HOUSE OF COMMONS

Science and Technology Committee

Oral evidence: Genomics and genome-editing, HC 854

Wednesday 29 March 2017

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Watch the meeting

Members present: Stephen Metcalfe (Chair); Victoria Borwick; Chris Green; Carol Monaghan; Gareth Snell; Graham Stringer; Derek Thomas.

Questions 188 -250

Witnesses

I: Professor Waseem Qasim, Professor in Cell and Gene Therapy, Institute of Child Health; Alastair Kent, Director, Genetic Alliance UK; and Dr Kathy Niakan, Group Leader, The Francis Crick Institute.

II: Dr Andy Greenfield, Programme Leader, Medical Research Council's Harwell Institute; Robin Lovell-Badge, Senior Group Leader, The Francis Crick Institute; James Lawford Davies, Partner, Hempsons; and Philippa Taylor, Head of Public Policy, Christian Medical Fellowship.

Written evidence from witnesses:

- Genetic Alliance UK
- Christian Medical Fellowship

Examination of witnesses

Witnesses: Professor Qasim, Alastair Kent and Dr Niakan.

Q188 **Chair:** Good morning; welcome. Thank you very much for joining us for this continuation of our inquiry into genomics and genome-editing. Perhaps for the record you could introduce yourselves and say in what capacity you are here this morning.

Professor Qasim: I am Waseem Qasim, a paediatrician and cell and gene therapist based at the Institute of Child Health in Great Ormond Street Hospital. We look after children who undergo transplantation, which is an area ripe for applying some of these new technologies.

Alastair Kent: I am Alastair Kent, director of Genetic Alliance UK, which is the UK umbrella body of approximately 200 patient support organisations for families affected by all forms of genetic disorders. We try to provide a patient and family voice on issues of science and health policy and practice.

Dr Niakan: I am Kathy Niakan, a group leader at the Francis Crick Institute. I have 20 years of research experience, specifically in human embryology and stem cells at Harvard University and the University of Cambridge. I am applying genome-editing technologies in human embryo pre-implantation development in vitro.

Q189 **Chair:** To begin with, could I ask each of you to outline briefly the potential that you believe genome-editing techniques have?

Professor Qasim: In the first instance, we see applications in medicine for engineering cells that are collected from patients, modified and returned to those patients. We call that ex vivo gene modification. We anticipate in the next few years applications primarily in the area of immuno-therapy, which is engineering immune cells and getting them back to patients, but maybe over a longer timeline we can see attempts to try to use gene-editing to repair certain genetic defects, where cells are engineered and given back to correct an inherited disease. In the longer term, there may be applications directly in patients to try to correct conditions affecting them because of a single gene disorder.

Alastair Kent: My members support families affected by the sort of diseases that Professor Qasim indicates might be amenable to correction through genome-editing. It is important to remember that for families affected by these conditions, although there have been significant advances in our understanding of the basic biology of the diseases, the vast majority remain incurable. Many of them—about 80%—affect children, and they cross generations; they affect families both vertically down the generations but also horizontally in terms of the risk to first-degree relatives and so on. Families in that position see the techniques and potential of genome-editing as a hugely important opportunity to transform their lives, or the lives of future generations, through a

technique that potentially will lift the threat of a progressive, intractable, incurable disease.

Families recognise that we are at the early stages of potentially quite a long journey before the technique is widely applicable in clinical practice. They are optimistic about the potential but realistic about the length of time it might take to see the results. They are keen that the technology should be supported and developed in a responsible environment so that its benefits can be realised.

Dr Niakan: Genome-editing in human embryo research has the potential to be transformative in enabling us to understand fundamental, basic processes of human development within the first week of development. That encompasses the time from immediately after the egg is fertilised and divides to make two cells, four cells, eight cells and ultimately approximately 200 cells just before implantation. Those 200 cells have the potential, if implanted, to continue to develop. We study them within the first week of in vitro development.

A subset of approximately 20 cells within those 200 cells has the unique potential to give rise to the embryo proper—the foetus. At that point, the unique 20 cells do not have a morphology as such. The 20 cells are called epiblast progenitor cells. If they were established in vitro, they would have the potential to give rise to embryonic stem cells in a petri dish. The way genome-editing could enable us to grasp the basic process of how those 20 cells are allocated and set aside is fundamentally important for our understanding of stem cell biology.

At the moment, we know that in early human development there are critical decisions somewhere between the eight cells and the formation of 200 cells—technically referred to as a blastocyst—that allocate and set aside the 20 epiblast progenitor cells that have the potential to make the embryo proper, and the other 180 or so cells that have the potential to form the placenta. We do not know which are the critical genes responsible for that early decision.

The reason why that is so important is that we know the formation of the blastocyst is quite inefficient in an IVF clinical context, and one out of two embryos fails to reach that stage. Of the embryos that form the blastocyst, one out of two fails to implant and continue to develop. We need to gain quite a lot of information to enable us better to understand that early developmental process.

Q190 **Chair:** Obviously, you are approaching this from different angles. In terms of widespread clinical use and the transformative effect it could have on patients—you have already said this is what people are waiting for patiently—when do you think it will realistically be a widespread therapy that will be available for all who need it?

Professor Qasim: That is a very big question. I would focus on what we can do and what is achievable in the next three or five years. At the

moment, we are focusing on therapies for cancer, for example, where we collect white blood cells and reprogramme them to fight leukaemia in particular. The results of those kinds of studies are quite impressive. We are getting very high remission rates, but we realise that it is very difficult to make those kinds of therapies for each individual patient. You have to collect cells, bring them to a laboratory, engineer them and get them back to the patient. It takes 10 or 14 days and costs tens of thousands of pounds per patient, so the first application of the editing technology has been to introduce extra measures in those cells to make them universal. One donor's cells can be given to a dozen, 20 or 100 patients, and that will change the economic argument for those kinds of therapies. Those trials are getting under way now. Formal phase 1 trials are under way in London for the first time to assess that technology, and we will have some answers towards the end of this year and the middle of next year. The plan would be to put those into larger phase studies.

The technology is not standing still. The tools we have used to treat the first patients are not necessarily those we will be using in two, three or five years' time, because they are evolving so quickly. We started off with a reagent called TALEN, and in the laboratory we are now on to something called CRISPR, which is pushing fast into clinic, and we expect applications for that kind of technology within the next year—similar to the kinds of applications I am describing. Your question was, when will it be available more widely? We will have to learn from the first applications, which are quite carefully considered and are in the patient for a period of time, so that we can assess the response and so on.

Alastair Kent: I am not a medic; I am not a scientist. Our members are hopeful that we will see progress and that a growing number of clinical applications will become available over the next three to five years perhaps, but they have been here before in terms of the promise of technology being, as it were, overstated in the time it will take to bring it to the clinic. We are optimistic that there will be an opportunity to treat an increasing number of diseases, moving out from the rare cancers and so on to other forms of genetic disease. On the other hand, it is more important from our members' point of view that we do it right than we do it quickly.

Q191 **Graham Stringer:** Dr Niakan, I know that your research focuses on the first seven days. What are the potential implications, benefits or problems in extending the 14-day rule?

Dr Niakan: In our specific research area, we focus on the first seven days because that is the critical stage when those unique 20 cells arise. We are interested in how they arise and their implications for stem cell establishment and derivation. That is the critical time window in which those developmental events occur. That is the main focus of our research. It may be that certain aspects of our research would also benefit from an additional few days, between seven and 14 days, when we gain insights into how those cells become slightly more specialised.

Beyond that, our research would not immediately benefit from extending that.

That said, there may be other investigators who could gain insights into how, for example, germ cells, egg and sperm cells, arise in a human context, if the 14-day rule were to be extended. That is just one example. Our specific research focus is on how those specialised unique embryonic stem cells arise, and that occurs within the first seven days of human development.

Q192 **Graham Stringer:** Professor Qasim, do you have a view on the implications of extending the 14-day rule?

Professor Qasim: That is not an area that I think is relevant to our practice. We are at the clinical end, pushing things out as medicines and therapies. Questions around how you modify embryos and so on are not really something I can comment on.

Q193 **Graham Stringer:** In your introductory answers, you talked about being able by genome-editing to stop the development of particular diseases in children. Do you think we are going to move past that point, so that you can look for genetic dispositions to cancer, diabetes and so on? Do you think we will move into that area?

Professor Qasim: At the moment, we are focusing on conditions where we know a single gene is affected, probably in stem cells. By stem cells, I mean cells taken from the bone marrow that can repopulate the entire blood system. Those are ideal conditions to try to fix by using gene-editing technology. We already have a programme of gene therapies where genes are added back to cells to correct them. Those are rare immune disorders. Some are now reaching the stage where they are beginning to become licensed medical products. Companies are taking them on to develop them into therapies. Our focus, and where the technology will be used, will be on single disorders where we have identified one gene that is involved and we are trying to fix or replace that single gene. It is more sophisticated to try to alter multiple genes. You were talking about a predisposition to various conditions such as diabetes, asthma and so on. That is much more challenging. Our focus in the foreseeable future is on single-gene disorders.

