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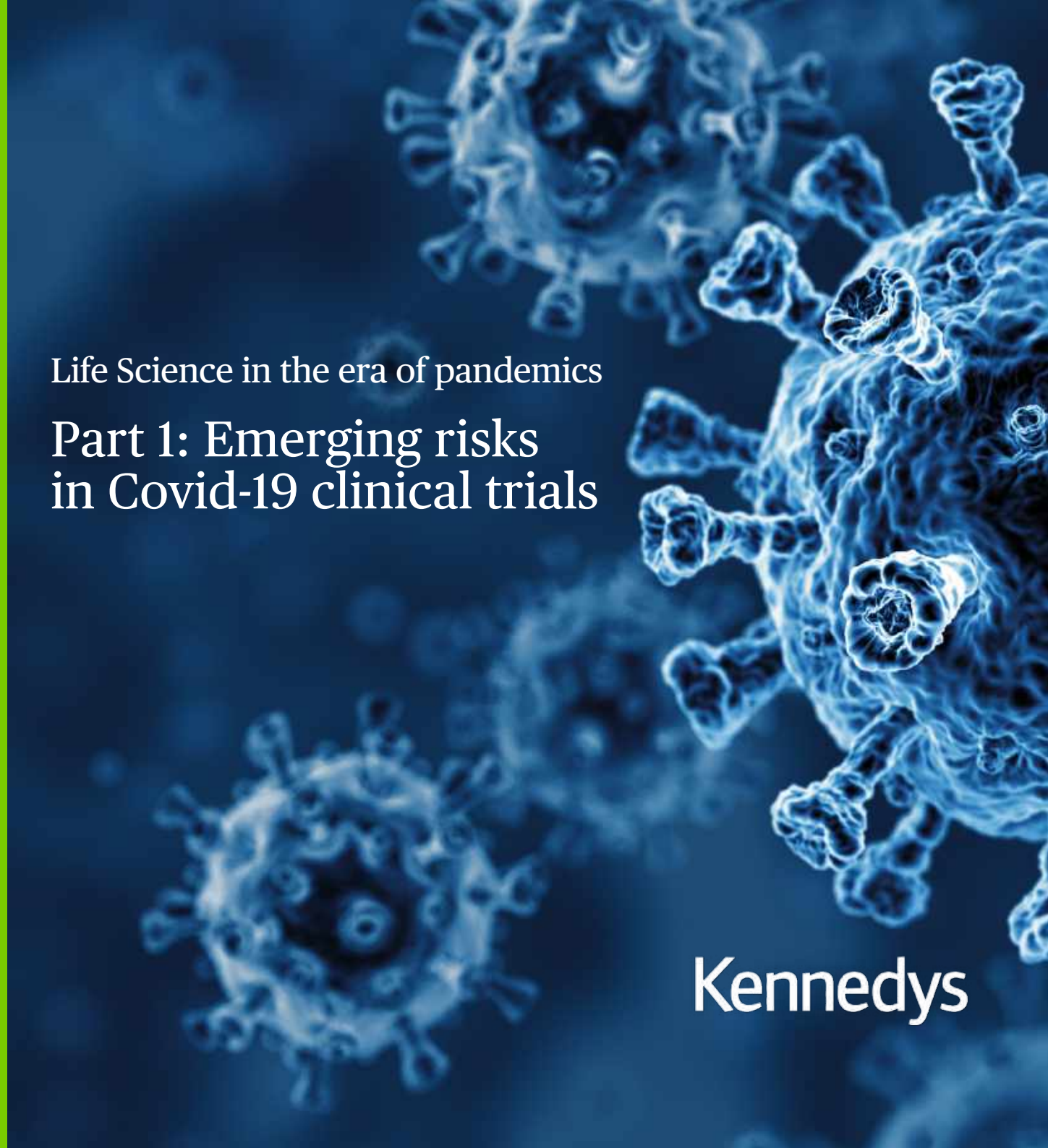
Life Science in the era of pandemics

# Part 1: Emerging risks in Covid-19 clinical trials



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# Emerging risks in Covid-19 clinical trials


