NUFFIELD COUNCIL ON BIOETHICS

Response to the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing's consultation on draft Governance framework for human genome editing

The Nuffield Council on Bioethics welcomes the opportunity to respond to the WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing's consultation on draft Governance framework for human genome editing. Our response is based on our 2018 report, *Genome editing and human reproduction: ethical issues* and our 2016 report, *Genome editing: an ethical review.*

We would like to emphasise the importance of an approach that seeks to establish a ground for consensus on issues of whether to proceed to clinical translation (notably in the reproductive context) than one which produces a roadmap for clinical translation first and invites researchers to follow it.

We would also wish to assert that aspects of genome editing raise ethical issues of public and international importance, such that they should be dealt with as matters of public policy rather than clinical translation or commercial innovation. Recognising that many jurisdictions do not have effective legal controls in force, and that there is no international authority capable of enacting universal measures, we would enjoin all jurisdictions to bring heritable genome editing unambiguously within the control of relevant public authorities and to make its abuse subject to appropriate sanction.

Q4: ENGAGEMENT
The Committee is interested in promoting useful public education, engagement and empowerment on human genome editing. Do you know of any public engagement activities on emerging technologies (including human genome editing)? Yes/No. If Yes, please detail the activity(ies) and explain whether you consider this activity(ies) useful. Otherwise, write "No".

Yes.

In our 2018 report we recommended that genome editing should be subject to 'broad and inclusive societal debate' (see paragraphs 4.98 ff). 'Societal debate' is debate within a society that informs the approach taken by individual states (given that the nation state is a natural horizon for the imposition of laws, regulatory controls etc.) We further recommended (para. 4.103) that such debate requires institutional support to counteract the threats to the quality of debate in the public sphere in many societies around the world. (On the international dimension, see answer to question 8 below).

There is a wide variety of initiatives and activities on emerging technologies, and on genome editing specifically, both invited (for example, to inform policy making) and uninvited (for example, to assert the interests of patient groups and researchers). Relevant UK examples include:

UK Research funders have commissioned the National Co-ordinating Centre for Public Engagement (NCCPE) Genome Editing Public Engagement Synergy (GEPES) programme.

The UK Royal Society has commissioned a multi-method process that identified concerns and baseline opinions among limited sample of UK public.

Engagement on "Basic understanding of Genome Editing" by Progress Educational Trust (PET) and Genetic Alliance UK and PET public meetings – developed understanding of communicating with non-specialists

The Guardian, with Involve have carried out an innovative project called 'The Gene Gap' to inform reporting of new science in mainstream media with a range of social narratives developed through discussion groups.

*** Do you have any suggestions for effective public engagement on human genome editing? Yes/No, if Yes please detail your response. Otherwise, write "No".**

Yes.

No single activity or initiative can be the privileged locus of public debate. It is important to recognise both the instrumental aspects of public engagement (i.e. in relation to specific applications of well-advanced research) and the broader involvement of society in shaping of science and technology (which is part of responsible research and innovation). This is important in the present context to the extent that genome editing is understood to raise issues of public policy and not merely of biomedical practice or commercial freedom (see answer to question 8 below).

The Council of Europe Bioethics Committee (DH-BIO) has produced a *Guide to Public Debate on Human Rights and Biomedicine* (Council of Europe, 2020; 'public debate' is the rubric for Art 28 of the Oviedo Convention and includes what may be conventionally described 'public engagement').The *Guide* makes clear the special importance of public debate in relation to emerging biotechnologies and in the present historical moment. It also guides public authorities to reflect on the rationale and objectives for public debate initiatives, the timing and circumstances of public debate, how publics are defined, etc. In other words, a key message is that there is no pre-established template for effective public debate and, to be effective, public debate must be produced in and according to a particular set of circumstances.

In 2016 the Nuffield Council and Sciencewise held a workshop on "Public Dialogue on genome editing" which resulted in a short report (NCOB, 2016a) which was followed by a Sciencewise roundtable.

Q5: REPORTING OF UNETHICAL RESEARCH
The Committee is exploring possibilities for recommending the creation of an international 'whistleblowing' mechanism for the reporting of unregistered, unethical or illegal uses of human genome editing on individuals (somatic genome editing) or germline genome editing, whether in the lab or clinically for attempts at making heritable alterations (i.e. reproductive uses). Do you know of any such mechanism(s) that could be useful at an international level? Yes/No. If yes, please detail the mechanism(s) and explain whether you consider this mechanism(s) desirable/practical/useful. Also, please comment on the potential objections or roadblocks to the creation of such a mechanism(s). Otherwise, write "No".