Q194 **Graham Stringer:** You see that as long term.

Professor Qasim: That is a much longer-term ambition.

Q195 **Graham Stringer:** Finally, I have an ethical question. Do humans have the right to edit their own genes and those of their offspring?

Professor Qasim: I can think of very particular circumstances where there would be justification for doing that—in particular, as we have heard, genes passing down through generations causing very debilitating serious disease. In those situations, it is very hard to argue against wanting to try to correct aspects that are causing that amount of disease.

Alastair Kent: The simple answer to your question is: under defined circumstances, absolutely. You have to put yourself in the position of a couple with a child who is going to have a short life affected by multiple hospital interventions for which nothing effective can be done, and there is no disease-modifying therapy available. That is the worst possible outcome for any parent. No parent has a child in the expectation that they will suffer that kind of experience.

If this technology were to provide a safe way of preventing the harm that the malfunctioning gene brings about, it would radically transform the situation for many patients and families. It would enable them to contemplate having children who would potentially grow up healthy and free of the disease, without the necessity of having to consider antenatal testing and the termination of a wanted pregnancy. It is potentially a very liberating technology for families, and brings with it considerable expansion of opportunity for families who may currently choose not to have children because of the risk of transmitting lethal diseases to them.

Q196 **Chair:** I do not think anyone would deny that that would be a good use of the technology, but is there a limit to what we should be using it for? Are there things we should not be worrying too much about, although we could?

Professor Qasim: I am not quite sure how to answer that question. Obviously, there can be considerations that you do not want to try to confer properties that are not naturally present. You could think about athletes doping and that kind of thing, but that is not something we would be contemplating.

Q197 **Chair:** I meant in the treatment of disease. Are there diseases that we perhaps should not be focusing on eradicating, because they are not life-limiting or life-threatening, but we could at some point edit them out?

Professor Qasim: That is a broader question for society as a whole. We really are focused on the patients in front of us and the conditions we see causing disease and disability at the moment.

Alastair Kent: The sort of things you might be thinking of are diseases that would be controlled by a very large number of genes interacting. We are a very long way from being able to see this technology being developed to the point at which that would be feasible. It would not happen overnight; there would be warning of the direction of travel, such that if it was felt to be desirable to restrict or regulate it in some way there would be ample opportunity to take the necessary steps to bring in that kind of regulation.

Q198 **Derek Thomas:** Mr Kent, my question follows on from that. I would be interested to know how we enable open and informed debate about gene-editing, particularly among scientists, policy makers, patients and the general public. Is a lack of knowledge among non-scientific groups hindering progress in the field?

Alastair Kent: Yes. There is considerable confusion out there, even among the patient community who you might assume were a relatively well-informed group of individuals. There is confusion about genomics, genome sequencing, genome-editing and other techniques such as the mitochondrial transfer process and what have you. In certain elements of the media those terminologies seem to be used interchangeably, almost as if they were the same thing. There is a very important need to be absolutely clear as to what you are talking about and what are the opportunities associated with those particular types of technology.

To give you an analogy, genome sequencing gives you 3 billion letters. You then need bioinformatics, clinical interpretation and so on to turn those letters into a book. With 3 billion letters you can write an awful lot of different books, but genome-editing is what you can do with the information in the book. Clearly, they are very different things. They have applications. With whole-genome sequencing you can provide precise diagnostics; you can work out the disease pathways; it can lead towards innovative therapies; and you can give information to patients and families about their future. Genome-editing is, if you like, the other end of the spectrum. You have tools that will enable you to change the information in the book for the better.

Q199 **Derek Thomas:** Do the things you have described arise because of lack of knowledge, or almost a deliberate attempt to try to slow progress through ideological or even faith-based resistance?

Alastair Kent: I do not think it is a deliberate attempt to slow the process of developing and advancing the research and the clinical opportunities. I think we have devoted insufficient resources to making sure that people are able to understand the concepts and distinguish between the different processes in a straightforward and comprehensible way.

Q200 **Derek Thomas:** Are the needs and sensitivities of pre-existing communities of genetic disease sufferers being considered properly? Would money be better spent on treatment of those groups rather than prevention in their offspring? Is it one or the other?

Alastair Kent: I do not think it is an either/or situation. Of course, for people who are alive today with life-limiting genetic diseases, there is an urgent need for them to receive timely and high-quality healthcare that provides them with the opportunity to enjoy as good a quality of life as possible, but our opportunity to intervene is constrained by our lack of knowledge. Many families, given the opportunity not to have to experience the need for high-quality clinical care because they have a profoundly disabled child with a genetic condition, would rather see progress moving in that direction, although until it does we need care and support.

Q201 **Derek Thomas:** How can we best embed genome-editing into the healthcare system and realise the benefit for patients?

Professor Qasim: At the moment, NIHR is supporting me, for example, with a programme of funding to develop the next phase of gene-edited immune cells. Those kinds of funding pathways are now critical to lift the developments out of the basic science laboratories, identify the ones that can be used for therapies and bring them into the clinical arena. We need people and expertise to understand what is usable, how we are to apply it and in what situation. There is funding to cover that bridge.

Other aspects are needed. The UK has set up various programmes to develop cell and gene therapy—the catapult and so on—but the amount of spend is nowhere near as high as other countries are putting in. Some commercial funders and private companies are putting large amounts of money into developing those kinds of platforms. It may well be that that is where the big jumps will come from, after the initial translation steps.

Dr Niakan: On human embryo research, it is considered internationally that the UK is the world leader and the best place in the world to conduct such research, given the very strict oversights, clear regulatory procedures and continued auditing of what is happening in a research context. The other additional huge benefit is the ability to horizon scan, looking for new technologies and developments, and having proactive regulations that address those key questions. Genome-editing is a very good example of that.

In 2009, there was a very carefully considered discussion by the Human Fertilisation and Embryology Authority's scientific and clinical advances advisory committee, their horizon scanning panel and their ethics and law review, where they anticipated the potential for genome-editing to benefit basic research. That shows that, when our application for a licence was considered, the justifications for the work had been considered many years before us, and there were very proactive regulations around the area that enabled us to conduct the research in a legally compliant way. That shows the strength of the regulatory process here.

Q202 **Chair:** Perhaps you would care to comment a little bit on how we engage in debate around the area you are researching, and how informed the public need to be about what is and is not possible and about what you are doing. Do you have a view on that?

Dr Niakan: It is essential. The foundational research we are doing at the moment can very much inform public debate about what is possible given the current technologies and that, as new technologies are developed, they are carefully considered in a regulatory framework. That is quite appropriate. In terms of enabling additional public debate, it is important that we as scientists collectively and policy makers allow that public debate to occur in a transparent way. There are very good precedents for this in the UK in mitochondrial replacement therapy. The HFEA had a very proactive approach in leading the public debate on that issue.

Q203 **Chair:** Has lack of understanding and scientific knowledge at any point

hampered your research thus far?

Dr Niakan: At the moment, no, because, thankfully, I think that internationally there is consensus for the support of basic research of the type we are doing, and there is a clear distinction between basic research and germline genome-editing for future debates. On foundational research, as an international community we have all agreed that it is quite important to inform public debate about what might be possible in the future.

Alastair Kent: For the information of the Committee, Genetic Alliance UK, in partnership with the Progress Educational Trust is currently undertaking a series of activities to consult our members and the public about what they understand, and how they would like to see information communicated to them in order to be able to appreciate the nuances. We are undertaking focus groups, online surveys and so on to try to establish that. We will be publishing a report in due course.

Chair: We look forward to seeing that.

Q204 **Chris Green:** There is always pressure on resources and holding down costs within the health system. Mr Kent, what benefit is there in using novel gene therapy techniques rather than traditional and perhaps more widely available treatments?

Alastair Kent: If this technology works, it should be a one-time fix for particular conditions. At the moment, we are seeing a number of therapies for rare genetic conditions being developed by industry, but they tend to be treatments rather than cures. They are lifelong therapies. They may arrest the trajectory of the condition, but they do not necessarily reverse it and reinstate functions that have been lost.

From the point of view of the individual—the patient—there is the prospect of transition from being in a state of chronic disease to being in a healthy state. Professor Qasim mentioned the immuno-deficiency therapies being developed at the Institute of Child Health, which have transformed, for children who received them, life expectancy of a few years to apparently a normal life expectancy, free of disease. It is the difference between being a chronic patient, with continuing engagement with health and support services throughout the duration of life, to a life potentially unencumbered by that. Obviously, the implications for the health service are that there is a one-off fix rather than a continuing commitment to treatment and support.

Professor Qasim: The comparative treatments might be, for example, bone marrow transplantation, costing hundreds of thousands of pounds; enzyme replacement therapy, which at the moment has a recurring cost of tens of thousands of pounds per year; and solid organ transplants. They are all expensive, high-cost treatments, and we would expect some aspect of gene engineering to allow the costs of those kinds of treatments to come down.

Q205 **Chris Green:** Just as with conventional treatments, there are side effects. What is the risk of so-called off-target events occurring in research and clinical practice?

