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Report from the MHRA Patient Forum on Biomodifying Technologies

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INTRODUCTION

What is this report about?

This report provides an account of a patient forum hosted by the UK Medicines and Healthcare products Regulatory Agency (MHRA) on the 30th January 2020. The forum was organised to discuss emerging new medical technologies, described as 'biomodifying technologies'.

The event brought together representatives of patient organisations and medical research charities, individual patients or family members of patients, members of the MHRA (the UK national regulator for medicines and medical devices), and related agencies, and members of the 'biomodifying technologies' project.

What are 'biomodifying technologies'?

One of the most promising areas of medical innovation is the idea of using our own cells and genes to treat disease. Scientists have been studying these possibilities under a variety of labels including 'gene therapy', 'tissue engineering' and 'regenerative medicine' for several decades. From a regulatory perspective, the use of cells and genes as therapies most commonly comes under the category of 'Advanced Therapy Medicinal Products' or 'ATMPs'. This broad category is further divided into sub-classifications of 'Gene Therapy Medicinal Products', Cell Therapy Medicinal Products' and 'Tissue Engineered Medicines'. So far, only a limited number of cell or gene-based therapies are currently available, such as the use of stem cells from bone marrow to help the engraftment of the body's immune system after chemotherapy.

We came up with the term 'biomodifying technologies' to describe particular tools and techniques that scientists use to modify living biological material – cells, genes and proteins.
These can be understood as 'foundational' or 'gateway' technologies. Scientists can use these tools to conduct many types of experiment in the laboratory, opening up many possible areas of application. However, only some of these possibilities come to be developed as treatments for disease.

Three new biomodifying technologies are of particular interest to us and were discussed in the patient forum:

1. *Induced pluripotent stem cells (iPSC)* takes ordinary cells of the adult body and 'reprograms' them so that, like the cells of an early embryo, they can become any type of cell in the body, eye, liver, heart and so on. They have the same genetic material as the original donor.
2. *Gene editing* describes the alteration of DNA using molecular tools. Gene editing tools can identify particular sequences of genetic material with the overall DNA ('the genome') of a living cell . They can then modify the targeted sequence in a variety of ways- cutting it, adding new material, or changing the sequence without cutting it.
3. *3D printing* involves adding multiple very fine layers of material, one on top of the other, to create a complex three-dimensional solid object. 3D bioprinting takes this concept and applies it to living organic material.

What is the 'biomodifying technologies' project?

The biomodifying technologies project is a collaboration between academic researchers at the Universities of Oxford, Sussex and York. The research has been funded by the UK Economic and Social Research Council (ESRC), through grant number ES/P002943/1.

The project team is a mix of researchers in sociology and law. Over the last three years, we have been looking at which clinical applications of gene editing, 3D bioprinting, and induced pluripotent stem cells are being developed, focusing on what is happening in the UK. We have been trying to understand what makes some applications worth pursuing and whether this is different for scientists, for doctors and for companies. We have also been looking at the way regulation, Health Technology Assessment (HTA), which assesses new medicines in terms of value for money, and reimbursement for pharmaceutical products affect which products get developed. With the patient forum, we want to bring patients, families, representatives and charities into the conversation.

Based on our research, we have identified what we think are some of the important features of these technologies. Our aim in hosting the forum was to find out

- i) if the issues we have identified matter to patients, and if so how.
- ii) if there are other concerns that might be equally or more important.

What are the potential clinical applications of biomodifying technologies?

Induced pluripotent stem cells (iPSC)

These stem cells act similarly to cells in a human embryo. Using iPSC is now seen as a more ethical route to clinical goals than using human embryonic stem cells. IPSCs can be used to make particular cell types, which can then be used to replace some or all of a patient's tissue that has been damaged by disease. Potential applications of iPSC include:

- iPSC-derived brain cell transplants to alleviate Parkinson's disease progression
- iPSC-derived nerve cells to repair spinal injury
- iPSC-derived red blood cells or platelets for transfusion
- iPSC-derived liver cells to mitigate or repair liver disease
- iPSC-derived pancreatic cells to replace dysfunctional insulin secreting cells in diabetes
- iPSC-derived retinal pigment epithelial cells to treat Advanced Macular Degeneration (AMD)

Gene editing

Clinical applications of gene editing focus on changing genetic variations associated with disease into sequences associated with normal, healthy functioning of cells and tissues.

Gene editing therapies are being developed for a number of conditions where changing the activity of one or more genes is likely to produce therapeutic effects. Examples include:

- Severe-Combined Immunodeficiency (SCID)
- Thalassemia and other anaemias
- Haemophilia B
- HIV / AIDS
- Duchene Muscular Dystrophy (DMD)
- Spinal Muscular Atrophy (SMA)

Diseases of the blood cells are seen by scientists as particularly strong candidates because blood cells can readily be modified outside the body and then transfused back into the patient.

Gene editing tools are also being used to manufacture 'next generation' cell-based 'CAR-T' therapies, which are used to treat various forms of leukaemia. CAR-T cells modify a patient's own white blood cells to better fight cancer.

3D bioprinting

The promise of 3D bioprinting is to be able to construct complex 3D structures made of tissue, such as a new liver, lungs, kidney or heart. This could alleviate the considerable shortage of organs available for transplant.