Yes.

We have not examined specific whistleblowing regimes in relation to genome editing (our reports predated the most salient case of malpractice) although our examination, (NCOB 2014) identified the dangers of 'organised irresponsibility' (Beck, 1995) and exposed the limited efficiency of self-regulation and the risk of incubating malpractice.

Among the failings that led to the premature clinical use of heritable genome editing in China is the weakness of self-regulation of research, combined with the facility of genome editing that has extended the range of users beyond elite scientists and those strongly socialised into recognised norms of scientific practice. This points to organisational and cultural difficulties within research.

Given the public interest implications of genome editing this is not a matter that can be fully managed internally by the 'Republic of Science' (Polanyi 1962).There is therefore a need for clear mechanisms operating at three levels, at least, to support and protect whistle-blowers. These levels are institutional (e.g. universities, with routes to senior management outside faculties, disciplines or business units concerned), legal (e.g. through regulatory authorities) and public (e.g. protection of public interest disclosure to journalists).

Q6: PREVENTING AVOIDANCE OF REGULATORY OR ETHICAL OVERSIGHT
The Committee is interested in understanding how to prevent instances where researchers or companies locate controversial activities in countries with weaker regulatory infrastructure for no reason other than to avoid regulation and ethics guidelines that exist in other countries. Do you have any comments on how such instances should be prevented?

Yes.

It is important to distinguish questions of weak oversight from questions of states having divergent conclusions about ethical acceptability.

In relation to weak oversight, in many of cases resources to support oversight and enforcement may be restricted, leading to the possible exploitation of destinations that either have weak infrastructure or that might be in pursuit of inward investment. In this case development support and international assistance in capacity building may be desirable – as noted at para 14(d) of the governance framework (for example UNESCO programme of capacity building for ethics committees).

In relation to variant sovereign ethical positions, one approach is to support the elaboration of, and compliance with, international law. Genome editing raises recognised human rights issues and is an area in which the application of international instruments is continually being elaborated. Use may be made of widely accepted human rights frameworks and institutions for the promotion of explicit positions, and for the negotiation tolerable margins of appreciation consistent with national sovereignty and peaceful co-existence (Mills, 2018).

We note that biopolitical measures may be adopted by some states that involve restricting or placing conditions on the movement or status of persons, for example by analogy to cross-border surrogacy arrangements. In view of this, we wish to emphasise our recommendation that "governments in the UK and elsewhere give consideration to bringing forward an international Declaration affirming that people whose genomes have been edited should be entitled to the full enjoyment of human rights." (NCOB 2018, para.4.107).

Q7: PRINCIPLES
The Committee has identified 5 ethical principles to guide both its work and future efforts on the effective governance of human genome editing, as follows. Five ethical principles to guide the Committee's work and efforts on effective governance of human genome editing:

- **Transparency** - a commitment to share information on what is happening, how and why it is necessary;
- **Inclusivity** - a commitment to draw on the full contributions of all parts of global society, thereby providing diverse points of view, skill sets and additional methods of program management and measurement;
- **Responsible stewardship of science** - a commitment to rigorous science, to follow ethical practice in scientific and clinical conduct, and strive to maximize potential benefits while minimizing potential harms;
- **Fairness** - a commitment to fair dealings in relation to all persons and groups, and equitable access to opportunities and potential benefits, and support for efforts to encourage research and development of medical interventions that are appropriate and feasible for the widest possible range of populations; and
- **Social justice and non-discrimination** - a commitment to celebrate and promote diversity by rejecting patterns of discrimination based on personal or group characteristics including gender, race, ethnicity, sexuality, age, and disability.

Do you have any comments on one or more of these 5 principles?

Yes.

These are all laudable principles for an indefinite range of applications. We would make three, general points.

First, the selection of principles to emphasise in relation to genome editing should be guided by the anticipation of the particular mischief to be averted. Here it is worth emphasising the role of broad engagement that the panel has identified.

Secondly, given that compliance with principles in any given case can be a matter of construction, it is likely that contradictory outcomes can be made to appear consistent with a given principle. So, an important question is where the authority lies for determining compliance with principles and how this is standardised through practice. 'Responsible stewardship of science', for example, could mean securing or foreswearing certain lines of research, particularly where this has morally ambiguous potential. Hence the importance of governance.