Professor Qasim: That is an important question. The reagents at the moment have been studied quite extensively in the laboratory, and we try to understand the frequency of those off-target events, and events that are on-target but cause side effects. Sometimes we are not 100% sure what other effects may be caused in addition to the ones we want to see. The first application of cells that we engineered and gave back to patients was time-limited. We left the cells in the patient for a period of time and then they were removed. As confidence grows and we understand the implications, I am sure experience will build over time. The technologies we have to understand off-target effects—the sequencing technologies—are improving all the time; so, we can have more detailed signatures of what we have actually done.

Ultimately, we will not know until we have had long-term follow-up of the patients. The ones we are treating at the moment are going into what we call long-term monitoring studies that last 15 years. We expect over that period of time that, if anything is going to manifest, it will declare itself.

Dr Niakan: It is essential that basic pre-clinical studies continue and we learn a bit more about how the specific methodology for targeting genes occurs. What are the key reagents we need to be most efficient and efficacious in those targeting events? Looking at the so-called guide RNAs that direct the enzyme to a specific DNA sequence, it is still not entirely clear what predicts whether a specific guide RNA is the most efficient and precise. That is where screening those various components in other cellular contexts is extremely important, before they are used on sensitive material like pre-implantation human embryos in a clinical context. Those foundational studies have to be at the heart of any research project.

Q206 **Chris Green:** My final question is on the current regulatory environment. Are there any shortcomings or anything that needs to be improved? Given the triggering of article 50 today, would post-Brexit Britain be a slightly better place? Would you be able to influence British legislation in the regulatory environment?

Professor Qasim: MHRA over the last 15 years or so has had a very progressive attitude to taking some of the new therapies into trial. We have had an active dialogue; discussions have gone backwards and forwards. That has enabled us to take things into phase 1 trials in a relatively smooth fashion. Colleagues trying to undertake the same work in other European centres have been held up because the interpretation of the EMA regulations in those countries has been different or maybe more onerous than in the UK.

Q207 **Chris Green:** There is already a variation.

Professor Qasim: There is certainly a good environment in the UK to undertake phase 1 studies. The advantage of the NHS is that it is an enormous resource of very homogenous therapies being applied across the country; so, access to patients and trial patients in the UK is good.

Q208 **Chris Green:** Are there any shortcomings at the moment?

Professor Qasim: There will always be shortcomings in trying to develop things that go into phase 1. There is access to the raw materials we need to develop these products, a lot of which come from overseas. We take reagents from Germany, France and other countries in Europe. I admit that I am worried about what will happen when the environment changes and we still have to import those materials and pay for them, with changes in currency and so on. We have already seen that in some of our work.

There may be advantages. Going forward, the UK may be attractive for undertaking these kinds of studies, but there is a big unknown question about how the replacement structures for the EMA to regulate new medicines will be put in place, and whether drug companies—pharma—will want to operate in the UK and Europe at the same time, or whether they will try to do trials in Europe first and then bring it to the UK. That is a big unknown, and we do not know the answers.

Dr Niakan: In terms of expertise in the STEM field—science, technology, engineering and medicine—it will be very important to safeguard, if possible, the ability of individuals who have specialist skills to continue to work in the UK. That is really important.

As to research funding, because the EU fails to fund any human embryo research, whether it is genome-editing, stem cells or basic molecular biology, one benefit to the UK would be if there was increased funding in science. That area of research could flourish, because we would be eligible to apply for that type of funding.

In terms of the regulatory process, our research is overseen by the HFEA as well as the Research Ethics Committee to give us advice about patient information sheets and consent documents. Those two regulatory authorities function in parallel to oversee the types of research we do. There was a question about regulatory procedure, but it was a very robust and fair system. That system is emulated. Individuals, regulators and policy makers external to the UK look to the UK to see how policies are established here, and in effect copy them elsewhere, because it is so robust. That is a benefit.

Alastair Kent: As far as early stage clinical development is concerned, opportunities could be created outside once the Brexit process has been completed, but if the technology is to develop to the point at which it is commercially applicable in healthcare, from an industry point of view I think they will need to see a European market for it, not just a UK one.

It is important to acknowledge that both the MHRA and the HFEA have been very interactive in their discussions of how to regulate in this area. They have reached out to stakeholders—patients, families, academics, clinicians and other interested parties—and it has been possible to have a very open dialogue. That has enabled us to have the proportionate and appropriate regulatory framework that many of our colleagues elsewhere in the US and Europe see as highly desirable.

Q209 **Carol Monaghan:** A lot of my questions have already been answered, but it is good to hear you echo some of the concerns of the Committee, Dr Niakan. This Committee has been very strong in pushing for the rights of EU nationals working in the science and technology field. You said the EU will not fund any sort of research in this field. Is that at all? Is any Horizon 2020 money going to any groups on this?

Dr Niakan: Horizon 2020 funding is ineligible for human embryo research of any kind whatsoever. If the UK could in some way make up for the loss of EU funding by increasing science funding within the UK, it would enable this area of research to flourish.

Q210 **Carol Monaghan:** That is interesting. I had not realised that. I am sure the Chair knows that, but it was new to me. Thank you.

You have all mentioned issues about licensing and that the environment here is better than it is in other areas of Europe and in the US. Are there any issues around licensing that could be improved to make life easier for you in terms of both research and the clinical work you might be doing?

Professor Qasim: I would say the picture is probably about right at the moment. It is thorough; extensive reviews go on and there are external inspections and so on. The environment is allowing us to proceed with caution on the new technologies; so, I would say it is pretty good at the moment.

Dr Niakan: I agree. I would echo that. It gives the public confidence to have continued inspections, audits and licence renewal applications via two regulatory authorities. We ensure both that patients are properly informed in their consent and that the research is conducted in a way that is legally compliant and consistent with what the public have agreed.

Q211 **Carol Monaghan:** Are there any improvements that we should be making or that the Government should be looking at?

Professor Qasim: I would say it is about right at the moment.

Alastair Kent: Where innovative technologies come along that potentially challenge the existing framework, both the MHRA and the HFEA have been quite proactive in saying that essentially we are stretching the elastic to the point at which we need to look perhaps at modifying the framework to take account of things we hitherto thought were not biologically feasible. Mitochondrial donation and transfer work is a very good example of that. There was a very strong public engagement

programme undertaken by HFEA to help them reach a conclusion about what an appropriate regulatory framework would look like, and that was used to inform policy makers in this place as to changes that were felt to be appropriate and desirable.

Q212 **Carol Monaghan:** What role do you think the public should play in that? We had an inquiry on science communication and we know there is a lot of misrepresentation of science in the public sphere. Should the public have a role within licensing? Perhaps the concerns of the public should be taken into account.

Alastair Kent: It is essential that there is public trust in the system of regulation and licensing. Bodies such as the MHRA, the HFEA, the HRA and so on stand in proxy for the public that there is a regulatory framework fit for purpose, and that where, in general, there is consensus that things ought to be allowed to happen, they are permitted, and where things ought not to be allowed to happen they are prevented.

When you engage with the public, and patients and families as a subsection of the public, there is generally overwhelming support for high-quality regulated research, even in areas that some might deem controversial or ethically challenging. Agencies such as the MHRA and the HFEA perform pretty well their role as guardians or guarantors of the public probity of research and development undertaken by the academic and clinical community and industry in this country. Many people are completely unaware of it, but if you have an interest and you want to find out how it is done, it is quite straightforward to understand the process. The information is in the public domain and is relatively accessible with a bit of work.

Q213 **Carol Monaghan:** Are you confident that public concerns are taken into account when we consider ethically challenging issues?

Alastair Kent: I think public concerns are taken into account. I do not think public concerns, where they exist, have the power of veto. If there was a very severe reaction to a particular development, I feel confident that the regulatory agencies would not simply adopt a "We know best" approach; they would consider it and determine what would be an appropriate course to follow, whether that was to embark on a better constructed programme of engagement, consultation and explanation, or to seek a change in the regulation to prevent or promote a particular line of development.

Dr Niakan: The Research Ethics Committee application process involved consideration by a wide demographic of the public. It was a diverse committee made up of several individuals from a variety of different backgrounds. Within that context, they were very interested to know how the public would perceive the work, and we had a very open discussion about it: what safeguard measures were in place and how we had considered the views of the public. We articulated that very clearly. That

was a very useful process to go through within the Research Ethics Committee itself.

More broadly, for transparency, all our applications are publicly available online and can be downloaded from the HFEA website for anyone to view and scrutinise, including our inspections and any issues that may have transpired from inspections not only of our research but of all research on human embryos in the UK. It is an extremely transparent process.

Q214 **Carol Monaghan:** My final question is probably directed at Professor Qasim. Are we making the most of commercial opportunities for genome-editing, and are there particular treatments that lend themselves better to commercialisation than others?