However, scientists are still a long way from being able to 3D print whole replacement organs 'on demand'. Creating complicated 3D structures, that have blood vessels and nerves, and which function properly (e.g. hearts that actually beat with the proper rhythm), is very difficult and the technology is not currently equal to this task.

Simpler tissues such as cartilage, heart valves and bone, and thinner 'layered' products such as skin, bladders, and trachea are seen as the most feasible early targets for human applications. It should be noted that there have not been any clinical trials of 3D bio-printed products carried out to date.

Why are these 'biomodifying technologies' important?

New technologies require new ways of doing things and new ways of organising ourselves and our societies. The more a new technology is different from what went before, the bigger the social change that accompanies it. Think of how much everyday life changed with the shift from horsepower to steam-power, or when steam-power was replaced in turn by petrol and electricity. More recently, the shift to widespread digital, internet-based technology has changed everything from the way we shop (online retailers), to how we communicate (mobile phones and social media) and our entertainment (for example 'on demand' streaming services). Biomodifying technologies may not produce social change as radical as the motor car or the internet, but they are sufficiently different from conventional pharmaceuticals and medical devices (such as pacemakers, hip implants) that they are likely to require some changes in the way healthcare is provided- and funded- if they are to be successful.

As academics working in the field of sociology and law, the biomodifying technologies project team are interested in understanding these changes. Sociologists want to understand the effects on society, and on particular groups such as patients or doctors. Academic lawyers are interested in how the law affects complex processes such as healthcare and medical innovation and how best to regulate these to support desirable outcomes.

Novel technologies, especially biotechnologies, can raise significant societal and ethical concerns, as we have seen with human embryonic stem cell research. The focus of this Patient Forum however is primarily on patients. We recognise that patients and patient organisations, charities, families and carers have an important role in any processes of change. Patients and those who support and look after them are always the most affected by changes in medicine. One important aspect of this is how any new treatment or clinical practice will affect the quality of their daily life- are there debilitating side effects, does the treatment address the features of the condition that matter most to patients?

Another strand, which we think is equally important, is to look at the wider organisational changes that accompany any new therapy: does it require frequent clinical visits or long hospital stays; can it be administered at home; can it be accessed at local hospitals or does it require travel to specialist centres; is it practically accessible by everyone or might the potential high costs of such therapies

require strict eligibility criteria that restrict access? Does it fit in with patient's experience in managing their conditions or does it require them to learn new patterns of behaviour, new warning signs and so on?

Many of these elements could be changed, if the needs of patients, families, and carers are identified early on in the design process. There is scope for technologies, and the way they are delivered and made available, to be tailored to better suit the needs of their users, if people producing the technologies take the time to ask about, and value, patient needs rather than making assumptions about what is important and what will be acceptable. This is true for healthcare technologies including therapies like our three case study technologies. This is why we think it is important to start this conversation now.

Biomodifying technologies have several specific properties that might necessitate changes in the healthcare system, each with the potential to affect patients in different ways. During the morning session of the patient forum we gave short presentations on each on the aspects of these new therapies that we thought were most significant. These were organised around three themes:

1. Customisation

Each of the three biomodifying technologies offers some potential for customisation or personalisation of treatments. This would mainly involve tailoring the intervention in some way to the biology of the individual patient.

IPSC therapy made from a patient's own cells would reduce the need for immune suppression during treatment. However, each batch of cells would only be suitable for that one patient, which may be slow, expensive and difficult to scale up.

Gene editing: Rare gene mutations might require a unique targeting sequence designed for one individual patient, or a very small number of patients in the world with that particular mutation.

Bioprinting materials for transplant could be tailored to the body size, and the exact nature of the injury for the patient needing a transplant. This would be of particular importance in treating children, since the shortage of suitable-sized organs for transplant is particularly serious.

Customisation is not inevitable. Many commercial developers would prefer a standardised product that can be delivered to larger patient populations. Scale-up is challenging but is a topic attracting a lot of investment and energy from developers. Nonetheless, 'biomodifying technologies' are emerging at the same time as considerable headway is being made in personalised medicine initiatives such as the 100,000 Genomes Project. These aim to sort patients into narrower, more specific diagnostic and treatment categories based on genetic and other molecular information. It is therefore a good time to start thinking about customisation.

Making more tailored therapies could mean that quite limited subsets of patients with any particular condition would be eligible for clinical trials of gene editing, iPSC-derived cell therapies or bioprinted materials. This could make results of trials difficult to interpret. What works for a subset of patients with, for instance, diabetes, heart disease or cancer, may not work for the wider group. Or perhaps concentrating on one sub-group would mean missed opportunities to treat other groups?

It could also lead to perceptions of unfairness. Evidence from 'personalised' cancer care suggests that patients experience distinctly different care pathways. This makes it harder for patients and clinical staff to collect and share experience-based information about coping

with the risks, benefits and side effects of different procedures, and how to manage everyday life whilst going through demanding care schedules.