Thirdly, there is a potential for principles come into conflict or appear to require incompatible practices. A 'commitment to fair dealing' for example, may conflict with 'non-discrimination'. Placing the principles in a simple hierarchy might lead to as many problems as it resolves. This is again to stress the importance of governance as a process not only for determining compliance but for resolving conflicts according to values.

*** Are there essential principles missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".**

Yes.

We wish to draw attention to the two principles set out in our 2018 report, the principle of the 'welfare of the future person' and the principle of 'social justice and solidarity', and the

interpretation given to those principles in that document. Most importantly we wish to draw attention to how these are derived from reflection on the interests and responsibilities engaged by human heritable genome editing in a contemporary sociotechnical context and proposed in order to guide to the elaboration of governance as part of a public policy process (see question 8).

Q8: ESSENTIAL FEATURES OF A GOVERNANCE FRAMEWORK
The Committee considers core features of a governance framework for human genome editing, as listed here: The Committee considers that a governance framework:

- **Is transparent, inclusive, responsible, fair, and socially just;**
- **Covers basic research that takes place entirely within a laboratory environment, including basic research on gametes and embryos; and clinical trials that enrol human participants, whether for non-heritable editing (i.e. somatic cell editing) or heritable editing (i.e. germline editing in reproduction). It also includes the emerging areas of in utero (non-heritable) genome editing on fetuses, and all types of genome editing technology, including base editing, prime editing, epigenetic editing, etc;**
- **Covers both health-related and non-health-related research;**
- **Is robust, flexible, scalable, sustainable and appropriate for use at the international, regional, national and local levels;**
- **Inspires trust by having been developed through informative and participatory approaches involving experts and non-experts;**
- **Identifies and addresses relevant issues, using a range of laws, policies, and regulatory mechanisms, developed in collaboration with the widest possible range of institutions, organizations and peoples; and**
- **Provides those who occupy specific governance roles for human genome editing with the tools and guidance they need.**

Do you have any comments on these features?

Yes

Despite the scale of its ambition (to cover the complete, heterogeneous range of jurisdictions), the framework document offers a comprehensive and thoughtful approach with many excellent elements. We are very pleased that the framework covers ‘basic research’ as the distinction between ‘basic’ and ‘applied’/ ‘preclinical’ research has tended to insulate the former from full or appropriate scrutiny and public interest.

There is an ambiguity in the governance document between the notions of a (1) governance framework (as in the title ‘A DRAFT Governance Framework for Human Genome Editing’) and (2) a framework for (the development of) governance. The high level of the document places it closer to the latter description, and as such the ambiguity could become problematic.

The comprehensive ambition and high level of generality invites the question whether it is reasonable coherently to bring ‘human genome editing’ under a single governance framework, or whether research, clinical trials, medical interventions, reproductive innovations etc. would be better addressed with dedicated (but related and consistent) governance provisions. In other words, does the framework add value as a bridge between on the one hand principles and elements of good governance generally (by being more specific); and on the other hand the dedicated governance of a coherent area of practice (by imposing conceptual coherence)? In our submission that value would be transversal, i.e. in

securing international alignment. An important question, therefore, will be how, as a viable international instrument, the framework relates to the elaboration of high-level frameworks based on human rights.

Are there essential features missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

Yes

To the extent that this list can be treated as a specification for a governance framework, understanding how the elements and structure that are subsequently introduced meet this specification is made difficult by the ambiguity referred to in the previous answer.

A general comment is that the framework offers largely structural approach, whereas it is important also to envisage governance as a process and to recognise where power is distributed within the governed system. In particular, we wish to draw attention to the danger, in a 'multilevel' governance system, of privileging research interests or entrepreneurial freedom in genome editing (see answer to question 9).

Q9: ELEMENTS FOR A GOVERNANCE FRAMEWORK
The Committee identified core elements of a governance framework, these included key challenges to be considered when developing oversight regimes, different mechanisms that may be employed individually or collectively as part of governance efforts, and a wide range of institutions, organizations and peoples that may need to be involved. The Committee allowed that not all of these elements will be equally important, or appropriate, in different settings and contexts. For example, different mechanisms may be a better fit in some countries than in others. Equally, different groups and individuals may be more or less pertinent, or able to engage, depending upon whether governance efforts are happening in an individual institution, or in an inter-governmental organization.