Professor Qasim: Over the past five years or so, at our centre we have had quite a lot of involvement with companies coming to us to ask for help in translating some of the developments into new therapies. The clear example is the therapy for gene-editing that got into clinic last year. In making the jump from developments in laboratories into the clinic, there is a lot of translation expertise; so companies are coming for that. There have been three spin-outs from UCL in the last couple of years to take out gene therapy-type projects. They are small, start-up ventures, and it will be some time before they mature and develop into larger companies. There is a definite interest, especially in the anti-cancer-type therapies, where there is a clear market already waiting. There is a route to clinic that can be seen through the various levels of trials and authorisations that are required.

In the US, the first of those therapies is about to obtain licences as medicines; so people can see what in the US would be the reimbursement model and where the profits will lie for that kind of therapy. It is a bit more difficult to see how that will work for some of the rarer disorders we deal with, but certainly larger companies are buying into it. GSK has a rare diseases portfolio and is picking up some of those conditions as well, and we expect to see more of that.

Q215 **Victoria Borwick:** Given the success of your somatic research programme, perhaps you could tell us what you think are the greatest barriers to delivering an effective clinical genome-editing service. What support do clinicians receive? We are quite keen to have some positive things in our report.

Professor Qasim: I can speak about numbers and what is going on in our own centre. We undertake, let's say, 100 bone marrow transplant-type procedures a year. What limits that is the availability of bed space, specialist nursing staff, laboratory processing capacity and all those kinds of infrastructure support aspects. They will all be relevant to delivering the new therapies as well, because they are going to be done in hospital in relatively intensive environments. There will be rate-limiting steps; they will be the limiting factors. The question is how the NHS can cope with these kinds of therapies at the clinical end, aside from us

manufacturing and providing therapies that need their own infrastructure—the clean room facilities, the diagnostics and the testing that goes around it.

At the moment, there is a limited number of laboratories or facilities in the UK that can do that. We have one; there is one in Manchester, and elsewhere in the country new ones are being set up. There will be a period of time before there is enough capacity to address the unmet need. One of the critical things we deal with is that we have to make disabled viruses—we call them vectors—to deliver some of the reagents. The capacity to do that is saturated in the UK; there is a waiting list to try to get into the laboratories to manufacture those types of goods. That needs addressing; it is a bottleneck.

Q216 **Victoria Borwick:** Do you get them from overseas?

Professor Qasim: It is possible to get them from overseas, but it is a global issue. There is a bottleneck in the capacity to manufacture those types of reagents. I expect there will also be bottlenecks for some of the newer reagents coming through, to have them at a sufficiently high grade to be able to use them, certainly for the next few years. Ultimately, it will become unlocked as more people pile in and capacity builds up.

Q217 **Victoria Borwick:** What is the solution for your capacity?

Professor Qasim: Our own centre is building a new research facility, which will have an eight-room GMP suite, as we call it, but it will not be ready for another two years or so. In the meantime, in our own centre we are cobbling things together to try to push through multiple campaigns at the same time for the same facility.

Q218 **Victoria Borwick:** To what extent does the therapeutic use of somatic editing open the door to future non-therapeutic use? Inevitably, one has to get buy-in from the public for the work you are doing. It is very easy to explain to somebody that for leukaemia or a disease they have heard of we are trying various things. If somebody has breast cancer or something, we are obviously making changes. To be able to explain to the public why some of these things are happening, and to take people with you, is very important. Could you give us a view as to what extent the therapeutic use of somatic editing might open the door to non-therapeutic uses? One hears scare stories about designer babies, eugenics and all those sorts of things, but sometimes it is a way of removing disease.

Dr Niakan: In the basic research we do, it is important to distinguish that avenue of research, which is widely supported, and potential alternative uses at the moment. That said, it is very important to engage in an open public debate about alternative uses, with the foundation of knowledge about what is possible at the moment. There is a great need to engage the public very openly in the discourse about sensitive areas.

Q219 **Victoria Borwick:** We have all read about babies with three parents and

things like that, and there does not seem to be total outcry in the media; so, in that sense I think people still appreciate very much the work you are doing.

Dr Niakan: The safeguards in place and the clear boundaries about what is and is not legally permitted, especially in this country, give the public confidence in allowing permissible work to be carried out, and inform the broader debate.

Q220 **Victoria Borwick:** How do we bridge the gap between basic research into genome-editing and clinical delivery to patients? Are our research groups well co-ordinated? What would your recommendations be?

Professor Qasim: We are trying to pull out the best of the reagents that are in development. One of our problems is that the reagents and the technologies are developing so quickly. Every issue of a journal you pick up has some improvement on the technology, and at some point we have to say, "We are going to go with this one and try to take it through into a therapy." By the time we get to the phase 1 trial and the first things are going into a patient, we usually know that there is already a better version in the laboratory, and we are rapidly trying to push that through. There is a hamster-wheel element to it where you are continually trying to keep up.

We have very good links with the university and the basic development scientists who help us take the best of the reagents through. There is an impetus among the funding bodies to pick out projects that have clear applications at the end of development that may be useful for medicines and so on.

Alastair Kent: We also need to think about the workforce we will require to deliver these technologies. At the moment, we have highly skilled experts like Professor Qasim and Dr Niakan, who have spent years acquiring skills and knowledge. Their skills are very rare in the broader medical and scientific community. If this is to become an available therapy for those who need it, we need to think about capacity building in terms of workforce skills and workforce planning.

Professor Qasim: The Brexit issue is very pertinent. Most of our researchers in the laboratories are non-UK, and there may well be an impact if they are not allowed to stay and continue working in this arena.

Q221 **Gareth Snell:** All of you touched on the necessity for high-quality and well-regulated research. Professor Qasim, in your last comment you referred to the internationality of the research being done on this subject. In the research environment, how do we compare with our international competitors? Are we good? Are we great? Are there things we could do better?

Professor Qasim: We are in the top league and compete very effectively with the north American centres. We have had successes where we have managed to break through and get things into clinic ahead of other

groups. That is owing to collaborations not just in this country but outside it, across Europe and north America, where expertise on some of these techniques has been shared quite extensively. You start to worry about how much collaboration and sharing of some of the underlying expertise in technology there would be if barriers went up. For the last two days I was at a meeting in Marseilles for a European collaboration of transplanters. You can see how much data sharing goes on. I expect that to continue; I do not think it will change. What is more of an issue is how we keep hold of the expertise we have built up, a lot of which is non-UK-based.

Dr Niakan: For human embryo research, the UK is arguably the very best place in the world to do it, given the proactive regulatory framework and the safeguards in place. It is important, and it is not a coincidence, that some of the greatest breakthroughs in the field, including IVF and stem cell therapy development, all originated in the UK, as the research is able to flourish within a tight regulatory framework.

Q222 **Gareth Snell:** It is good to know that we are at the pinnacle of that research, but presumably there are things we could be doing better. You must have a wish list of things. Presumably, the north Americans are our nearest competitors. Are they doing things much better than you are? Can we emulate what they are doing?

Professor Qasim: The scale of investment on which they can draw is much greater. You can put zeroes on the ends of the numbers going into some of these technologies. Although we have new companies being spun out, and small ventures are coming out, it would be nice to see some of them being grown and developed in the UK into big players, to take some of the processes right through to wide-scale distribution. The worry is that they will be mopped up and bought, by American companies in particular, and then it will be back to the drawing board to build it up again.

Dr Niakan: In terms of human embryo research, it may be worth considering that a broader discussion has been initiated within the HFEA and other policy makers like the Wellcome Trust about how to make the process of consenting embryos for research fairer and more equitable across the country, so that all individuals and couples undergoing IVF are given equal opportunity to donate research in this area.

Alastair Kent: From our perspective—the patient and family perspective—what will help enormously is greater certainty that, if research translates into clinical benefit that is able to change the course of life-limiting diseases, there is a reasonable prospect of being able to access that intervention through the NHS. Despite things like NICE guidelines, there is still considerable variation in terms of access to IVF on the NHS depending on where you live. Having the confidence that, if something can be done, you have a reasonable prospect that it will be done in a timely and effective manner will help to create a climate that succours research, builds clinical competence and gives momentum to

roll the technology forward in an efficient and beneficial way to address very significant unmet health needs.

Chair: Thank you all for your attendance this morning and your very full answers. It is much appreciated. I am sure you look forward to seeing our report in due course.

Examination of witnesses

Witnesses: Dr Greenfield, Robin Lovell-Badge, James Lawford Davies and Philippa Taylor.

Q223 **Chair:** Good morning; welcome. Thank you very much indeed for joining us for this morning's second panel. To start with, for the record could you introduce yourself and say in what capacity you are here this morning, and who you may be representing?

Philippa Taylor: My name is Philippa Taylor. I am representing the Christian Medical Fellowship where I am head of public policy. The Christian Medical Fellowship has about 5,000 doctor members. It is one of the largest Christian charities; it has the largest representation of Christian health professionals.

Briefly, from an ethical perspective, as an organisation we are particularly concerned with germline modifications that will affect every cell in an adult human being, including germ cells in passed-down generations. That is my particular concern over and above somatic cell engineering. The implications of that will be my main focus today. On Monday, it was interesting to hear Lord Winston talk in a debate about that in particular as a dangerous idea.

Q224 **Chair:** I am sure we will explore that. Thank you.

