This response was submitted to the Call for Evidence held by the Nuffield Council on Bioethics on *Genome editing* between 27 November 2015 and 1 February 2016. The views expressed are solely those of the respondent(s) and not those of the Council.

1. Is there anything special about the genome that makes intervening in it different from other ways of manipulating nature?

The possibility of making heritable changes in the genomes of individuals and populations through gene-editing techniques opens the potential for a significant acceleration in human intervention in the most basic processes of life. This does not mean that gene editing presents a greater threat than other ways of manipulating nature. We are perfectly capable of manufacturing existential threats to the species and planet without gene-editing technologies. To the contrary gene-editing techniques may open possibilities for more finely grained and targeted interventions in disease prevention and treatment, plant breeding to meet rising nutritional needs and increasing environmental challenges, and many other areas that will benefit humankind.

In short: *an emphasis on the long term implications of directed evolution in hereditary design, the complexity and uncertainty of epigenetic and ecological interactions, and of the potential future commercial developments of genome editing make it somewhat distinct.*

Science and society

2. What obligations do scientists involved in developing and using genome-editing technologies owe to society and what freedoms should society allow to these scientists?

Scientists have the basic responsibility to work towards outcomes in their research that will benefit society, including but not limited to expanding our understanding of the natural world. This should be understood globally and encompasses political, social, economic and environmental outcomes. Scientists (like others) should work towards creating the kinds of futures seen as desirable from the perspective of the democratic polities that they are embedded within. This is of course complicated as there are many substantive visions of the good life within a democratic society. Consequently, scientists should be prepared to enter into public debate and democratic deliberation making use of and sharing their expertise concerning the possible outcomes of specific forms and pathways of research and innovation. Deliberation and decisions about desirable outcomes, orientations and futures should be made on the basis of informed reflection that will often go beyond immediate areas of scientific expertise, and subsequently must be carried out in dialogue with various public(s) and stakeholders, especially those whose voices are often not heard in political discourse. Scientists also share in the responsibility for disseminating their findings in a manner that allows the public to deliberate in an informed and responsible fashion over the desirability of specific research outcomes and pathways.

It may be beneficial for those who wish to pursue a career in this field [gene-editing]*, especially those who oversee or direct laboratory research to undertake training or a period of sustained advanced-learning that goes 'beyond ELSI'* [Economic, Legal and Social Issues] *to cover 'PEELSA-ST' (political, economic, ethical, legal and social aspects of science and technology) (see Calvert et al. 2015). Scientists themselves must be enabled through reflexive tools and social theory to critically assess the ways in which their work or innovation meets the needs of society, and reflect upon who defines those needs and why and whose needs are or are not considered?* This will allow researchers to better engage and deliberate with ethicists, social scientists, stakeholders, various publics and policy makers about the socially desirable orientation of research and innovation.

It is in turn important that scientists be allowed the contained spaces to pursue basic research unhindered (to the extent possible) by overriding concerns for public acceptance or commercialization. Scientists should also be allowed to carry out fundamental research without fear for their personal safety. This

holds for gene-editing research on human embryos if carried out under proper regulatory guidance and oversight for research purposes only.

3. Do genome scientists have any special obligations to society that are distinct from those of other scientists?

It is desirable that scientists working in areas of public concern and apprehension be well equipped not only to understand those concerns, including their root causes which may not always be well expressed, but also to communicate with public(s) and stakeholders in an accessible and responsible fashion. In some cases extra training for scientists working in areas of particular public concern like gene-editing seems warranted.

4. What obligations do governments have towards society to ensure 'safe' science or otherwise to shape the scientific research and development?

Governments and supra-national institutions like the EU have a responsibility toward the long-term health and prosperity of citizens and others living within their sphere of competence and governance. This includes inter-generational responsibility, responsibility for future generations, long-term environmental responsibility and to varying extents responsibilities to global justice. When dealing with questions of heritable alterations to population genomes, as is the case with gene-editing technologies, particular attention must be paid to questions of ecological dynamics and responsibility for future generations. Robust regulatory frameworks for research and innovation are a key element of socially desirable development and dissemination of biotechnologies.