**Contributors**

**Alex Forrest**
Head of Life Sciences - Overseas Group, Chubb

**Renate Pochert**
Senior Risk Engineer, Chubb

**Karishma Paroha**
Senior Associate, Kennedys Law


## Best practice is slipping in clinical trials as the scientific community races to respond to Covid-19. Chubb considers the risks that are emerging as a result and how they can be mitigated

After the Chinese authorities shared the Covid-19 genome with the international community in January 2020, it took just six weeks for the first candidate vaccine to be shipped for human clinical trials. By 31 July, there were 26 candidate vaccines in clinical evaluation and 139 at the preclinical stage, according to the World Health Organization (WHO). The pace at which these candidates were prepared shows how far both our understanding of the disease has come and the speed with which science can move.

Alongside this preventative approach, hope can be found in the many potential treatments that are being studied. As of 5 August, 2,906 trials were under way around the world, attempting to halt the progress of Covid-19 at different points along the biochemical pathway it takes into the human body - targeting the virus before it enters cells, preventing it from replicating within cells or reducing its impact on organs, for example. Diverse therapeutic approaches are being trialled, from antivirals to steroids and blood plasma transfers.

However, as the scientific and medical communities throw everything they have at Covid-19, and regulators create greater flexibility around clinical trials, trade-offs are being made between best practice and pragmatism, creating an evolving risk environment.

### Scattergun approach

Many potential treatments are not totally novel compounds, which must go through a slow, methodical process of research that can take up to ten years to complete. Most are existing products or novel therapeutics that were already being explored for use against other pathogens or diseases.

“We are seeing a bit of everything being thrown at the problem, from diabetes drugs to anti-fungals,” says Alex Forrest, Head of Life Sciences - Overseas Group, Chubb, explaining that there is less scrutiny around the selection of Covid-19 clinical trial targets than normal. “Ordinarily you might go through a more measured thought process analysing what is your lead target - what is most likely to make a difference - so that when you get to the clinical trials you are then only looking at a couple of options. Whereas what we’ve seen at Chubb is up to 200 trials with something in the order of 40 different molecules being looked at, which is really unparalleled.”

# 2,906 trials

targeting Covid-19 were happening around the world by early August

Many involving products that had already been developed to treat other conditions

## From trials to treatment

There is also a danger that in a pandemic the boundaries between the normal clinical setting and the research setting can merge and overlap. This rarely happens in normal clinical trial practice, where there are clear delineations between trials, compassionate use and licensed clinical practice.

“Clinical trials need to stick to their primary purpose, which is research and discovery, validating a hypothesis. It would be unwise to start giving drugs to research subjects that could otherwise be excluded, and there is a concern the scope of trials is being broadened far past what is needed for that research,” says Forrest.

## Changing endpoints

Another pattern emerging from clinical trials during the pandemic is changing endpoints - the factors measured as the primary criteria for success. The study into antiviral medication remdesivir, for example, set out to show reduced mortality but actually found that people taking the drug spent less time on ventilators.

“Changes and revisions to primary endpoints should be uncommon,” says Forrest. “They can lead to misguided research or sub-optimal patient care by introducing bias into the research.” Sometimes there can be legitimate reasons to change but any late endpoint change introduces the potential for manipulation to make a drug successful when there could be a better therapeutic option undiscovered.

## The wrong kind of lens

Compounding this fractured research process is the intense public gaze as people wait for news from the scientific community that a viable vaccine or cure is being developed.

It is not uncommon for research to be released ‘pre-print’ - before it has been interrogated and validated by peers - but previously only specialists were reading these articles. Now, with everyone from journalists to amateurs scouring scientific journals for signs of hope, research is being circulated publicly before it has been through the peer review process, giving the work more credence than it is due.

One example of the real-world impact this can have is the WHO’s hydroxychloroquine trial, which was suspended as a result of a pre-print article in a leading medical journal that has since been retracted after the data was found to be unreliable.

“The scientific community is trying to release helpful information quickly but also knows the integrity has to be there in terms of research. It can be quite damaging if people suddenly see all of these retractions and it could risk undermining the integrity of the scientific community through distrust,” says Forrest.