James Lawford Davies: My name is James Lawford Davies. I am a solicitor and partner at Hempsons, a law firm in London. I am a lawyer specialising in the regulation of human tissues and cells, particularly reproductive and genetic technologies.

Robin Lovell-Badge: I am Robin Lovell-Badge, a scientist at the Francis Crick Institute working on embryology, human genetics and stem cells. I am here because I have helped to organise a number of meetings and committees dealing specifically with human genome-editing, both somatic and germline, so I have accumulated knowledge of what other people think about this as well as what I think.

Dr Greenfield: I am Andy Greenfield. I am a programme leader at the Medical Research Council's Harwell Institute. I run a research programme that is essentially investigating the way genes function during embryonic development, but using the mouse as a model. Our primary aim is to understand human genetic diseases via the provision of high-quality mouse models of human genetic disease to investigate the molecular basis. I am also a member of the Human Fertilisation and Embryology

Authority and I chair its licence committee. I am also a member of the Nuffield Council on Bioethics, and in 2016 I chaired an ethical review of genome-editing.

Q225 **Chair:** Do humans have the right to edit their own genes or those of their unborn child?

Philippa Taylor: I do not believe they have the right to edit the germline genes. We must make very clear the distinction between germline and somatic editing. Somatic editing obviously has issues around safety, but other than that I do not believe it has major ethical concerns. Once we start to edit the germline, I think we are in a very different field. We really should not be doing that. It is a major Rubicon that has never been crossed in the past for very good reason, because once we start editing the germline any changes are passed down the generations. It has absolutely unknown consequences, effects and implications, which raise a huge number of issues, way beyond safety, about the purpose of what we are doing, the bridge to what it might lead and issues around consent. It raises a whole host of ethical issues. The fact that so many countries around the world have legislated on it and have always legislated against it is a very good reason why so many scientists across the globe have said this is not a Rubicon, line or bridge that should be crossed.

James Lawford Davies: As a lawyer, I naturally think about rights in the way they are interpreted by the courts. I would say there is no absolute right to have access to a treatment or technology. There is a right to fair access, but access can be limited by its cost, safety and efficacy, and that is why we have regulators to determine what treatments are made available and to whom. I would say there is no absolute right.

Robin Lovell-Badge: The question you ask reflects an old debate. We have been debating this issue for many years. Any new technology that has come along that could be relevant to the possibility of altering our genes has triggered that debate, but in the past it has always been a possible excuse to say, "We know the techniques are very inefficient and unsafe and of course it would be unethical to use those methods." Now the situation has changed in a number of ways. It has changed because the techniques of genome-editing are far more efficient and precise and allow you to make very accurate changes. We know that from a lot of research done in animals. That is why there are the somatic treatments we have been hearing about. The situation has also changed because we know an awful lot more about human genes, genomes and genetic variation than we used to. If you have had a chance to look at the National Academies report, of which I was part, its view is that now it is right perhaps to unlock the door, not open it wide, to the possibility of making germline changes.

Dr Greenfield: I want to make it clear that I am not here to lobby, and any opinions I express are my own personal opinions. I am not representing any organisations. Clearly, we do not have the legal right at

the moment to edit genes for reproductive purposes. That would be unlawful. A gamete or a zygote that underwent a genome-editing process would not be a permitted gamete or zygote. Do we have the natural right to do such a thing? I am inclined to say yes, but it would be under prescribed circumstances. If we think about what we can do under the HFE Act to prevent the transmission of deleterious mutations that cause severe debilitating diseases, we can already use pre-implantation genetic diagnosis. PGD allows a couple to prevent the birth of a child that would have some of those conditions and they do so by de-selecting an embryo of the relevant genotype.

It seems to me that if the intention writ large is to prevent the transmission of those conditions, another technique that does exactly the same thing, but effects it in a slightly different way, at least has to be on the table in terms of justice. Couples that use PGD to prevent the birth of children with serious conditions are acting out of compassion, not from eugenic thoughts or a purely selfish desire to have an easy life. I believe they are acting out of compassion, so it seems to me to be entirely reasonable and plausible that genome-editing could be performed as an act of compassion, indeed an act of love. I see no contradiction whatsoever.

Philippa Taylor: In response to one of those comments, it is important to distinguish that technology has changed and advanced hugely, but that does not mean the ethics have changed. That is a big, important distinction that needs to be made.

Q226 **Chair:** Thank you for that. The US National Academies noted in a report that genome-editing should be used only "in the absence of reasonable alternatives." Do you agree with that?

Robin Lovell-Badge: I agree with that. If there were clear safer alternatives, they should be used in preference. You would use genome-editing only where the condition you were trying to treat or prevent was a serious genetic disease. I think we are very clear about that in the report.

Q227 **Chair:** Does screening not find those conditions?

Robin Lovell-Badge: You could, for example, do either pre-natal screening or pre-implantation genetic diagnosis and then select embryos in many cases, but not all. There are cases where you have individuals who are homozygous for a dominantly inherited genetic disease. Huntington's is one example, but there are many others. There are cases where both parents are homozygous for recessive mutations, and they could not have a disease. There are other situations where it is very hard to obtain enough embryos to select appropriate ones that would be free of a disease. That could be in cases where the mutations may also affect fertility—for example, older women with BRCA1 mutations—or cases where you need to select more than one trait at the same time.

For example, in relation to saviour siblings, a study was reported at a summit meeting we held in December 2015 in Washington DC on work done to try to use PGD to select embryos for the purpose of a saviour sibling. Eight families were involved in the study and a huge number of embryos were obtained. You can follow the graph down. With each family having an average of five cycles, it ended up with only one baby being born who was an appropriate saviour sibling. Only one of the eight families benefited, so incorporating genome-editing into that scheme would have allowed more to benefit.

At the moment, there may be rare cases where you can say a parent is homozygous or both are homozygous recessive alleles, but that is no reason not to be concerned about finding a solution if they want to have a genetically-related child. As other techniques like conventional medicines and somatic gene treatments increase, there will be many more individuals where the homozygotes are dominant genes, or both parents are homozygous recessive alleles who reach reproductive ages, might want to have children and would not want to pass on even one single copy of an abnormal allele.

Dr Greenfield: Although it is too soon to say, it could be that the techniques of genome-editing improve to such an extent that they become utterly safe and efficacious, and would probably be superior in that sense to PGD, because PGD requires taking cells from the embryo, usually trophectoderm cells—cells on the outside. If you could avoid taking cells from the embryo, that is probably the best thing.

Q228 **Chair:** Do you want to comment, Ms Taylor?

Philippa Taylor: I think alternatives is a really important issue. I do not think it is the only one, but it is very important because there are alternatives. As we have heard, PGD and pre-natal screening will not cover all cases but it will certainly cover the majority of them, but there are other alternatives—for instance, egg donation and adoption. It is interesting that some ethicists say we have to be careful that in looking at adoption we do not undermine adoption itself as a good procedure. Some people say that maybe for some couples there is a duty to adopt. That is a very different way of looking at things, because in some ways we undermine the importance and value of adoption as an alternative.

The other really important thing in all of this is that it is very easy to slip into "parents need a genetically-related child." There is a very big difference between need and want. It is important that we distinguish the two and challenge the idea of prospective parents needing a genetically-related child. The reality is that it is want. I understand that want; it is not something I would in any way underestimate, but it is a want rather than a need. It is important to note that, especially in view of the implications of going down this line.

Q229 **Carol Monaghan:** What should be the ethical basis of the principles by which we govern genome-editing? How do we distinguish between what

is acceptable and what is unacceptable?

Philippa Taylor: I am happy to let someone else go first and then I will chip in.

Dr Greenfield: It is very important that our individual ethical commitments are on the table. For instance, if one believed that a single cell, a human zygote, had all the moral status of an adult human being, clearly you would not be able to do my job. I license human embryo research that results, obviously, in the destruction of embryos. If I felt that ethically that was homicide, I would not be able to do it, so clearly I do not accept that.

My beliefs ethically are hugely complex; you cannot possibly expect anyone to unpack their ethics in 30 seconds. They would be, vaguely, commitment to human flourishing and to the reduction of the burden of human existence, which in part consists of the impact of heritable and non-heritable diseases. I have the sense that if we can do something, either scientifically or non-scientifically, to reduce the burden of human existence and promote human flourishing that would be a good thing.

Q230 **Carol Monaghan:** At what point do we move into the unacceptable area?

Dr Greenfield: We have to look at the problem as a spectrum. We can all think of biological traits and conditions that are inherited and are so appalling they barely allow us to consider them for too long. All of us have probably met individuals who have suffered such experiences, with children who die within days or weeks of birth. The biological contribution there is 100%, and there is very little that can be done.

Earlier, Stephen Metcalfe asked whether there are certain conditions that we should not be attempting somehow to treat or do away with. There are some biological conditions that can lead to a shortened lifespan; for instance, being a girl in some countries will lead to a very short lifespan and potential infanticide, and being part of an ethnic minority would have the same effect in certain jurisdictions. Sometimes there are biological properties that do not innately and intrinsically have any negative effect; it is society that is the problem. It seems to me that there is a large area in between, where we have to consider, on a case-by-case basis, whether, for instance, it would be justified to prevent the birth of a child with a condition, or whether it would be better to focus our attention on making life better for those individuals, so that there was not such a disability, in effect.