Science, morality and law

5. What conventional moral principles, if any, do genome editing challenge?

Gene-editing, like many other developing technologies, challenges conventions and in some cases intuitions about the distinction between nature and artifice and the "born and the made." These distinctions are often infused with value judgments that genome editing will require us to further investigate. In this context projects like the recent Nuffield Council report on "Naturalness" are helpful.

6. To what extent can the moral questions raised by genome editing be addressed using existing moral frameworks or approaches?

There are existing intellectual and ethical resources to address these questions.

7. To what extent are laws and legal frameworks necessary or desirable in seeking to ensure adherence to the moral principles that should inform genome editing?

Genome-editing should be done within the context of a regulatory framework informed and oriented by moral and political debate and discourse (see also the response to question 4)

8. What other issues do you feel need to be discussed in the context of genome editing? What do you consider to be the issues of greatest moral concern raised by genome editing?

While **gene-editing** per se may not raise any particularly novel problems not already raised in debates about genetic modification and GMOs, there do exist some interesting and important questions pertaining to the greater scope and precision offered by gene-editing technologies. Scar-free gene-editing methods, for example, lead to some novel challenges, especially in relation to plant gene editing: "the ability to detect changes made by genome editing is less certain than current GMO technology. This could mean that it will be transferred more freely between counties but with the issue that it may go undetected. This could create an environment for future public backlash" (see appendix 1). We agree with the position of the BBSRC that a risk and impact based approach should replace the current methods-based approach in governing the utilization of genetically edited plant species. The possibility of scar-free editing nonetheless raises the potential of edited organisms crossing regulatory-territorial boundaries undetected. This would potentially conflict with consumer right-to-know and could create further backlash and adverse public attitudes.

We would be wary of splitting hairs when it comes to the interpretation of the EPA definition of "artificially modified." Gene editing techniques are artifice even if they have been developed from "natural processes" and make use of naturally occurring cellular repair mechanisms. Though perhaps more arduous from a public acceptance perspective, philosophically and scientifically sound education should take precedence over the risk of regulatory sophistry about artifice and "natural processes." (Newsom and Wrigley 2015: 18)

In relation to human gene editing, the possibility of undetectable edits would paradoxically seem to address the concerns raised about genetic modification by the German Philosopher Jürgen Habermas whose intervention on the topic (*The Future of Human Nature*) emphasized the potential psychological consequences on autonomy as a result of knowing that one's genome had been modified or edited.

In relation to the potential and use of **gene drives** we emphasize a point made in the appendix: "the success of gene drives will depend on our ability to predict the effects of the intervention properly on a systems and global scale."

We also emphasize the importance of ensuring that **access and benefits** of eventual gene-editing technology are distributed equitably. In the briefing paper prepared for the Council by Newsom and Wrigley, the analogy is made to cosmetic or aesthetic surgery to illustrate how the scope and use of gene-editing technology could proliferate if permitted for eventual human use and were to be available via the private sector. This would likely require new and greater regulatory supervision. Also, similar to concerns raised about the exacerbation of inequities due to different levels of access to various forms of human enhancement technologies, we think it important to keep a vigilant watch on how gene-editing technologies relate to dynamics of inequalities at national and global levels. This is of course most significant if they are eventually permitted for human application, but is also relevant for all other areas of application (plant, microbial, animal).

Researchers and policy makers should also be attentive to the development of appropriate mechanisms for assuring equitable access and benefit sharing at the global level. Mechanisms like the *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization (ABS) to the Convention on Biological Diversity* are likely to become increasingly important with the proliferation of technologies making use of genetic resources. Such mechanisms are important in ensuring that gene editing technologies benefit as many as possible.

References:

Calvert, Jane, Andrew S Balmer, Claire Marris, Susan Molyneux-Hodgson, Emma Frow, Matthew Kearnes, Kate Bulpin, Pablo Schyfter, Adrian Mackenzie & Paul Martin (2015) Taking Roles in Interdisciplinary Collaborations: Reflections on Working in Post-ELSI Spaces in the UK Synthetic Biology Community. *Science & Technology Studies*, Vol. 28(3) p.3-25

Newson, Ainsley J. & Wrigley, Anthony (2015) Identifying key developments, issues and questions relating to techniques of genome editing with engineered nucleases. Background paper Nuffield Council for Bioethics. [online] Available at: http://nuffieldbioethics.org/wp-content/uploads/Genome-Editing-Briefing-Paper-Newson-Wrigley.pdf