2. Uncertainty and acceptable risk

A degree of uncertainty about the safety and efficacy of new therapies using biomodifying technologies (customised or not) is inevitable. Developers and regulatory agencies are working together to establish acceptable safety standards, but there are limits to what data from animal experiments can tell us about how cell and gene therapies will work in humans.

If, for example, iPSC-derived liver cells are being transplanted to repair a damaged liver, how pure does the sample of transplanted cells need to be? Given that a transplant might contain several million, or even a few billion cells, is it acceptable to proceed given that it may simply be impossible to check every single cell for quality?

Does it matter that the changes made by these technologies might be irreversible?

Unlike many standard clinical trials, the first human trials of cell and gene therapies will be patients receiving an active dose of the treatment, not healthy volunteers receiving a very low dosage.

As patients play such an important role in developing these therapies, it is important to consider what the appropriate role for patients, patient charities and representatives ought to be in making key decisions:

- What level of risks, and what types of risks, are acceptable?
- What information might patients want to know before making any decisions about taking part in a clinical trial for untested new therapies?
- How should patient consent be handled?

3. Evidence, patient registries, and data management

It is not only the short-term performance of novel biomodifying treatments that is uncertain; long-term outcomes are also hard to predict.

Many of these treatments are potentially cures but proving that someone is permanently cured of a chronic disease could require long term, even lifetime, medical follow-up and monitoring. Similarly, detecting any long term unforeseen adverse effects of biomodifying treatments also requires longer term medical oversight.

Increased monitoring of patients who have received a cell or gene therapy is also important for demonstrating their economic value, especially if a ‘pay by results’ approach is adopted as some commentators have suggested.

They are likely to be very expensive- as much or more than the most expensive cancer drugs currently available. Many cancer drugs are too expensive to demonstrate clear-cost benefit according to the current evaluation methods of the National Institute for Health and Care Excellence (NICE) so the government set up the Cancer Drugs Fund to pay for these outside the normal NHS budget. Biomodifying technologies might also require some adjustments to the way we pay for new treatments as they may simply be too expensive to fit into the annual budgets of some NHS Trusts.

This suggests a need for databases or registries of information on patients receiving these novel therapies, and the short and long-term outcomes of treatment. Given the potentially

small numbers of patients initially receiving such treatments, it may be necessary to create an international data set by pooling information on patients from multiple countries.

Developing such an information infrastructure to support biomodifying therapies raises important questions about the role of patient charities and groups in providing and potentially collecting, storing and negotiating access to, or ownership, of this data.

Delivering complex biomodifying therapies is also likely to involve ever-closer collaboration between commercial companies and public bodies like NHS hospitals, and this may require patients' medical and treatment data being shared between public and private groups. We already see examples of this in the three UK Advanced Therapy Treatment Centres, which are collaborations between academic scientists, companies and the NHS.

Does the involvement of commercial partners affect patient perspectives on how data is best collected, stored, shared and used?

Other issues

We also recognise that this should be the start, not the end of a conversation. During the forum, we wanted to hear from patient groups and research charities about any other aspects of these novel therapies that we have overlooked and which they think would be important to look at.

How did we produce this report?

The morning session of the forum consisted of introductory presentations on each technology, followed by general discussion. Each presentation ended with the opportunity for participants to ask questions, including asking speakers to explain any points they had made or provide more information. The MHRA also gave a presentation on their role in assessing the safety and efficacy of any new medicines or medical devices before they can be made available in the UK.

After a break for lunch, the afternoon part of the forum was structured around four sessions. In the first three sessions, the three topics of customisation, risk/uncertainty, and data collection/management were each presented by a member of the biomodifying technologies team. Each topic was discussed in turn, through a series of small group discussions, with approximately 20 minutes allowed for each discussion. The attendees, including patient representatives and MHRA participants, were divided into 5-6 groups, each based at a separate table. This was to help make sure everyone would get a chance to speak.

Each presentation ended with a short series of questions. These questions are listed in Appendix 3. The questions were intended to prompt discussion, but participants were free to ask their own questions and raise new ideas and topics as they saw fit. During these group discussions, one member of the biomodifying technologies team also sat at each table. Their job was to chair the discussion and to take notes on the discussion. It was not possible to record 'word-for-word' what each participant said, so instead their job was to take short notes on the main points discussed in each group- how did the group members respond to each of the topics, what arguments and reasons were offered? Each group also had a representative from one of the MHRA divisions, who was also able to respond to any scientific or regulatory questions the other participants raised, as well as taking part in the discussions themselves.

When one biomodifying technologies project team member was presenting, another team member took their place in the group to make sure no discussion was ignored. The fourth session of the day was a general discussion where participants could raise any questions, topics or ideas on which they wanted more information or which they felt had not been covered so far. After the forum, each of the biomodifying technologies project team members wrote up the notes they had made on the afternoon's discussions. There were analysed by the Principal Investigator, Michael Morrison.

Analysing data derived from multiple conversations involves looking for broad patterns or themes that recur across more than one group, or that come up in relation to multiple topics (for example 'choice' and 'autonomy' were important to participants when talking about taking part in clinical trials, and also when they discussed personal information).

To do this, each of the written notes was uploaded to a specialist piece of software for analysing qualitative (textual) information, called NVIVO. This software does not analyse the data for the user, but it helps the researcher (in this case Dr Morrison) to identify patterns in the different group discussions. A pattern can be any idea or topic that recurs across several parts of the discussion.