These questions are now very much in the literature. You can open a journal and read those kinds of discussions all the time. As a biologist, I want to focus on the biological givenness of suffering and pain. It is a reality; it is not all socially constructed. It is important to say that, but it does not mean that we do not have obligations to individuals with disability to make their lives right now the best they can possibly be. I absolutely buy into that, but I do not see a contradiction in giving the

choice to parents not to have a disabled child and also loving and caring for disabled adults, and giving them every right they are entitled to.

Robin Lovell-Badge: I think you are asking where to draw the line between treating disease or suffering and additional things like designer babies, enhancement or whatever. In the National Academies report we set out a series of principles. Details were added to those with respect to genome-editing. If you followed those, you would end up not having to worry too much about either designer babies or enhancement. Basically, we are saying that it has to be for treating or avoiding serious disease. If you are to make a change in the DNA sequence, it has to be the common version of that particular DNA sequence in humans. For example, you could do genome-editing to increase muscle mass somatically or through the germline just by mutating a gene called myostatin.

Of course, some people might want larger muscles to give them an unfair advantage in sports. That would be felt unacceptable. If you simply mutated the gene to confer an advantage like that, I think any regulator would say that should not happen. If you have a robust regulatory system and good oversight, you can prevent misuses. The HFEA is very used to regulating pre-implantation genetic diagnosis, and, as Andy said, if you have that sort of regulation, you do not end up with any abuses.

James Lawford Davies: The way we regulate embryo research today reflects the ethical principles established back in the 1980s when Baroness Warnock's commission first looked at how this field should be regulated. It was acknowledged from the outset that there could never be consensus about embryo research and the status of the human embryo. Instead, there was a compromise, which is reflected in the regulations: the embryo has a special status, but it is subject to very strict regulation and inspection. It may be used for research purposes but only within that regulatory framework. If you stray outside it and use a human embryo in a research project without a licence, you commit a criminal offence.

In order to obtain a licence, you have to satisfy the HFEA of a variety of different criteria, which again reflect that special status and the Act's ethical underpinning. It must be for a purpose that is set out in legislation; it must be a necessary or desirable project for one of those purposes; you must establish that it is necessary to use human embryos rather than some other material; and you must have ethical approval from a recognised research ethics committee. All of that structure reflects the fact that Parliament recognised that there was a special status for the human embryo and decided to subject it to the sort of tight regulation that we have.

Philippa Taylor: You are asking a huge question. It could probably do with a parliamentary committee of its own. Very simply, and maybe more practically, the ELSI principles are important; ethical, legal, social and safety issues are useful and important in driving some of our thinking on it. Issues around the long-term welfare of the child are important too.

It is also important to warn that utilitarianism is not a good principle to go by. I see a danger of that in the way we are progressing at the moment, very much ignoring the means for the ends. There is a danger that we are looking too much at the ends and not at the means of how we are doing that. I have a lot of concerns about the ends themselves, but we must not ignore the means—the way the research is done as well as the purpose of that research.

Issues have been raised about treatment. It is important to mention that when we are drawing lines they are often quite arbitrary, and it is very easy to cross a line. At the moment we have a very clear line that says no to something like germline. Once we cross that, even if it is for treatment purposes rather than enhancement, it is very difficult to hold the line. It will become a very grey line and one that is easy to cross, whether it is for different disorders or for less serious disorders. It can also be a bridge for other countries to use the technology that is developed. Once the current Rubicon is crossed, the line to be drawn is very arbitrary.

The treatment enhancement distinction is a useful one in many ways, but it is also quite limited. As has been hinted, some treatments would be an enhancement for someone else—for instance, muscle mass or whatever. It is also quite a grey line. There is some usefulness in it, but it is quite a grey line. The difference between treatment and enhancement is, therefore, not easy to regulate in order to hold that line, so it is quite a difficult distinction to draw in regulation. A much better distinction is the one between somatic and germline. Ethically, I would by far prefer to maintain that line and principle rather than treatment enhancement; otherwise you basically start crossing the bridge, because you say, "As long as something can be used for a therapeutic purpose, that is okay." But how do you decide what is a therapy, what research can be done for which disorders and which diseases? After that, it is very arbitrary.

Q231 **Carol Monaghan:** I am going to come to some of that.

Robin Lovell-Badge: You can use somatic treatments for enhancement as well, so that does not get rid of the issue of enhancement. What is important is that it is a risk-benefit analysis. I would hope that the risks of doing any form of enhancement are too great for any regulator to approve.

Q232 **Carol Monaghan:** I asked the previous panel about treatments. If I could change tack slightly, how do we decide who gets to use genome-editing? Are we going to use it mainly for conditions such as cancer where probably a lot of people would benefit, or can you see a role for it in the much more expensive treatment of people with genetic conditions? If anyone has particular views, fine; I don't need to hear from every panel member.

Robin Lovell-Badge: You will know from your previous work on human genomes and genetic disease that there are an awful lot of genetic

diseases. If there are 5,000 different genetic diseases—we are talking about simple Mendelian ones—in theory an awful lot of people could benefit somehow from ways of treating those genetic diseases. Each one may be quite rare, although there are some much more common genetic diseases, but the total number of people who suffer from genetic disease may be as high as 5%. That is a lot of people. Cancer is an obvious case as well.

In terms of somatic treatments, a lot of people could benefit. The initial cost of using genome-editing for gene therapy may be high. I hope that will come down, as we have heard earlier today. The cost of doing a germline intervention is a one-off and, hopefully, would not be so extreme. It should be reasonable. It would certainly be more than a standard IVF or PGD, but it would not necessarily be a huge amount. That is a one-off treatment that would benefit the individual born and perhaps their children. Therefore, that may free up costs to be distributed more widely.

Carol Monaghan: If no one has anything to add, I will move on.

Philippa Taylor: Can I add something briefly? I think we have to be careful. If we are looking at germline-editing, are we talking about a treatment? We are not really talking about cures. If we were talking about cures, we would be looking at those who have the disorder and are already born. I am not saying this is right or wrong; you know my position. I am saying there is a distinction between not creating a child that is born with a disorder and treating an embryo, baby or whatever with that disorder. It is important we do not always use the word "cures" when they are not cures; they are just preventing someone with that disease from being born.

Dr Greenfield: I agree. The treatment is usually for the mother; it is the woman's body that is the basis of much assisted reproductive technology. It is true that the treatment is for the mother.

Q233 **Carol Monaghan:** Dr Greenfield, to what extent does genome-editing have implications for animal research? We know that biologically similar testing needs to be carried out to confirm the feasibility of a particular treatment. Is this going to open the doors for more clinical trials, possibly on humans?

Dr Greenfield: There are probably two areas to look at. One would be basic pre-clinical research of the sort I do myself involving mice. There, genome-editing has been transformative. You probably hear that word all the time and it sounds a bit sensationalist, but it is true. If we think back five years, what we could do in generating a particular model of a human disease in a mouse was limited to certain slightly clunky old technologies involving stem cells, screening, injection, chimeras and endless rounds of breeding. Now it is possible to get 80% to 90% of a litter with the particular genetic defect you have engineered.

The problem is that there is push and pull. We can use many fewer mice by using genome-editing than we hitherto would have done with older technologies. The problem is that it has become more attractive. Many more people have now seen the powerful things you can do. You can introduce a particular point mutation into the mouse that models a particular point mutation that potentially causes a human condition—if I say anything that does not make sense, just tell me. The problem is that it is not always easy to tell which mutation in that human genome is causing that condition. The mouse work allows you to ask whether, if you make that change in the mouse, you get a similar condition. These things would have been almost impossible five years ago or would have taken too much time and money. They are now doable, so it has been transformative in that sense.

Moving beyond the laboratory animal, the Nuffield Council on Bioethics will soon start a whole programme looking at the potential of genome-editing in livestock, with a particular view to considering food security. Profound ethical issues arise even in the context of discussing food safety and security. There is no doubt that genome-editing at the very least has given us an opportunity to revisit our attitude towards animals. We have to revisit it. For instance, we have to make sure that we do not intensify farming any more than I suspect it has already been intensified. We do not want to use genome-editing as a way of heaping misery upon animals. Nobody I know who uses animals wants to do that, but it is nevertheless an incredibly powerful technique for the provision of pre-clinical models.

Q234 **Carol Monaghan:** Do you have a brief comment, Mr Lovell-Badge?

Robin Lovell-Badge: You can add to the pre-clinical models. The animal models are important because they allow you to test the role of a gene in the whole physiological context of a live animal. There is a lot of research using genome-editing on human cells in culture as well. That includes induced pluripotent stem cells, which allow you to have a patient-specific pluripotent cell line from which you can study the role of a particular gene, using genome-editing techniques to correct the suspected mutation to see whether you rescue a phenotype in vitro. They are sometimes incredibly powerful techniques.

