CRISPR and the DNA of modern healthcare

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Progress in the field of genetic engineering in the last 60 years – from the discovery of the double helix to gene editing technology CRISPR – has been extraordinary.

When it was unveiled in 2012, CRISPR technology was hailed as a game-changer for the life sciences sector, offering hope of finding safe and effective treatments for many genetic diseases. It may also hold the key to a vaccine for COVID-19.

While there is much we do not yet now about this cutting-edge technology, developing safe and effective cures using CRISPR will only come through of extensive research and clinical trials – and each stage of the process comes with risk. For sponsors and chief risk officers (CROs), ensuring the proper design of protocols, and partnering with insurers that understand the risks, are key to providing safe and high-quality trials.

With much interest in this cutting-edge area of life sciences, we consider some of the fundamentals of CRISPR, the risks and opportunities to look out for.

What is CRISPR?

- In simple terms, CRISPR - or Clustered Regularly-Interspaced Short Palindromic Repeats, referring to how it interacts with DNA[i] - allows scientists to alter genetic material within individual genomes to correct genetic defects or to treat and prevent disease.
- CRISPR is shorthand for CRISPR-Cas9, which refers to specialized stretches of DNA containing the protein Cas9 found in the immune systems of bacteria and other single cell organisms.
- Cas9 acts like a pair of molecular scissors. By itself, Cas 9 acts indiscriminately, cutting up DNA within cells. But with a guide RNA attached to it, this complex process can be used in a precise and targeted fashion. It can be programed by scientists to find a particular DNA sequence and make a break in the sequence. Once the break has been made a scientist can delete, alter or replace the gene sequence ultimately making the gene behave differently.
- Compared to earlier methods of genome editing, CRISPR is hailed as having potential to make the process “faster, cheaper, more accurate, and more efficient”.[ii]

Current developments

- While it is relatively early days in the development of CRISPR, research is already moving at pace. Trials aimed at curing a hereditary blindness have begun this year and will be the first time CRISPR has been put to work directly into the human body.[iii]
- While earlier trials have involved the removal of genetic material from the body before editing, this trial involves the direct application of CRISPR to the patient’s retina.
- There have been CRISPR trials that have shown signs of promise and results from these first human trials have trickled in over the past few months. In one such trial, three people with inherited blood disorders were successfully treated after their bone marrow stem cells were gene edited with CRISPR.[iv]
- In tackling the COVID-19 pandemic, a biotech firm has been successful in repurposing CRISPR technology to detect the virus in human cells. The diagnostic kit is the first CRISPR product to receive FDA approval[v] while a team at Stanford University has developed a treatment that inhibits COVID-19 in lung cells that will move to animal trials shortly.[vi]
- Earlier this month, scientists Emmanuelle Charpentier and Jennifer Doudna were awarded the Nobel Prize in Chemistry for their work on CRISPR.[vii]

- These leaps forward for CRISPR, just a little over a year since the first human trials began, present new risks for CROs and sponsors to consider.

Trials risk landscape

There is still a lot we do not know about the safety of this technology and unresolved ethical questions, particularly around the editing of embryos and passing changes into the germline.

A major risk area is the unpredictable ways in which CRISPR can behave. The potential for off-target mutations to occur in clinical applications of CRISPR has been known for some time.[viii] These occur where unintended changes are made to genomes away from the intended target site, and can, to some extent, be modelled and predicted.[ix]

Having a clear understanding of where off-target mutations may occur makes them more easily detected and eliminated.

Notably, however, a recent trial using embryos revealed significant unwanted changes can also occur at or near the target site. These changes may be more substantial than previously thought and may be missed by standard assessment methods.[x]

This underscores the need for caution and for greater work to map-out how individual genomes react to CRISPR, particularly how they heal post cut and what it means for the function of otherwise healthy genes. Those involved in trials need to develop a way of detecting unwanted mutations early in the trial process and address the risk in their protocols.

As long as on and off target mutations remain a possibility it is important that trials are designed in a manner that prevents any unwanted changes being passed down the germline.

Progress in developing safe and effective cures using CRISPR requires extensive research, robust protocols, many phases of clinical trials and a clear understanding of the risks involved at each stage of the process.

As the amount of research projects and trials grows, the sector needs to approach any trial in a controlled fashion and understand the potential for errors and omissions or bodily injury in order to manage their risk exposures.

Managing the risks

Risk managers conducting research into this area need properly designed trial protocols, regulatory approval and informed consent of those participating. Ensuring rigorous standards are upheld can help reduce the potential for human error that can result in errors and omissions claims against those running the trial.

There is limited, if any, data on which risk managers can make informed decisions on risk, making having specialist insurance in place through experienced brokers and underwriters all the more important. Moreover, as the technology is evolving at pace understanding of the risks and how to mitigate them also needs to evolve at pace.

Failing to stay up to date with the rapid changes of this technology presents not only a risk to the success of the trial but potentially to those taking part.

Errors or omissions by the CRO in the running of the trial resulting in lengthy delays could bring about suits from sponsor corporations where it causes them a financial loss.

Similarly claims could arise from bodily injury to one of the trial subjects arising from a failure to monitor of the trial.

Even the best designed trial carries risk. Organizations that understand the risks and factor those risks

into the design of the trials are more likely to succeed. In a rapidly developing sector working with insurance partners that have the experience to understand the complexity of the sector will help the continuous growth of this complex and fast-moving sector.

For more information please visit the Beazley website at www.beazley.com

[ii] https://scitechdaily.com/crisprs-potential-and-dangers-is-crispr-worth-the-risk/
[ii] https://ghr.nlm.nih.gov/primer/genomicresearch/genomeediting
[iii] https://www.newscientist.com/article/2246020-three-people-with-inherited-diseases-successfully-treated-with-crispr/
[iv] https://www.newscientist.com/article/2246020-three-people-with-inherited-diseases-successfully-treated-with-crispr/
[v] https://cen.acs.org/analytical-chemistry/diagnostics/COVID-19-diagnostic-uses-CRISPR/98/web/2020/05
[vi] https://www.fiercebiotech.com/research/stanford-team-deploys-crispr-gene-editing-to-fight-covid-19
[vii] https://theconversation.com/what-is-crispr-the-gene-editing-technology-that-won-the-chemistry-nobel-prize-147695
[viii] https://www.sciencedirect.com/science/article/pii/S216225311630049X
[ix] https://www.nature.com/articles/s41467-020-17418-8
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