NVIVO allows the analyst to create themes or 'codes' and assign bits of the text in different documents to them by highlighting them in a particular colour. For example, in the discussion of long-term data collection, participants in several groups expressed opinions about which types of organisation (companies, the NHS, governments) could or could not be trusted to

look after and use patient's information responsibly. These parts of the discussion could then be assigned to the theme 'trust'. 'Choice' might be coded in red, while 'trust' might be coded in green. The software also allows the user to pull out all the text that belong to a particular 'code' or theme, and compare what was said in different groups. Because people often cover several topics or points of interest in one short discussion, any particular piece of text can be assigned to more than one code. This also helps the analyst see how different themes relate to each other.

Patterns or themes are identified by careful reading and rereading of the notes from each discussion group. Many possible themes were identified but in the end only the most robust and the most useful were used in the analysis. The final codes are listed and explained in Table 1. Discarded codes included 'hopes and expectations', 'identity/community', 'NHS', 'regulation', 'responsibility' and 'values'. Most of these codes were discarded because they could be better explained as ideas within another broader theme. For example most of the text coded under 'hopes and expectations' came under 'the 'futures' part of the 'futures and sustainability' code. Others such as 'NHS' and 'regulation' were discarded because they were mainly discussed in relation to other topics that were already used as codes. For example 'the NHS' was mainly discussed in relation to other topics such as 'trust' or 'access'.

'Robust' themes were those that occurred in all or almost all group discussions (and not just in one or two groups) and 'useful' themes were those that related most closely to the aim of this exercise- to explore what, if anything, about biomodifying technologies matters to patients and to get a sense of how participants' preferences and concerns were presented.

THEME	HOW IT WAS APPLIED
Access and equity	Captures discussions about access to therapies (for example through clinical trials), and access to personal health information, especially with regards to what would, or would not be fair and justified in each situation.
Futures and sustainability	Captures discussions of what might happen in future, including hopes, concerns, and uncertainties. Includes discussion about how what is put in place now can, or should be, sustainable for the future
Personalisation/customisation	Captures discussions about what personalisation or customisation of therapies might look like and what would or would not be welcome about personalised therapies
Risks and benefits	Captures discussions about the (potential) risks of biomodifying technologies and the (potential or hoped for) benefits, and what could be done to manage the risks and realise the benefits
Trust	Captures discussions about which people, organisations, or groups were considered trustworthy or not by participants, and why this was so.

Table 1: Codes used in the analysis of the reported discussions from the patient forum

There are always multiple ways of coding any text based on real conversation. There is never only one absolutely correct interpretation. However, that does not mean all themes and all interpretations are equally good. One way of assessing validity is to look at the data and see if the themes proposed make sense in light of the reports of what was actually said.

In addition to the *validity* of interpretation, the *utility*, or usefulness of the analysis can also be judged in terms of how well the reported themes answer the research question or questions; in other words do they help us to understand what we wanted to know when we organised the forum?

One of the limitations of this study is, that it is by its nature, exploratory. The forum involved some patients and patient group representatives (from the groups listed in Appendix 1) but they cannot be said to speak for all patients or even all charities and patient organisations in the UK. As mentioned above this should be thought of as the start of a conversation not the end. One of our hopes is that this report will help to stimulate discussion among the wider communities of patients, families, carers, healthcare professionals and others, and perhaps prompt people to come up with new questions for academics, policy makers, regulators and therapy developers to think about.

The next sections will report on the group discussions in the patient forum, and then consider some future steps we might take.

MAIN FINDINGS FROM THE PATIENT FORUM

Presenting the findings

'Access' emerges as an important theme for the whole discussion. The discussion of access can be divided into two broad areas- access to therapies, especially access to clinical trials, and access to data and results (again from clinical trials in particular). The reporting of these findings is organised to reflect these two major topics from the day, with access to therapies presented first followed by access to data.

Both sections take a broad view of 'access', using the term to include discussions of

- **'who'** gets access?
- **'how'** access can be organised, managed, made fair and accountable?
- **'why'**- what reasons for these decisions and ways of organisation things are justified and supported by our participants.

The other themes – sustainability, risks and benefits, trust, customisation– are used to structure the discussion within the two main sections on access to therapies and access to data. Some themes apply mainly to one section or the other and some came up in both discussions.

1) Access to therapies and clinical trials

For several participants the key questions were who would have access to any new therapies based on biomodifying technologies, and who would be making these decisions?
This acted at the collective level- which disease areas would be addressed first, and how might different patient groups get their voices heard and express their priorities?

One group questioned whether commercial concerns might skew priorities for development, while another asked whether initial market approvals for narrow patient populations defined by strict biological and medical criteria might in time lead to biomodifying technologies being made available to wider patient populations, with the added hope that larger patient populations might also mean developers could charge lower prices while still recouping their costs. It was also suggested that it would be helpful to know more about the real cost of producing cell or gene therapies and how companies set prices, although this information is almost always confidential.

Access was also considered at the individual or personal level. Patient autonomy, with individual patients making the choice about whether or not to take part in a clinical trial, was advocated.