Q235 **Chris Green:** State-sponsored eugenics has rather fallen out of fashion. What are the risks of a permissive regulatory regime? Might we see the introduction of so-called liberal eugenics?

Philippa Taylor: Eugenics is an interesting one, isn't it? It is bandied around as a term. It is an important issue to consider, whether or not you term it eugenics. I am concerned that, once we allow the genetic manipulation of human life, it will be almost impossible to hold the line to prevent it being used for other diseases. Once we start to modify human lives, I do not believe we can realistically hold a firm line. We face a eugenic future—in other words, one where we are attempting to improve humans by choosing their genetic traits. That is a really important point.

In some ways, this is a new form of eugenics. I do not like using that term, particularly because it has so many connotations, but the point is that it is distinguishing between those who are fit and unfit and it is all about improving future people. That is what I am concerned about. It builds on the whole concept that people do not just expect the right to have a child; they are now starting to expect the right to choose a particular kind of child. This starts to turn children almost into modifiable products.

That is where we are starting to go. It is not just me and a few others who are saying this; lots of people have warned about a possible eugenic future, including Lord Winston. He talks about how genetic technologies could be exploited in the future to produce more intelligent, stronger and attractive offspring. Current controls will not be able to keep pace; people will want to modify their children to enhance desirable characteristics. We are not there yet, but he is warning that this is a bridge. He is warning about the long-term implications.

Stuart Newman, professor of cell biology, has said that the attempt to improve future people is not medicine but a new form of eugenics. It is a term that is used. You know that Savulescu has talked about it and advocated the use of germline technology for enhancing and developing certain characteristics in people. I think it is a real danger. I do not think we are there yet, but I see it as a huge concern for the future.

Q236 **Chris Green:** If you share those concerns, how do we legally stop this happening?

James Lawford Davies: I think we have already. Part of the answer to the question goes back to your original question. I do not know whether we have a permissive regulatory environment; we have a potentially permissive one, but we have chosen for many years to regulate this field, particularly the use of human embryos, whether for research or treatment, in a very tight, robust way, and to subject it to constant scrutiny, inspection, oversight and monitoring by an independent regulatory body. You can look at the way in which pre-implantation genetics and, more recently, mitochondrial donation have been regulated.

Key to that regulatory framework is the distinction between therapeutic and non-therapeutic use. Those treatments are available only where there is a significant risk of a child being born with a serious disease or permutations of that. At the moment, the use of germline gene-editing would not be permissible. It would be a criminal offence to use an embryo that had been subjected to germline gene-editing in treating a woman. In the future, if it were to be permissible, I am confident that it would be subject to an approach in regulatory restriction similar to the one we see in relation to PGD and mitochondrial donation, where it is strictly limited to therapeutic use in circumstances where there is a significant risk of serious disease.

Robin Lovell-Badge: I very much agree with what James has said. I think the UK is in many ways a perfect place to do this, with a tentative move towards germline modifications, because we have the appropriate regulation. We have a really good science base in understanding human genes and genomics, as you will have heard earlier. We have projects such as the human genome project that tell us even more about the role of specific genes. In that respect, it is good. If you want to talk about doing things like making people cleverer, taller or whatever, we just do not know enough. It will be an awfully long time before we know how to do that. We know how to make people shorter or stupider, but we do not know how to make them more intelligent.

Q237 **Chris Green:** Surely, technology is changing all the time, but is it right that the ethics are pretty universal and in a sense timeless?

Robin Lovell-Badge: I do not quite understand. Ethical views change as well. If you put several ethicists in the same room at the same time, you will end up with at least twice as many views as there are people in the room, probably. However, it has to be judged according to what is possible. That is perhaps a utilitarian view you do not like, but you do not want to do something that is going to create harm to the individuals involved or to society; so if you are regulating on that sort of basis the regulation will be proportionate. You will be treating or avoiding diseases. You will not be taking it beyond that.

Q238 **Chris Green:** But you can easily see what the language of harm would be. If you do not have particular advantages, you are disadvantaged and, therefore, you are harmed; so, you ought to be given those advantages.

Robin Lovell-Badge: Of course. I do not have children, but we, collectively, always want our children to be in a better place than we were. We send them to the best schools we can, and all those things. We are always trying to advantage our offspring. It is about having appropriate regulations and a risk-benefit analysis, and not to allow things to go too far.

Dr Greenfield: Robin said something very important. When we do ethics, we have to make comparisons. We must not forget the other salient ways in which we affect the lives of people, including future generations. Town planning does that; education does that. There are many ways we impact on the lives of our children and on their children.

Q239 **Chris Green:** If I do not like the town in which I am living, I can move somewhere else. I cannot change my genes so easily.

Dr Greenfield: I am not sure that is true all the time. There was a recent analysis of those distinctions. There are people who like to stay local; that is what they want to do; so I am not sure that is entirely true.

I do not think it would be appropriate for me as chair of the HFEA's licence committee to comment on the quality of licensing in this country; I will let others do that. Philippa made a point about arbitrary distinctions

being made in regulation. Sometimes those arbitrary distinctions are very powerful. There is nothing wrong with them. The 14-day rule is a good example of that. There are no morally relevant distinctions between a 13-day and 15-day embryo, not really. You could have a metaphysical discussion about this, but that is not the purpose of the line; that is to misunderstand why we drew the line where we did. It is not meant to match the contours of the intrinsic ethical values of these entities; rather, it is a way of saying stop. It is a regulatory line. It seems to me we could do that with the other features. We could simply look at the 400 or so conditions that are currently licensed by the HFEA for PGD and say, "Only those and no more." James will tell you that we could simply make that so.

Q240 **Chris Green:** I will have to move on. Mr Lovell-Badge, the Defense Advanced Research Projects Agency of the US Department of Defense—DARPA—was a sponsor of the recent National Academies report in which you were involved. What potential does genome-editing have for future military applications?

Robin Lovell-Badge: Interestingly, in the discussion with DARPA when the report was being released, they were a little upset that we did not have anything in the report about weaponising the technology. We discussed it, but we felt it would be inconsistent with the principles we laid out in the report for the types of applications one might use, whether somatic or germline.

Q241 **Chris Green:** What was their interest?

Robin Lovell-Badge: They never really defined it, at least not to me, so I cannot say. DARPA are interested in all sorts of things that might surprise you. They are interested in tissue engineering, because it may be useful for helping to repair people who have been fighting in wars and have damage from gunshot wounds and so on. They are generally interested in any sort of technology that might have benefit to soldiers, not necessarily their ability to fight but their ability to deal with the often horrible damage they receive in fighting wars and in armed conflict. They were almost certainly interested in the somatic genome-editing part. Maybe that would be a way of helping some people to recover from certain problems.

Q242 **Chris Green:** There are arguments about being unable to get the consent of an unborn child. Is that a legitimate concern?

Philippa Taylor: That is a difficult one, isn't it? There are lots of things for which you do not get the consent of unborn children. The importance of this issue is that you are not getting consent for something very profound in terms of changing the genetic structure of the child, and the trickle-down effect on that child's own children and future generations. It is much more profound and significant than the school you choose to send your child to or where you live. The fact that you are changing your genetic heritage and passing it down to future generations is a very

important and disturbing development, which is why consent is a major issue. It is important that you cannot get consent in making such profound changes to their genetic make-up and the consequent risks to that child or future adult. That is a massive issue and we should be highly concerned about it.

On the reference to the 14-day rule, I think it was an arbitrary line that has been well held, but the fact that it is arbitrary is shown by the massive pressure to adjust that line and move it. If it were not arbitrary, there would be more reasons not to change it.

James Lawford Davies: The very blunt legal answer is that we do not recognise the rights of the unborn child as a matter of UK law, but there are protections in place. For example, a clinic has a duty to consider the welfare of any child that may be born as a result of the use of reproductive technology. That is enshrined in statute; so, there are ways in which the interests of a future child are taken into account.

Robin Lovell-Badge: If a method is available that would allow a child to be born without a disease, you have to think how that child might feel if that method was not used.

Dr Greenfield: The consent of a future person is a red herring. Obviously, we cannot get that. I am not accusing anyone on this panel, but it is ironic that some people who speak about the importance of the germline in future generations and of not transgressing that barrier are the same people who say a woman should not necessarily have an entitlement to a germline. The germline is important. That is why, for instance, people want to be genetically related to their children. The irony is that we can downplay the germline in one case but play it up in the other case.

Q243 **Gareth Snell:** We have had a wide-ranging discussion that has touched on a lot of issues. Dr Greenfield, briefly, do you think that the HFEA's criteria for working with human embryos are stringent enough? Do you think you are still the suitable regulatory body?

Dr Greenfield: Yes and yes.

Q244 **Gareth Snell:** Does anyone else want to comment?

Robin Lovell-Badge: I agree.

James Lawford Davies: I make a living out of taking the HFEA to court; so, it is a difficult question for me to answer. I think the framework governing embryo research is a mature, robust, comprehensive, facilitative regulatory one. Sometimes I have concerns about the way in which it is implemented, but as a regulatory framework it is solid and, as was alluded to earlier, is often the envy of the world.