Challenges

The Committee identified 8 challenges to be considered when reviewing, creating, or strengthening measures for the governance of human genome editing (see below). While not every issue will need to be specifically addressed in all resulting measures, the Committee is recommending time be set aside to consider each of them in some depth. Challenges to be considered when developing governance measures for human genome editing (for a full description of each, see the Draft Governance Framework):

- **Differences in ethical views and values within and across nations**
- **Differences in social priorities within and across nations**
- **Differences in culture within and across nations**
- **Differences in public awareness, perceptions, and preferences**
- **Differences in capacity**
- **Maximising benefits**
- **Science that is dynamic and fast paced**
- **Competitive environment for science**

Do you have any comments on these challenges?

Yes

We welcome the approach of identifying the challenges that governance frameworks are expected to address. This reflection is important in clarifying the justification for bringing genome editing (in its various related applications) under governance. In particular it reveals the need to articulate the case for international governance (i.e. the reasons why aspects of genome editing should not be subject to subsidiarity), and the extent to which governance may be left to nation states and lower level institutions. We would urge the Expert Advisory Committee to articulate this case in the clearest terms since the primary relevance of its work follows from it.

With your context in mind, are there any challenges missing from the list? Yes/No, if Yes please provide details. Otherwise, write "No".

Yes.

We have two points of emphasis to draw out.

Re. item (d) in the draft governance framework: While global governance may be determined and function hierarchically, in a way that subsumes minor discourses and diverse voices at the local level, there is value in mechanisms that operate transversally to this multilevel hierarchy to provide a continuous critical reflection that would not otherwise become visible in the higher levels of the governance structure. This international effort is importantly distinct to the national public engagement recommended in item (d). One initiative that offers a resource of this kind is the Global Observatory on Genome Editing, which promises to develop a critical discourse through a kind of comparative ethnography of minority traditions (Hurlbut et al, 2018). Space for engagement with this, and the critical reflection it represents, should be found in the orthodox governance system.

Re. item (h): It is perhaps implicit that the competitive challenges to which genome editing gives rise can be corrosive both to scientific culture of selfless collaboration and to global public good. Techno-nationalism is a perennial problem with biotechnology (in which the progress of knowledge is fostered by sharing, whereas economic technological advantage depends on advancing ahead of others).

Q10: MECHANISMS
A governance framework for human genome editing might be comprised of different mechanisms. Some mechanisms will directly regulate the use of technology (such as international, regional, national or federal laws, or enforceable codes). Other mechanisms will aim to provide indirect ways to alter behaviour, change how a technology is used, and strengthen a culture of responsibility. The Committee identified 12 mechanisms that might regulate/inform the use of human genome editing, as follows (for a full description of each, see the Draft Governance Framework):

Laws and regulations

- **Professional codes of ethics, conduct and practice**
- **Funding requirements**
- **Insurance requirements**
- **Accreditation, registration, or licensing**
- **Standards and guidelines**
- **Publishing requirements**
- **Moratoria**
- **Institutional policies or guidelines**
- **Research review**
- **Licensing or marketing approval requirements**

- **Professional self-regulation**

Do you have any comments on these mechanisms?

Yes.

Here, particularly, the draft framework looks more like a 'governance compendium' than a framework for governing genome editing. It will be important, therefore, to indicate how the mechanisms should be fitted to the challenges, particularly as they might appear in a given national sociotechnical context.

Are there mechanisms missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

There is an implicit reference (in item (e) of the draft governance framework) to the proposed register of genome editing research that the Committee has previously recommended. We submit that to be effective, any register would need to cover basic research (at least human embryo research) and treat research on clinically relevant sequence variants (such as those targeted by the first papers published on CRISPR in human embryos) as Dual Use Research of Concern (DURC), attracting enhanced scrutiny and controls. The reasons are first, that such research lacks justification pending more basic research and suggests a premature translational ambition; secondly, laboratory demonstrations of the editing of clinically relevant variants could very easily lead to clinical translation in a reproductive context. Likewise, any moratorium should cover this 'basic' research as well as clinical translation in order to resist momentum to carry research prematurely into clinical application, without sufficient debate about whether this is acceptable and, if so, for what indications or purposes.

Another way to govern human genome editing technologies is by encouraging, fostering changes in the behaviour of those involved in doing the research. The Committee has identified some mechanisms that can be used to have that effect (see below).