# Vioxx

was on the market for five years before it became clear the anti-inflammatory drug increased cardiovascular and stroke risk

One risk of fast-tracking Covid-19 clinical trials is that adverse reactions to drugs could emerge later down the line

# 12 years

Time taken on average for a drug to go from concept to approval for use in patients

## Risks and mitigation

In the current frenzy of research activity, product owners whose pre-existing drugs could be trialled against Covid-19 outside of their ownership need to be mindful of the role they play. “Companies have to be careful when marketing to either doctors or the public that they can give their drug a go. They should also actively stay connected to the market and what is going on with their products and make sure that nothing untoward is happening,” says Forrest.

Some producers are being proactive here. “We are seeing a lot of information on Covid-19 from producers who are reaching out to the Food and Drug Administration in the US, issuing alerts to inform users not to use their products off-label or not as intended,” adds Renate Pochert, Senior Risk Engineer, Chubb. “They are trying to protect themselves.”

There are also direct risks to fast-tracking trials. “If we are fast-tracking drugs and vaccines there is the potential for more unknown adverse reactions to these drugs when they are on the market, which may manifest five or ten years down the line,” says Karishma Paroha, Senior Solicitor and Barrister at Kennedys Law.

The biggest example of this in recent years is the anti-inflammatory drug Vioxx, which was on the market for five years before being pulled in 2004 when it became clear that it increased cardiovascular and stroke risk. The drug has been linked to thousands of deaths and resulted in a litigation event of almost $5 billion.

Despite some regulatory flexibility, organisations should not expect any leniency should Covid-19 trials or products compromise patient safety. “Covid-19 has not suspended product liability laws,” explains Paroha. “In the EU, the fact that a product complied with applicable regulation does not provide producers with a defence against liability. Thus even if new Covid drugs comply with the rules, including those that may have flexed during the pandemic, this will not necessarily protect a producer from claims in the future.”

Given the magnitude of risk, whereby vaccines will be rolled out on a huge scale before long-term side-effects can really be understood, some drug companies are asking governments directly to indemnify them against product liability claims.

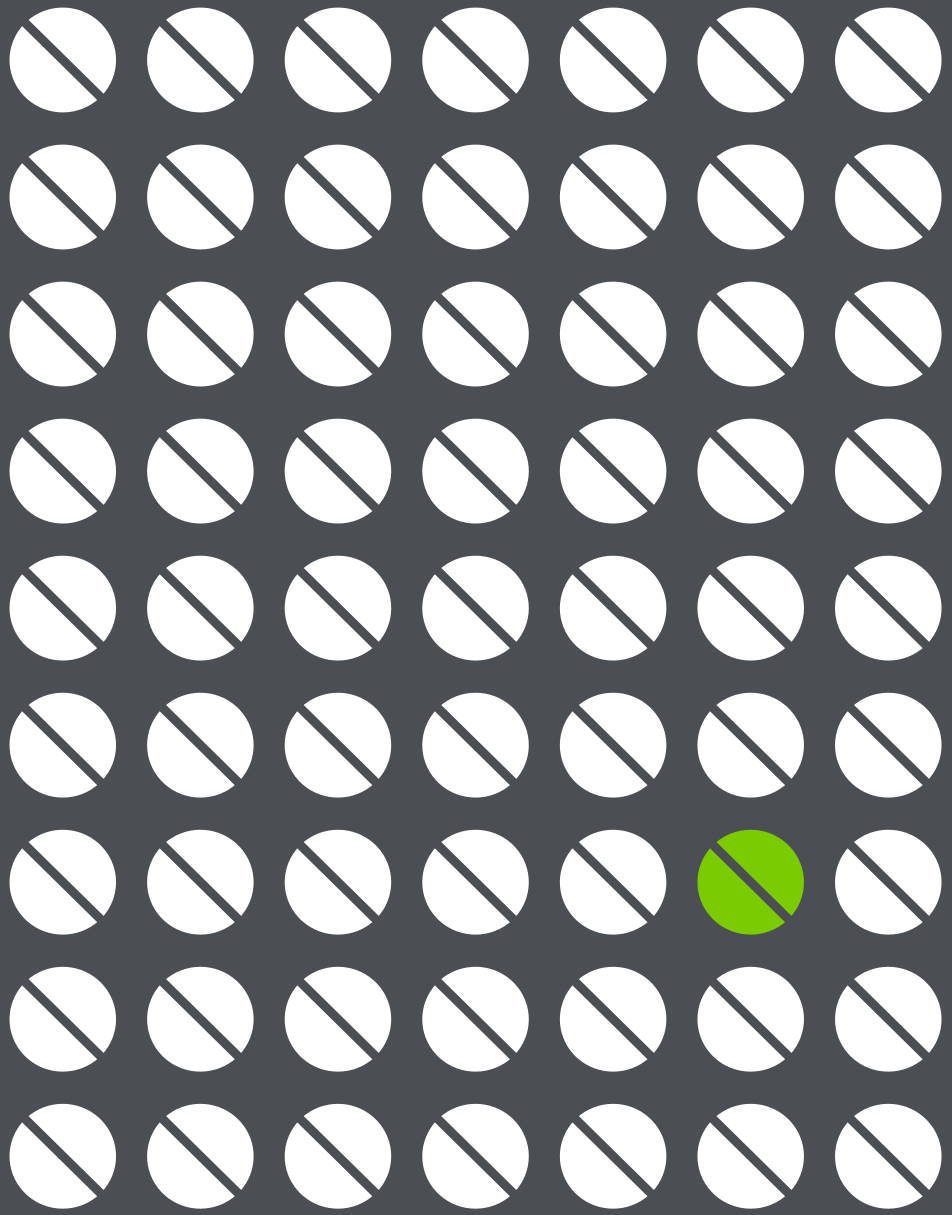
Within the vaccine space another concern is how different patients react. “The reaction in people to these vaccines can differ because we have so many environmental influences these days that can affect genes or the immune system,” says Pochert.