APPENDIX 1

Plant Science

Current research

What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks?
Genome editing has been shown to work in a number of plant species, however, reports to date do not show the same high frequencies as those seen in non-plant species. Within most crop plants the current technical limitations are: 1. The rate and cost of transforming most crops 2. The lack of high expressing/inducible promoters and 3. The inability of UK researchers to easily carry our field based experiments.
What are the main directions of travel? What are the envisaged endpoints/ applications?
Progress in plants appears to be slower than seen in other species but given time it is envisaged that similar modifications to those seen in non-plant species will be achievable. End points relate to being able to modify **yield** and **quality traits** as well as **disease resistance**.
What is the rate of travel? What are the expected timescales for realising the envisaged endpoints?
For rice we have arrived, but for wheat we are still 5-10 years away from being able to routinely edit the genome.
Are gene drives an area of particular interest or concern and, if so, why?
Not yet, but this may become a concern due to the competitive nature of plant breeding; for instance would a breeder be more likely to employ gene drive technology to ensure the wider use of these breeding material.

Conditions of research and innovation

What are the main 'drivers' and 'obstacles' for plant genome editing in relation to envisaged endpoints?
Drivers: Increase **yield**, **quality** and **disease resistance** as well as **speeding up the breeding process** via the modification of recombination. Obstacles: **Cost** and **speed of transformation** and **inability to carry out field based experiments**. **Low return on investment** means that government support is essential.
What direct or indirect influence does historical public discussion surrounding Genetic modification of plants have? What is (and what should be) the current level and focus of public debate

The public have been transfixed with plant GMO's. The question as to whether or not genome editing is GMO technology is important. If it is classified as GMO then it will take a considerable amount of time to adjust the public's view although this is gradually changing.

Public debate is always worthwhile but we have to accept that many people have a fixed view and will probably not change this view, educating future generations as to the pros and cons of GMO's is essential, but we need to accept that this is a task that will take many years.

The generation of a GMO plant with obvious benefits to the public (rather than the farmer or biotech companies) would be very helpful.

Outcomes

What are the main anticipated benefits and costs (including safety and other risks) of genome-edited plants? In what ways, if any, are they significantly different from alternative GM technologies?

Being able to edit the genome with base scale precision will revolutionise our ability to engineer crops to have greater yields, better quality and more resistance to diseases. Genome editing technology is less hit and miss than current mutagenises, which is widely used in the plant breeding business.

Are there particular issues raised by genome editing in relation to ecological stability, biological diversity, technology transfer between countries, and equitable sharing of the benefits of research?

No more so than standard GMO technology, but of course the ability to detect changes made by genome editing is less certain than current GMO technology. This could mean that it will be transferred more freely between counties but with the issue that it may go undetected. This could create an environment for future public backlash.

To what extent, and in what way does and should the distribution of anticipated benefits and costs of using genome editing in plants influence research and innovation?

The technology is driven by both academics, who strive to do the best most innovative research and commercial companies who wish to provide a return for their investors. Any benefits will be distributed as per all research developments, some at a loss of time and money and others will generate exciting profits.

To what extent are public and commercial interests in genome editing in plants complementary? In what circumstances might they come into conflict?

Both wish to develop new technology that will benefit humankind.

What other important questions should or might we have asked in this section?

We have to accept that the field of genome editing is moving fast and hence it is difficult to come to a consensus view as developments will overtake such views. For the moment we have to accept that this is a young, fast developing technology and we just need to keep a watching brief on where it will lead.

Whether governments can act with the speed that will be required in this field is questionable, and if they act at the wrong time it could result in gene editing work being transferred elsewhere and that country then losing any lead it had.

This a global technology, therefore it is difficult to see how a national policy will have any effect beyond encouraging the work to be done in that country or elsewhere.

Microorganisms

Current research

What is the current state of the art in the field? What are the current technical limitations and constraints/ bottlenecks?

Genome editing in particular with CRISPR/Cas9 (but also with TALENs, Zn-fingers, redET cloning) has encompassed all kingdoms of life. With CRISPR/Cas9, genome editing has become commonplace. Current technical limitations are around the introduction of the 'scissors' and the DNA of choice which will replace the edited locus into cells. In particular this is difficult in primary cells which are recalcitrant to plasmid transfection. Here lentiviral delivery vectors are often used, which have limited DNA cargo capacity and scar the genome.

