Genome editing

Strategic delivery:	☒ The best care – effective and ethical care for everyone ☐ The right information – to ensure that people can access the right information at the right time ☐ Shaping the future – to embrace and engage with changes in the law, science and society
Details:	
Meeting	Scientific and Clinical Advances Advisory Committee
Agenda item	3
Paper number	SCAAC (19/10/2020) 001
Meeting date	19 October 2020
Author	Matthew Mudford, Scientific Policy Officer
Output:	
For information or recommendation?	For recommendation
Recommendations	The committee is asked to: • advise the executive if they are aware of any other recent developments; and • discuss potential clinical applications of this technology and identify particular concerns or issues that should be highlighted; and • review whether any outputs from the HFEA are required.
Resource implications	None
Implementation date	NA
Communication(s)	To be determined
Organisational risk	☒ Low ☐ Medium ☐ High
Annexes	None

1. Introduction

1.1. The HFEA are the Government regulator responsible for ensuring that all research centres which use human embryos are abiding by the law. One of the core regulatory principles, defined by the Human Fertilisation and Embryology (HFE) Act 1990, is to “ensure that all licensed research by the centre meets ethical standards, and is done only where there is both a clear scientific justification and no viable alternative to the use of embryos”.

1.2. The HFE Act was amended in 2001 to allow human embryonic research, only to "(a) increase knowledge of the developing embryo; (b) increase knowledge about serious disease, or (c) enabling any such knowledge to be applied in developing treatments for serious disease”. As technology has advanced, particularly in the last decade, the potential for genome editing to contribute to these research aims has become clear.

1.3. Genome editing research using human gametes and embryos has already improved our understanding of gene function, DNA-repair mechanisms, early human development and genomic rearrangements; mutations such as deletions that change the gene content of a genome or the arrangement of the genes on a genome. Genome editing techniques can be used to study the relationship between genes and diseases, and to explore the possibility of disease prevention or treatment.

1.4. Genome editing can either be used on germline cells to induce inheritable changes or on somatic cells (all other cells) to induce non-inheritable changes. The latter is much closer to clinical implementation. The great potential for somatic-tissue editing to treat disease is clear and raises few ethical concerns or obstacles as long as patient safety remains paramount. It is the ability to create inheritable changes to the human genetic code, (germline gene editing or heritable human genome editing), that has raised so many concerns. The transfer of genome edits to future generations amplifies the potential risk and makes the long-term consequences much harder to anticipate.

1.5. Arguably the greatest advance in both inheritable and non-inheritable genome editing has been the development of CRISPR Cas9. CRISPR stands for Clustered Regularly Interspaced Short Palindromic Repeats and is a system adapted from a defence mechanism used by prokaryotes, silencing the genes of invading viruses by cleaving the viral nucleic acids. In genome editing, CRISPR is used to target a specific gene and together with an enzyme called Cas9 forms a complex (CRISPR Cas9) that can, with a high degree of precision, cut a target gene out of the genome which can then be replaced with another gene. This means that CRISPR Cas9 has the potential to be used to avoid the inheritance of diseases, by removing and replacing a defective gene.

1.6. Following the discovery of CRISPR Cas 9 the technology advanced quickly, becoming cheaper, easily scalable and more widely available. In April 2015, a study was published (Liang P et al., 2015) in which the researchers carried out changes in the human genome of non-viable human embryos using CRISPR-Cas9. They demonstrated that it was possible to cleave the mutated gene responsible for beta-thalassaemia in a human embryo. Unfortunately, when they attempted to replace the defective gene, the efficiency of the replacement process, called homologous recombination directed repair (HDR), was low and the resulting edited embryos were mosaic. The paper demonstrated the significant risk posed by limited specificity and fidelity. The research alerted the global scientific community to the

capability, limitations and risks of the technology and highlighted the imminent ethical, social, legal and safety implications.

1.7. In the UK, regulation has had to keep up with the speed of the scientific advancements and the complexity of the multidisciplinary considerations. The HFEA has had to consider the repercussions of genome editing while allowing important germline research under strict conditions. The HFE Act 1990 ensures that all research centres make embryonic research applications to The HFEA and these must be approved by the Licence Committee before the projects can commence. Genetically modified embryos have never been allowed to be used in treatment and cannot be grown in culture for more than 14 days. Even within those boundaries, embryological research in the UK has been able to demonstrate the potential for clinical application.

1.8. In 2016, for the first time, the HFEA granted a license to a project using CRISPR Cas9 technology to study genetically modified embryos at the Francis Crick Institute. Only a handful of UK centres have so far followed suit in applying for such a license.

1.9. The development of CRISPR Cas 9 technology meant that, globally, genome editing became simpler, more accurate and more affordable. In the scientific literature there have been hundreds of studies on germline gene editing in animal embryos in the last few years. Such studies on human embryos have remained relatively rare due to the complex ethical considerations.

1.10. In November 2018, Chinese scientist He Jiankui announced to the world the birth of twins whose genomes had been edited during IVF. Their genomes had been edited using CRISPR Cas9 with the goal of decreasing their lifetime risk of contracting HIV. The was international condemnation of the scientific, ethical, moral and regulatory standards that had been flouted.

1.11. Despite all the scientific progress of recent years, it is not yet widely felt that the on-target effectiveness of the gene-editing process can outweigh the off-target risk. Off-site targeting results in unintended point mutations, deletions, insertions, inversions and translocations, the consequences of which are extremely hard to predict and so are ultimately unmanageable.