This is a challenge for the many Covid-19 trials, as is the important issue of ensuring all ethnicities are represented in research, particularly given the disproportionate impact of the virus on ethnic minorities.

# Over 60 chloroquine

trials have been processed by Chubb alone

Greater coordination could have prevented duplication of resources when studying the effects of the anti-malarial drug on Covid-19 patients



## Key takeaways

- **It would be unwise for researchers** to give drugs to research subjects who could otherwise be excluded
- **Changes and revisions to primary** endpoints should be uncommon
- **Product manufacturers** should stay alert to how their products are being used
- **Regulations may have been** relaxed but product liability law remains the same
- **Lessons are being learnt about** how to structure trials more efficiently and global coordination

## To discover more contact

Alex Forrest
Head of Life Sciences - Overseas Group
aforrest@chubb.com

Thomas Sproho
Life Science Industry Practice Manager
Thomas.Sproho@Chubb.com

Karishma Paroha
Senior Associate, Kennedys Law
Karishma.Paroha@kennedyslaw.com

## Lessons learned?

With so many evolving risks in this era of fast-tracked research, it is important to consider what lessons can be learned from the pandemic. Hundreds of potential vaccines are being developed, and the global response has been uncoordinated. Lessons from the pooling of data in trials (meta-analysis) in such a rapid and uncoordinated global response will undoubtedly come. They could also be applied to vaccine development more broadly in the future. “There is a balance to strike between getting maximum speed whilst wasting resources, and optimising resources but going more slowly,” comments Forrest.

However, a controlling hand would certainly reduce any duplication of efforts and centralised data collection would have many advantages. “We alone have seen over 60 chloroquine trials and they’re all studying slightly different parts of Covid-19 progression, creating inefficiencies and unnecessary duplication,” says Forrest.

As well as better global coordination there may be learnings about how to structure trials more efficiently in general, making the scientific and medical community more agile and better prepared for the next pandemic.

## Conclusion

The urgency of the Covid-19 health crisis has led to a frenzy of clinical trial activity. But with all eyes on the goal of beating Covid-19 fast, best practice has been slipping in clinical trials. There are risk implications for the researchers running trials, but also for product owners whose drugs are being tested against the disease. While the regulatory environment is allowing for fast-tracked trials and greater leniency, that will not extend to compromised patient safety.

The context may be a very immediate health crisis, but the trade-offs being made are creating long-term risks that someone will be liable for and which must be managed accordingly.

**The next report in this series will explore medical device risk in the context of Covid-19.**

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