What are the main directions of travel? What are the envisaged endpoints/ applications?

1. Resolve the challenge of large and very large DNA delivery to efficiently engineer and not 'just' edit genomic sites of choice
2. Introduce efficient, high-throughput compatible tools
3. Endpoints/applications are new and customized ('tailored') cells and cell lines for a wide range of applications including:
    - **basic research**
    - **bioprocessing**
    - **green energy**
    - **new strains for drug production**
    - **cell-based assays**
    - **therapeutic products**

What is the rate of travel? What are the expected timescales for realizing the envisaged endpoints?

Gene editing is currently moving at an immense speed to a large part due to CRISPR/Cas9 which has made genome editing commonplace. The number of publications is immense and rapidly increasing on a daily basis ('CRISPR craze').

This is likely to abate with time, at which point the genuinely useful applications will be pursued more systematically.

Genome editing has been possible for decades (redET, Zn-fingers, TALENs) but the technical ease with which it can now be accomplished with CRISPR/Cas9 is unprecedented. What has not changed is that the edited genomes have to be assessed, characterized, tested for function, and, for therapeutic intervention, validated in a clinical context (for example). This can take decades. On these timescales it is irrelevant whether the genome editing took days (with CRISRP) or weeks (with Zn-finger or TALENs).

Many more scientists now apply genome editing routinely. In terms of end-points and applications this may not translate in the drastic reduction of timescales which the current prominence of genome editing in the scientific and public discourse may suggest.

Are gene drives an area of particular interest or concern and, if so, why?

Gene drives are interesting, but also present challenges which call into question whether they are the best way to eradicate disease.

It is, for example, not clear whether we can model the effects of gene drives in the context of biological systems on a global scale sufficiently. For instance, Sickle cell anemia, where evidently a 'bad' gene is at work, also confers better resistance to malaria. Our capacity to use this kind of technology safely and effectively depends on an understanding of biological systems and ecological dynamics: the success of gene drives will depend on our ability to predict the effects of the intervention properly on a systems and global scale.

Conditions of research and innovation

What are the main commercial applications of genome editing in microorganisms and what are the main economic drivers of development?

Commercial applications: Green energy, crops, basic science and human therapy.

Economic drivers: Examples include: The desire to use renewable energies for bio-fuels and at the same time not cause adverse effects such as global warming (by burning fossil fuels); Development of scalable E.coli production platforms.

To what extent is research that uses genome editing in this area continuous with synthetic biology? To what extent are the discussions, institutional capabilities, resources and measures surrounding synthetic biology relevant and helpful to genome editing in microorganisms?

Genome editing is a tool which is an accelerator and catalyzer of synthetic biology approaches wherever microorganisms are involved. Genome engineering IS a part of synthetic biology. It is at the very definition of synthetic biology, and discussions about genome editing are directly relevant to synthetic biology.

Outcomes

Are there particular biosafety and biosecurity considerations relating to genome editing in microorganisms? If so are they significantly different in degree or in kind from other research on microorganisms?
Not different from already existing considerations regarding GMOs. Genome editing is not a new concept that requires genuinely new regulations, it has just become more affordable, and technically attainable than ever before. Thus the risks of misuse, which have always existed when genomes were modified, have now multiplied. There is a strong movement to argue that there is no need for further regulation. However it is unclear if all stakeholders will be content with this position. A qualified discussion about the (long) history of genome editing and what has changed (its affordability and technical achievability) will help to put things into perspective.
Are there particular opportunities for genome editing research to contribute to bioremediation (e.g. mitigating the negative effects of pollution or climate change) or, alternatively, risks relating to habitat destruction or species extinction? If so, what are the risks associated with developing these opportunities and how serious are those risks?
Yes: Hypothetically (for example) one could engineer microorganisms to take the CO_2 out of the atmosphere to make carbon-based biofuels which will then release the same amount of CO_2 (but not more) when consumed.
What other important questions should or might we have asked in this section?
How can we make sure genome editing is understood to be a – very important – underpinning part of synthetic biology.