few changes in its graphical user interface to create a more intuitive user experience would increase both accessibility and usability of the site, without needing to collect new information or massively modify functionality. On the other hand, updating the functionality of the website to be cross-compatible with other common tools would be revolutionary. We should accept the centrality of clinicaltrials.gov and provide both private and public technical support to update this collective resource for the benefit of the entire industry.

As with all online applications, this approach is vulnerable to cyberattack and loss of function without recourse, as the site is functioning as a third-party resource. Accepting a central system means accepting the risk of a central cybertarget, which would require proper cybersecurity to be practiced by all stakeholders or risk infecting the others in the network.

3. Many major insurance companies insist on a unique cost analysis at a single site for the same clinical protocol. Investigators push through this bureaucratic milieu of documents, at the cost of time.

Suggested Disruptive Change
Sites are wasting their most valuable commodity – time – on multiple insurance cost analyses for a single site. Streamlining each separate analysis into one single insurance cost analysis for the largest providers would achieve the same end in a fraction of the time.

The primary disadvantage would likely be a longer initial analysis that could work for all. While this may increase the intensity of a single report, it should still ultimately save time.

4. Every trial requires redundant paperwork from various stakeholders. While documents may vary in formatting and specifics, the vast majority attempt to capture the same information but are different enough to create a major administrative hurdle to efficient trial execution.

Suggested Disruptive Change
Too much investigator time is also wasted on nearly identical site questionnaires. A centralised approach that expands site data will reduce the amount of time dedicated to an endless stream of site questionnaires for every study. This is more difficult for international trials, however, the purpose of generally reducing redundant paperwork remains.

This has the same disadvantage of likely lengthening the questionnaire. In addition, physical sites will have specific differences that need to be taken into account, otherwise this method will revert to the current status quo of individual site questionnaires.

5. Adverse events, and particularly serious adverse events, are a major source of tension within the current system (9). Pharmaceutical companies, clinical staff, and patients all want to avoid the development of adverse events. However, the current *modus operandi* is to avoid any proactive mentions of adverse events before they happen. While the goal may be to guarantee that each adverse event receives appropriate attention

during a clinical trial, a single event can stop a trial, regardless of its actual relation to the treatment. The guidelines for how to respond to an adverse event can be unclear, creating confusion as to the correct actions to take. Currently, investigators make a judgement call, which may or may not result in the ideal outcomes.

Suggested Disruptive Change

Adverse events are going to happen. Both the industry and regulators need to accept this reality and collaborate on a better response to them. If stakeholders can collectively produce better guidelines on adverse events and serious adverse events, we can reduce the current overwhelming burden of over-reporting all adverse events. The danger that must be avoided is under-reporting of adverse events, which replace one problem with a worse outcome.

6. Similarly, risk is not well predicted to determine the appropriate monitoring for each study (10). This risk-based monitoring (RBM) strategy is used, but currently struggles in the specifics of implementation (11). Site staff and stakeholders are not receiving the training they need to properly perform RBM strategies. Correspondingly, RBM has failed to deliver on its promise of safer and more cost-efficient clinical trials.

Suggested Disruptive Change

The RBM model is the change, it just needs to be implemented more effectively. The industry has the data and expertise to predict the relative risk of different therapeutics in clinical trials. It could centralise monitoring based on expected risks, which reduce burden on every stakeholder within the clinical trial ecosystem. Most importantly, by training site staff on how to implement whatever the current standard is in the ever-evolving world of RBM, we can progress to its promise.

We are already experiencing the disadvantages of RBM, which is rapidly changing with use, requiring new trainings and implementation. Only by directly addressing these problems will RBM work.

7. Clinical research is becoming a mature industry with a strong status quo bias (12). Opportunities to introduce disruptive change into the process of clinical research are often avoided because investigators are understandably risk averse, searching for incremental advancements. However, a system that fails to adapt effectively to the future will ultimately fall back or even collapse.

Suggested Disruptive Change

A new idea not mentioned here could change everything, if given the chance to thrive. Promoting the experimentation of truly disruptive ideas will ultimately benefit the entire industry. Individuals, companies, and investigators need support from the industry to feel comfortable taking the risk to try new processes and approaches that may fail. The clinical trial industry contains some of the most intelligent professionals in the world. If investigators are encouraged to pursue novel development they could eliminate inefficiencies and create a better future, faster, for patients in need of new therapeutics.

These changes differ in feasibility, in the expertise required to execute, and in the time needed to implement. However, they all have one thing in common – each would be a major beneficial disruption in the current status quo of clinical research. If the goal of clinical trials is to find the best treatments for patients, then improving the clinical study industry is a place ripe for positive disruption.

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