In this context, consent was important. Participants reported that the way a trial is presented and explained by physicians has a big effect on how genuinely informed the decision to participate is, what expectations patients have about the trial, and whether or not they feel positive about it.

It was recognised that consent was more challenging where people less able to give informed consent are involved, for example children or people with learning difficulties or dementia.
There was also some discussion of the geography of access, with one participant from the MHRA noting that biomodifying technologies were likely to be available only through specialist centres (probably large university-affiliated hospitals) at first. An extreme example

is the gene therapy product *Strimvelis*, which is used to treat severe combined immunodeficiency due to adenosine deaminase deficiency. It is currently only available to patients in Europe through one clinical site in Italy, so all prospective patients must travel there to receive the treatment.

However, there was also hope that other technologies- for example Artificial Intelligence and Machine Learning, might change this in future and allow more local production and administration of biomodifying therapies

Risk and Benefits
Overall 3D bioprinting was seen as the least threatening of the three case studies but all of the biomodifying technologies discussed were viewed as promising, with the hope that they might offer ways to cure rather than manage diseases.

Clinical trials were seen as both a possible way to get some therapeutic benefit from these new therapies, and as something experimental whose outcomes were uncertain and potentially negative.

Even when treatments work, one participant noted that receiving CAR-T therapy and experiencing the side effect of a 'cytokine storm' was a very unpleasant experience.The possible irreversibility of any adverse effects was identified as a particular risk with biomodifying technologies, especially gene editing which might create a permanent genetic change. Several groups discussed the issue of who would look after any patients affected by long-term side effects from taking part in a clinical trial of an experimental therapy. Whilst often described as trustworthy (in regard to data- see below) some participants also saw the NHS as underfunded and slow to respond to new challenges and needs that novel therapies might bring.

One participant felt that the NHS was not properly able to account for the long-term benefits of treatments that cure rather than manage diseases, and so these do not always appear cost effective. Another group suggested that NHS patients ought to be informed about the cost of biomodifying technologies to help decision-making and discussion.

Taking part in a trial was seen as a personal decision and it was recognised that weighing up the risks and benefits was different for different people in different situations. A patient's age (and how long they would have to live with any adverse effects) was one factor, and their quality of life, degree of suffering and the seriousness of their prognosis was another. Several participants felt it was more difficult for parents, especially if their children were asked to be in the first trials of an experimental new therapy where the outcome and possible effects were unknown. However, parents of children with serious, life threatening disease were also described as 'desperate' to find a cure and potentially willing to take high risks.

This also connected to the discussion of long-term monitoring and data collection (see below). One participant observed that follow-up could be good, as it would reassure patients when deciding whether or not to take the risk of joining a trial, but it could also become a burden if the patient- or the NHS - did not have the capacity for long-term involvement.

One of our regulatory participants noted that the standard regulatory approach was to control risk by restricting the most novel and uncertain interventions to patients with the most immanent life-threatening conditions, who were facing death if no successful treatment was

found. This shows one answer to the question of how it might be decided which patients are likely to get priority for access to treatments. Very seriously ill patients might need to get 'compassionate use' access in hospital if they are too seriously ill to be enrolled in a clinical trial.

They also discussed the existing safety measures such as requiring cell and gene therapies to be traceable, and requiring each product to be made under 'Good Manufacturing Practice' (GMP) conditions. GMP certified facilities must meet rigorous standards of cleanliness, air quality, and so on and are inspected to ensure they meet these standards before being approved.

Hype and unrealistic expectations were also raised as a different sort of risk. If biomodifying technologies are over-hyped as a cure for all diseases, then people (including governments and investors) might become disillusioned if there are any setbacks or adverse events in trials and put future developments at risk.

Customisation: costs and shared experiences
Across discussion groups, the idea of truly 'personalised' medicines, made for one specific patient only, was considered unlikely for a variety of reasons. One reason was that it was expected to be prohibitively expensive.

One of the MHRA members also noted that you would need very good pre-clinical evidence to justify giving a patient a truly novel, customised treatment instead of an approved mass-produced therapy or enrolling them in a clinical trial.

Experiences of existing technologies that are presented as 'precise' and 'cost-saving' such as MRI scanners was also used to question how precise and effective any intervention can truly be given the messiness of the real world healthcare system.

Truly personalised therapies were also seen as unappealing to patients. It was felt that no one would want to be the only one receiving a specific treatment. This might involve a unique level of risk.

Although the decision to participate in a clinical trial is a personal weighing up of risk and benefits, patients talk to each other about experiences of treatments, ways to manage their condition, how to navigate care et cetera. People can draw reassurance from knowing that other people have undergone a particular treatment or used a medical device such as a hip implant. This shared experience provides a shared pool of knowledge and know-how, which individual patients can draw on to make informed decisions. People now know, for example, that metal-on-metal hip implants are a poor option. Patients also communicate via social medial to share experiences and make their own evaluation of treatment options. One respondent suggested the question for patients was more like 'how much is it possible to know?'

More than one group also discussed the risk that excessive personalisation might erode this sense of community, fragmenting patient groups into ever smaller sub-groups and reducing the solidarity that comes from shared experiences and knowledge.