Philippa Taylor: Can I give two quotes? First, Lord Winston has said he does not think the HFEA is "capable of regulating either the commercial

aspects of reproductive technologies or the risks that people who undergo these technologies really run." Secondly, Sir James Munby, president of the Family Division of the High Court, has raised questions as to the adequacy of the HFEA's regulation and the extent of its regulatory powers. Those are two concerns raised by influential people that I would echo.

One aspect where that is reflected, and which has not been touched on at all, is egg donation. I would love to say more about it, but I will mention it briefly. Egg donation and the supply of eggs for this technology and other similar technologies is very poorly regulated by the HFEA. I have massive concerns about egg donation. That is one little example of how it does not always regulate well.

Dr Greenfield: I do not want to play the quote game. One could quote thousands of people. The HFEA works to the Act. The HFEA must uphold the Act. When I chair a licence committee, I have to uphold the Act. It cannot do things that are not in the Act. For instance, Lord Winston has previously complained about why the HFEA does not, for instance, control pricing in IVF. It cannot; it is not part of the Act or part of its role. Many of the complaints we hear about the HFEA are about things it cannot do, whether or not it wanted to.

Q245 **Victoria Borwick:** I want to ask about patenting and IP issues. Are they hampering the development of commercial genome-editing? Are they slowing down the science? If we could have quick answers, we would be most grateful.

Robin Lovell-Badge: As far as I am aware, there is no slowing down of research in the use of genome-editing methodology and reagents, which are widely available for researchers. There was a recent suggestion that the granting of new patents in the US will have no benefit on research. On somatic treatments, I suspect that the companies set up to do that would have to license the technology. In terms of germline, it is way too early. At the moment, I cannot imagine that any companies would get interested in it, but it is a possibility. If there is a company, they would have to license it, but for research purposes there is not much point.

James Lawford Davies: I agree.

Q246 **Derek Thomas:** It seems that the international community cannot really agree on regulation or guidelines for genome-editing. Do we need greater co-operation? Would this hinder UK research? In addition, as China has much more permissive ethical standards, how important is it that we have this kind of international agreement?

Robin Lovell-Badge: I do not think it will be possible to have some international law; very good dialogue at all levels is what is needed. China does not want to go on its own and not be accepted by the rest of the world, or at least most of its good clinicians do not want to do that.

They want to be part of the community. Having a good dialogue at all levels is what is needed to help that process so that it is not a barrier.

James Lawford Davies: I agree. People suggest that there should be some sort of international legislation or treaty governing this, which I think is unrealistic, but the conclusions of the National Academies report, which is not just an American report—numerous jurisdictions fed into it and it provides an international perspective—are very important in setting the bar high for research, whether it is somatic or germline, and potential therapeutic applications. Anyone who goes outside that agreed standard is rightly criticised by the scientific community and the scientific press for doing so. That is probably the most sensible way of agreeing an international consensus that will make irresponsible, sham therapies unacceptable.

Q247 **Derek Thomas:** Today is a big day for the UK and Europe. Would you have a similar response to future work within Europe? Would there be very similar co-operation or agreement?

Philippa Taylor: It is difficult, isn't it? We do not really know, so it is almost an unanswerable question, although it is an important one. I am not in a position to answer for what will happen. It is interesting that the UK is out on a limb in the research we are doing in modifying the germline of embryos. Along with China, we are out on a limb. Therefore, it is going to be very difficult for those doing research in this country to say they want to co-operate with international guidelines. There are so many guidelines in Europe as well—to go back to the European question—that would prohibit the research being done on this.

From some perspectives we are at the head of this and leading the way, but we need to recognise that from other countries' perspectives we are seen as almost maverick and very different. If you want to sign up to a guideline, why have we never signed up to the European convention on human rights and biomedicine that would prohibit germline? I know we have not for many reasons, but there are things we could sign up to. I can see why people would not want to, because it would restrict a lot of what is being done in the UK. From my perspective, I would love to see us sign up to some of the international guidelines.

James Lawford Davies: I have a number of concerns about how post Brexit UK law will be compatible with the evolving body of EU law, particularly in life sciences. It evolves and changes on a daily basis; it is not just a matter of adopting black letter law on day one; it is constantly changing. Having said that, as was suggested earlier, it is an opportunity for the UK to maintain and promote what I think is a fantastic regulatory environment to do research and offer treatment in this area.

Perhaps less obviously, I am concerned that over many years the UK has had a very positive impact on the development of European law. That will disappear. I worry that a gulf may develop between our approach, which is potentially permissive, and what may become a far more conservative

approach on the continent. We have seen certain European directives and regulations positively shaped by UK influence. It remains to be seen how that will change in the future.

Dr Greenfield: If we are a nation of mavericks, which I do not accept, we are one that is very attractive to other scientists throughout the world who want to come to the UK to do research. We are in a happy place to a certain extent. There will be no reproductive germline editing in the UK unless Parliament decides to change the HFEA Act. That is the way it should be. In order for you guys to do that, there will be a long debate. We will have to engage the public and all other stakeholders. My only plea is that we make sure that the level of that debate is high. We are in very deep waters; they are complicated ethically; they are extremely complicated scientifically. I hope we can do away with some of the tedious old tropes about designer babies, Frankenstein monsters and foods and so on, and have a proper, serious and grown-up discussion about ethics and science.

Q248 **Derek Thomas:** If we have a globe with different advances, or even different guidelines, in different countries, what is your judgment about the likelihood of people literally travelling from one country to another to seek the most advanced treatment available? Does anyone have a view?

James Lawford Davies: It is a certainty rather than a possibility or likelihood. We have seen that with reproductive technologies, particularly in pre-implantation genetics where certain treatments offered at Guys on the NHS would be a criminal offence in Germany.

Q249 **Derek Thomas:** Is it a concern? If so, should the UK make sure that we provide what is available here? Is it troubling?

James Lawford Davies: I do not think we should regulate according to the lowest common denominator. We have to maintain the standards. Equally, we cannot prevent people from seeking treatments abroad.

Robin Lovell-Badge: This is why a public dialogue is important. In the stem cell field we are used to sham clinics being set up all round the world offering bogus treatments. I do not think there are any in the UK, but even a country like the US, where the jurisdiction is the FDA, cannot deal with the hundreds of bogus stem cell clinics. It has to be backed with good public engagement, good regulations, good oversight and the ability to deal with occasions when things break down. As James says, you will not stop people going to seek treatment elsewhere.

Q250 **Chair:** You said we would not be able to embark on germline-editing until Parliament had discussed it, and you wanted the debate to be of a high quality, which I think is right. Do you think it is only a matter of time before those discussions are held and we potentially move to this, or are there examples where, although we have the technology to do things, we have not, and that line has been held?

Dr Greenfield: I do not think it is inevitable in any kind of metaphysical sense. Is there a tendency for us to move in particular directions with technology? Yes. The outcome of those deliberations is far more uncertain. It is by no means clear to me that the majority of the UK public have a specific opinion about germline-editing and, if they did, what it is. It seems to me that it is far too early to say. We might well initiate the process of deliberation and parliamentary discussion, but the outcome is far from clear.

Robin Lovell-Badge: We heard from Alastair Kent this morning that many of the patients who have genetic diseases, or their families, have a desire for this area to be addressed properly in terms of research, and ultimately want a change in the law to make it permissible. It is not inevitable, but there are some strong reasons for considering it. In the near future, probably not now—the technology is still a bit behind—the advances in the technology are so fast that there is a danger of regulation not keeping up.

Dr Greenfield: We want the ethics first, not as a reaction.

Philippa Taylor: You raise a very important point and in many ways what you suggest may well be right, but there is a danger that this is being driven by patient groups and scientists. It is important that we do not leave decisions just in the hands of almost invisible experts—whether in universities or ad hoc committees. An article in *The Guardian* warned against leaving decisions to parliamentary advisory committees; otherwise, we will find ourselves governed by technologies whose implications we do not foresee and whose development we choose to neglect. That is a real danger. It needs to be a much bigger decision.

In previous debates—for instance, on three-parent embryos—a lot of the discussion was driven by the media, which I think over-hyped a lot of the benefits and downplayed a lot of the safety concerns. I would be very concerned about that kind of thing happening again. We should make sure that the debates around this are more realistic and are not driven by vested interests.

James Lawford Davies: My experience of the mitochondrial donation process is very different from Philippa's. It is worth bearing in mind that it took over 13 years from the original licence application to do the research to the team in Newcastle being granted a licence to use it in treatment. During that time, there were two large public consultations. There were extensive parliamentary debates and four extensive science reviews. Alastair mentioned earlier the numerous public engagement exercises in which all sorts of people were engaged. I never felt that it was being science or media-driven. Thirteen years is a long time to scrutinise a new technology and take it from lab to treatment. If we move forward in germline treatment, I anticipate its being a long, careful and thorough process.

Chair: Thank you all very much indeed for your attendance this morning

and for some very insightful answers that will help inform our discussions as we go forward with our inquiry. It has been a very interesting session.