1.12. In addition to the scientific hurdles, social, legal and bioethical obstacles remain. There is yet to be widely endorsed proposal where the use of germline gene editing would be acceptable in treatment. There is great diversity of opinion which reflect the complexity of the considerations. However, some support is growing among bioethicists, physicians and the wider population that for couples who are at significant risk of having offspring with devastating genetic disorders such as myotonic dystrophy, it may be permissible to use genome editing to give them a healthy child once the risk becomes acceptable. There is currently no clear regulatory pathway to realise that ambition but several large international organisations are exploring whether there could or should be.

2. Recent regulatory developments

2.1. There have been several publications in the last year which pull together the best evidence and international collaborators to tackle the problem of how to construct a regulatory pathway towards the clinical application of germline genome editing.

2.2. 'Heritable Human Genome Editing', (HHGE) from the International Commission on the Clinical Use of Germline Editing has only just been published in September 2020. It considers whether, from a scientific perspective, genome editing methodologies could be developed sufficiently to permit responsible use. It identifies potential applications for the technology,

discusses pathways towards clinical use and defines the mechanisms for scientific governance which would be required. The report acknowledges that each country with the capability of using germline genome editing will need to establish its own regulatory framework, in line with its unique regulatory structures. It highlights the need for new models of international cooperation if these regulatory advancements are to be achieved. Some of the key scientific recommendations are:

2.2.1. No pregnancy should be established with a human embryo that has undergone editing until it is possible to make accurate genomic changes without undesired edits. Before any attempt to establish a pregnancy with an embryo that has undergone genome editing, preclinical evidence must demonstrate that heritable human genome editing can be performed with sufficiently high efficiency and precision to be clinically useful.

2.2.2. Use of human genome editing should be limited to diseases that cause serious morbidity or premature death. The edit should be limited to a substitution of a pathogenic genetic variant for a genetic sequence known in the population to not be disease-causing. No embryos without the disease-causing genotype should be subjected to genome editing and transfer so as to avoid any associated risk. This should only be done when the prospective parents have poor options as the chances of having unaffected embryos is low.

2.2.3. A proposal for clinical use should also include plans to evaluate human embryos prior to transfer using developmental milestones until the blastocyst stage and a biopsy at the blastocyst stage. The biopsy must demonstrate the existence of the intended edit in all biopsied cells and no evidence of unintended edits at the target locus or off-target sites.

2.3. The International Commission on the Clinical Use of Germline Editing recommended that an International Scientific Advisory Panel be established with a diverse, multidisciplinary membership and should include independent experts who can assess the scientific evidence of safety and efficacy of both genome editing and associated assisted reproductive technologies.

2.4. Also published in the last year are the reports from the meetings of the World Health Organisation's Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing. The World Health Organization (WHO) has established a global, multi-disciplinary expert panel to examine the scientific, ethical, social and legal challenges associated with human genome editing. The committee is tasked with advising and making recommendations on appropriate institutional, national, regional and global governance mechanisms for human genome editing. It is consulting with a wide range of stakeholders and has identified strategies to engage with both the scientific community and the lay audience so that information can be exchanged and societal views can be understood.

2.5. The Committee recommended that the WHO develop a registry of relevant planned and ongoing research. Anyone from government, academia, industry or community labs involved in genome editing research would be mandated to register and receive a unique identifier for their project. Funding would only be given on the condition that the research would be registered and only registered research could be published in journals. Failure to register would be considered as a fundamental violation of the principle of responsible stewardship of science.

2.6. The Committee also agreed that "it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing". They requested that all those

conducting or aware of research into genome editing of human germline cells and embryos to engage with the Committee immediately so as to better understand the technical environment and the governance arrangments.

2.7. The most significant outcome of the third meeting (a fourth is still to come) was an agreement as to the tools and guidance that would be required to develop a governance framework which could be implemented in different contexts.

3. Conclusions

3.1. The last SCAAC review of studies using genome editing techniques on human and animal embryos was presented to the committee in 2017. That was prior to the birth of the genetically modified twins which changed the global conversation about genome editing research. Complex ethical, social, legal and safety considerations have been brought to the fore.

3.2. There is potential for disease prevention and treatment but we must be acutely aware of the limitations and repercussions of the technology. Currently, the benefits do not outweigh the risks. For now, it would be irresponsible for anyone to proceed with clinical applications of human germline genome editing. However, where there is potential for genome editing to prevent serious disease or morbidity, a regulatory pathway could be established. It would require a multidisciplinary approach and international collaboration such as is being demonstrated by the WHO. The priority should be to minimise risks of research and progress gradually until the technology becomes precise enough to justify the first treatments.

4. Recommendations

4.1. The committee is asked to note this update and:

- advise the executive if they are aware of any other recent developments; and
- discuss potential clinical applications of this technology and identify particular concerns or issues that should be highlighted; and
- review whether any outputs from the HFEA are required.

5. References

Daley, G., Lovell-Badge, R., Steffan, J. (2019) *After the Storm — A Responsible Path for Genome Editing* New England Journal of Medicine, 380:897-899

Liang, P., Xu, Y, Zhang, X. et al. (2015) *CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes*, Protein & Cell; 6(5):363-372

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Tuerlings, E. (2020) *WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing - Background Paper*

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