The more preferable option was to have a range of tested, expert-approved options that patients could choose from, based on their personal preferences and specific needs.

However, there was also some scepticism about how much choice really existed, with one participant returning to the example of artificial hips querying, “how much people actually get to choose, or even really know in advance, which hip model they were getting- that it was basically a decision by the medical team”.

Some customisation was seen as purely aesthetic (e.g. colour of implants) and this was seen as more feasible and less troubling.

One group mentioned the book “Invisible Women” by Caroline Criado Perez, which describes how many technologies and ways of doing things are designed primarily for men, without considering if they also work well for women. The book includes examples of this approach in the design of medical trials and other areas, including digital health, that can, and have had negative consequences for women’s health. Customisation of therapies and treatment regimes might be one way to alleviate this, as long as women are explicitly taken into account when designing the range of customisation options.

Some form of ‘stratification’, as biomodifying therapies were developed for relatively narrowly defined groups of patients with specific disease features, was considered more likely economically and in terms of generating enough evidence to know if the therapy was effective or not.

This could have benefits- for example, treatment for small patient populations could qualify as orphan drugs, and be approved with smaller clinical trials, which might be less expensive and make new therapies available to patients more quickly.

However, stratification could also have a negative side in terms of access. One group observed that the idea of personalisation/stratification is great if you ‘fit’ but bad if stratification identified you as a poor responder or the ‘wrong type’ of patient and therefore ineligible. In this way, customisation could create new kinds of patienthood with benefits for some but disadvantages for others.

The question was asked, whether future clinical trials of biomodifying therapies could be designed as ‘umbrella trials’ where patients belonging to different stratified ‘sub-groups’ of conditions could all be included in one trial as a way of improving equity of access?

2) Access to data

Across groups, there was considerable discussion about the idea of some form of ongoing collection of data from people who had been treated with biomodifying technologies.
This discussion focused on what data might be collected, who might have access, what it might be used for, and who should take responsibility for these decisions.

Participants felt that the issue of which groups or organisations should have access depended very much on what data was collected and what the data was going to be used for by people requesting access.

Some general concerns were voiced about the security of data stored on computers and the risk of data theft of leaks by hackers. Privacy and data protection were also discussed across groups. Here a tension was recognised between personal privacy and the societal good that could be achieved by sharing pooled data on people’s biology, health and lifestyle. Several groups felt that patients were less concerned about privacy if real benefits could be achieved

by sharing data. It was suggested that, if health information from the wider public was also needed (as for example when 'healthy control' data is needed for genetic databases), they might put a higher price on privacy and data security, which might be an obstacle to wider data sharing.

There were also concerns among participants about 'bad actors' exploiting or freeloading off accessible data. As one participant explained: "In an ideal world, we would all be able to share all our data freely, but that is not the reality".

As a result, some form of 'managed access' where any collected data was held by a custodian who could set terms and conditions for access was seen as unavoidable. Discussions on which organisations or people might be a suitable for this role focused on issues of trust and responsibility.

Trust and sustainability

In terms of which people, or which organisations, ought to be responsible for collecting and managing data from patients receiving biomodifying therapies, the NHS was widely, though not universally, seen as trustworthy. As mentioned above, underfunding and a reliance on older IT systems were seen as potential weaknesses.

Several groups discussed the role of patients and patient organisations. There was support for patients taking an active role in managing their data and helping to decide who should have access to the data and for what purposes. Some felt patients had a duty to look after and manage access to their own data. Other groups argued that making data access decisions should be a shared decision between patients, researchers, clinicians, and potentially other such as pharmaceutical companies and regulatory agencies.

Regulation was also seen as having a role to play in providing a formal, legitimate framework for access decisions.

There was ambivalence about the role of commercial companies. Several companies were identified as examples of undesirable practice, such as selling access to personal data. However, other firms were recognised as producing useful software or devices to help patients monitor their health and collect information about themselves.

It was accepted that companies developing biomodifying therapies would require access to at least the data relating to their own products, but that they could be encouraged to provide some measure of financial support to the registry in return.

Some groups also expressed distrust of state governments as possible curators of patients' personal data.

A recurring reason for not wanting companies or national governments to be data managers was the difficulty of securing long-term commitment. Companies may go bankrupt, be bought by another company, or simply decide to disinvest for financial reasons. Governments, and their priorities, change after elections. This undermines participants' confidence in the ability of companies and governments to create sustainable data resources. This is particularly relevant for potentially curative new therapies, which might need life-long data to demonstrate that what is presented as a 'cure' really is a permanent remedy.

As one regulatory participant explained ‘In terms of bringing in data to support therapies, you simply don’t get that convergence without data integration’. However, it is not clear whether this lack of trust extends to ‘arms-length’ bodies funded by the state, such as the MHRA and NIBSC as these tend to be more stable, and their activities and structures do not fundamentally change, regardless the government if the day. An example is the MHRA, which was formed by a merger of two precursor agencies, the Medicines Control Agency and the Medical Devices Agency. The current MHRA continues to carry out the roles and duties of both precursor agencies.