Mechanisms that foster changes in the behaviour of those involved in doing the research (for a full description of each, see the Draft Governance Framework):

- **Public education, engagement and empowerment initiatives and activities**
- **Academic and professional training**
- **Academic, professional, and other conferences and information sharing opportunities**
- **Academic, professional and other (e.g., financial) incentives**
- **Technical advances or strategies**

Do you have any comments on these mechanisms?

Yes.

Inculcating good behaviour should be prior to the fall-back of enforced rules and standards. 'Another' should therefore not be understood to mean 'alternative' but rather 'complementary'. We welcome the fact that the Expert Advisory Committee recognises elements of scientific culture as potentially part of the problem and also part of the solution (see NCOB 2014). One aspect of this that could be emphasised is the need for efforts to replace the disjunction between 'science and society' with the concept of 'science with and for society'.

Are there mechanisms missing from the list? Yes/No, if Yes please provide details. Otherwise, write "No".

Yes.

There are many mechanisms, both formal and informal, hard and soft that could be envisaged. The crucial point, however, is that governance must work within the context of local culture. ('One size does not fit all'.) Please see comments above in relation to the value of a reflective or heuristic approach.

However, we recommend as a minimum that states bring HHGE under the control of public authorities and make its abuse subject to appropriate sanctions. Rather than starting with a moratorium, the limitations of which have been widely discussed, this has the and advantage of ensuring that the position is clarified in each jurisdiction preparatory to any further international discussion or the application of international law.

Q11: INSTITUTIONS, ORGANIZATIONS AND PEOPLE
A number of different types of institutions, organizations and peoples can play important roles within a governance framework. Some of these may be directly involved with establishing governance mechanisms. This may differ by country and mechanism. For example, in some countries industry organizations can feed into the development of regulations. In other places this does not happen. Different institutions, organizations and peoples may also be involved with enforcing or implementing different mechanisms. For example, in some cases members of the general public may sit on research ethics review committees. In other cases, they may not. Furthermore, different institutions, organizations, and peoples may have other roles in participating in governance, for example, through education, engagement or empowerment initiatives, other forms of training, or shaping public perceptions. The Committee identified an illustrative list of 17 different institutions, organizations, and peoples that can play important roles within a governance framework, see below. Institutions, organizations and peoples that can play important roles within a governance framework (for a full description of each, see the Draft Governance Framework):

- **Institutions undertaking human genome editing research**
- **Governments**
- **Health care institutions**
- **Industry associations and other representative bodies**
- **Professional scientific organizations**
- **Publishers of research findings**
- **Scientists including clinician-scientists**
- **Clinicians**
- **'Citizen scientists', 'biohackers', and their communities**
- **Funders of research**
- **International organizations**
- **Advisory and review boards**
- **Civil society and interest groups**
- **Legal practitioners and academics**
- **Patient groups and those who might be affected by human genome editing**
- **Science fiction writers, game designers, and TV and movie companies**
- **Social media activists**

Do you have any comments on this list?

Yes.

Once again, the list is compendious but the issue is really to understand the effects of concentrations of power within the research culture and the wider system of governance.

Are there institutions, organizations or people missing from this list? Yes/No, if Yes please provide details. Otherwise, write "No".

No.

Q12: FINAL COMMENTS
Is there anything else you think the Committee should be considering in terms of the governance of human genome editing? Yes/No, if Yes please provide details. Otherwise, write "No".

Yes.

Please see the following references referred to in this submission:

- Beck U (1995) *Ecological Politics in an Age of Risk* (Cambridge: Policy).
- Council of Europe Bioethics Committee (2020) *Guide to Public Debate on Human Rights and Biomedicine* (forthcoming, March 16 – see https://www.coe.int/en/web/bioethics/public-debate).
- Hurlbut JB, Jasanoff S, Saha K et al (2018) Building Capacity for a Global Genome Editing Observatory: Conceptual Challenges, *Trends in Biotechnology* 36(7):639-41.
- Nuffield Council on Bioethics (2014) *The culture of scientific research in the UK*.
- Nuffield Council on Bioethics (2016a) *Public dialogue on genome editing: why? when? who?*
- Nuffield Council on Bioethics (2016b) *Genome editing: an ethical review*.
- Nuffield Council on Bioethics (2018) *Genome editing and human reproduction: social and ethical issues*.
- Mills PFR (2019) Three venues for discussing human genetic engineering *Issues in Science and Technology* 35(3): 38-41.
- Polanyi M (1962) The Republic of Science: Its Political and Economic Theory, *Minerva* 1:54-74.