Some groups also raised the issue of international data sharing. Both positive and negative experiences were reported. One participant explained they had been part of a successful international network to share health data, including partners in the USA and Russia. Another shared a story of a planned data-sharing project that had been abandoned because of concerns about data protection. The impact of the European General Data Protection Regulation (GDPR) was also mentioned as something that would have an impact on any future international registries of patient or personal data.

Participants also drew on their own knowledge and experiences to discuss examples of existing good practice that could be applied to registries of data about patient outcomes from biomodifying therapies. These included existing international genetic databases, patient-led networks, and the national health databases used in Scandinavian countries. NIBSC representatives also mentioned the data resources they currently hold, which are managed access.

Choice and responsibility

Making it compulsory for any patient receiving a biomodifying therapy to contribute their data to a registry or database and undergo mandatory long-term follow-up was seen as probably not acceptable to most patients (although some element of follow up care is very likely to be needed, especially in cases where the patient experienced multiple comorbidities).

However, it was recognised that refusing to take part in follow-up care came with a cost. Patients’ not wanting follow-up or data collection could not expect to receive the most up to date care, since they would not be part of any ongoing research to improve these treatments (including new information about any side effects or interactions with other existing conditions or lifestyle choices).

Participants also wanted to know more about what follow-up might involve. The burden for patients is very different if long-term follow up requires long clinical visits with arduous or invasive procedures, than if it could be done with a simple checklist of questions.

Follow-up using phone apps, online services or telehealth services, which could be delivered at home, were seen as more acceptable and easier to comply with than hospital visits.

However, it was noted that data that existed primarily on patients’ smartphones or tablets would not be accessible to GPs and other health professionals who might benefit from being able to use it. A centralised repository with some form of managed access was seen as the most viable option.

It was suggested that patient organisations could play a role in encouraging and supporting participation in data collection schemes, providing they were fair and acceptable to patients.

Although there was strong support for patients having some say in deciding who can access their data and on what terms, there was less interest on the part of participants in accessing their own data. Some groups reported that patients were more interested in hearing back the overall findings from clinical trials and other research they had participated in.

Non-reporting of clinical trial data and non-publication of unspectacular academic findings were both recognised as problems that let participants and patients down by not making potentially important information (even if it is about what does not work) available.

Other issues

Topics that were mentioned by participants but that we did not have sufficient time to open up for further discussion included:

- Inheritable or 'germline' uses of gene editing to create a genetic change that would affect the whole person and that could be passed on to their children and their children's children and so on.
- The use of biomodifying technologies to enhance human abilities or create new ones.
- Health tourism, where people travel abroad to access medical services that are not available or are prohibited in their home jurisdiction.

Note: 'Germline' genetic modification is prohibited by law in many countries, including the UK. However, the birth of three babies from embryos whose DNA was altered using unauthorised gene editing of human embryos did occur in China in 2018.

What are the next steps?

The ESRC Biomodifying technologies project is coming to an end in September 2020. The team will continue to write and publish our findings from the project from the next several years (we have a lot of data!). Our hope is that this report will help start wider discussions among patent groups and charities, and among their members about biomodifying technologies. The project members at the Centre for Health, Law and Emerging Technologies (HeLEX) at the University of Oxford, will also look to do more work in this area. This will depend on two things: Firstly making a successful grant application to fund any new work and secondly, listening to the feedback from patients, patient groups, charities and others to understand what kind of questions would be most helpful to address.

In the interim, other researchers are also working on these topics:
Professor Anna Middleton, Head of Society and Ethics Research at the Wellcome Sanger Institute in the University of Cambridge is planning to launch a UK public consultation about the medical uses of gene editing. A similar study is already underway in Australia, and further studies are planned in other countries round the world.

Professor Melanie Calvert, in the Institute of Applied Health Research at the University of Birmingham has been leading a programme to develop relevant Patient Reported Outcome Measures ('PROMs') for advanced therapies, including cell and gene based treatments.

What are the key findings from this analysis?
These are the most important 'take home' messages to come from the analysis of the patient forum discussion. These summarise what we have learned from the event and can hopefully act as a starting point both for further discussion and debate and for action to make sure that the future design and delivery of biomodifying therapies incorporates patients concerns and needs.

- There was broad optimism and support for clinical applications of each of gene editing, induced pluripotent stem cells, and bioprinting. However, given the risk of novel therapies participants were concerned about what would happen after treatment- for example, what follow-up care would be provided, and whether follow-up requirements would be demanding or if they could be relatively 'light touch'?

- Truly unique 'personalised' therapies were felt to be undesirable and financially unviable. Stratification of patient groups into smaller sub-populations was seen to have potential benefits, such as smaller clinical trials, and potential for faster approval, but could also risk equitable access, as some sub-populations would be eligible for transformative new therapies and others might not.

- Compulsory participation in registries of patients receiving biomodifying technologies was felt to be unacceptable. However if participation was voluntary and fair, patient organisations and charities could play an advocacy role in encouraging people to take part and contribute their data.

- If registries of long-term outcomes of patients receiving biomodifying technologies are created, some form of managed access is seen as feasible. A trusted organisation would be needed to store the data, but there was also strong preference for patients or patient organisations and charities to have a role in making decisions about who has access and under what conditions.

- The long-term sustainability of any such data resource is important. Companies have a role to play, and will require access to data about their own products but a registry should be protected from market conditions that might cause it to be closed or sold off for financial reasons.

- Having an active and informed choice is important to patients and groups likely to be affected by biomodifying technologies. This extends to participation in clinical trials and to having an active say in how personal data is used and who has access to this collective information.

- Patients and patient groups have considerable experience of well-managed, fair, and successful schemes for collecting and sharing personal medical information (including genetic data), many of which are multi-national. This experience should be drawn on if, and when, any new registries for biomodifying technologies are set up.

- When discussing access to new therapies, there was strong support for fair treatment, especially the idea of equity, which includes both a commitment to equality of opportunity and that resources should be distributed according to need. This extends to questions of who has access to clinical trials and other routes by which novel medicines are made available prior to receiving market approval from the MHRA and economic assessment by the National Institute for Health and Care Excellence (NICE) or NHS England. The issue of fairness in pre-market access is less often considered by ethicists or policy makers but is important when therapies have potentially life-changing effects.

APPENDIX 1: WORKSHOP PARTICIPANTS

Representatives from the following patient organisations and charities:

Brent Patient Voice
Motor Neurone Disease Association
Alzheimer's Research UK
Myotubular Trust
Connate Support/ RareConnect
Leukaemia CARE
Parkinson's UK
Brent Health Watch
Cardiff 50+
Cystic Fibrosis
UK Thalassaemia Society
Independent Cancer Patients' Voice
Harrow and Hillingdon Patient Voice
Myotubular Trust
EURORDIS
Sickle Cell Society
Myotonic Dystrophy
Genetic Alliance UK
Duchenne UK
Cure Parkinson's Trust
Macular Society

Plus patient representatives from the areas of asthma and heart disease and a lay representative from the MHRA Medical Devices Expert Advisory Group (EAG).

The Biomodifying technologies project team

Michael Morrison	Principal Investigator and Senior Researcher in Social Science	University of Oxford
Miranda Mourby	Researcher in Law	University of Oxford
Jane Kaye*	Professor of Health, Law, and Policy	University of Oxford
Alex Faulkner	Professor in Sociology of Biomedicine and Healthcare Policy	University of Sussex
Edison Bicudo	Research Fellow in Sociology of Biomedical Technology	University of Sussex
Phoebe Li*	Senior Lecturer in Law	University of Sussex
Andrew Webster	Professor in the Sociology of Science and Technology	University of York
Andrew Bartlett	Research Fellow in Sociology	University of York

** These members were not present at the workshop.*

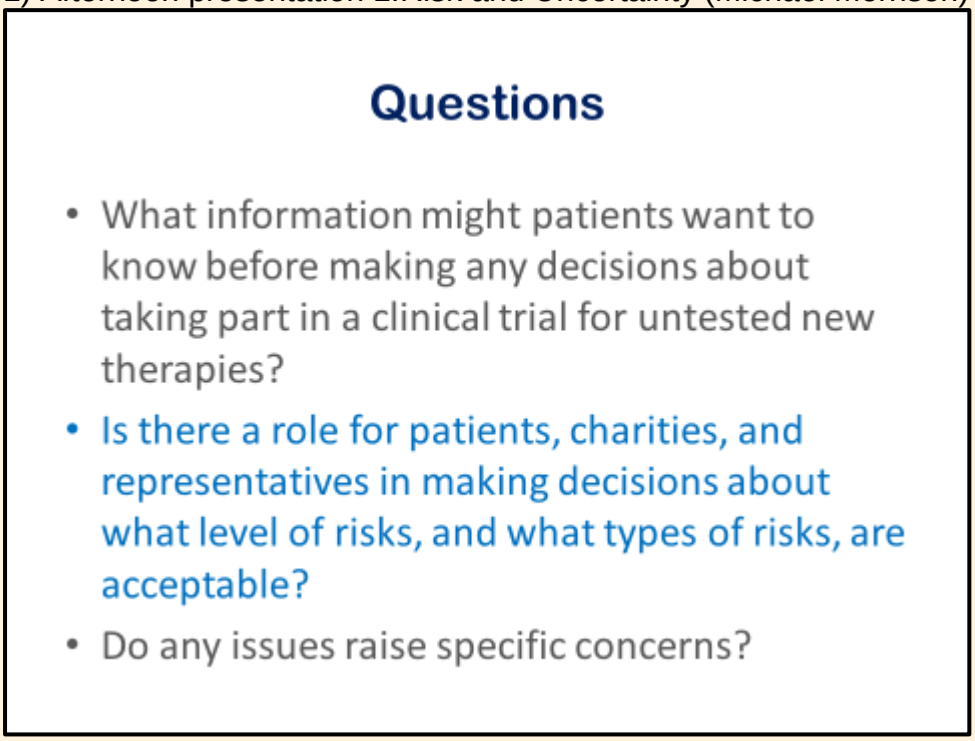
Medicines and Healthcare products Regulatory Agency units and Departments represented

Patient, Public & Stakeholder Engagement
Communications
Innovation Office
Inspection, Enforcement & Standards
Licensing
Medical Devices
UK Stem Cell Bank
National Institute for Biological Standards and Control

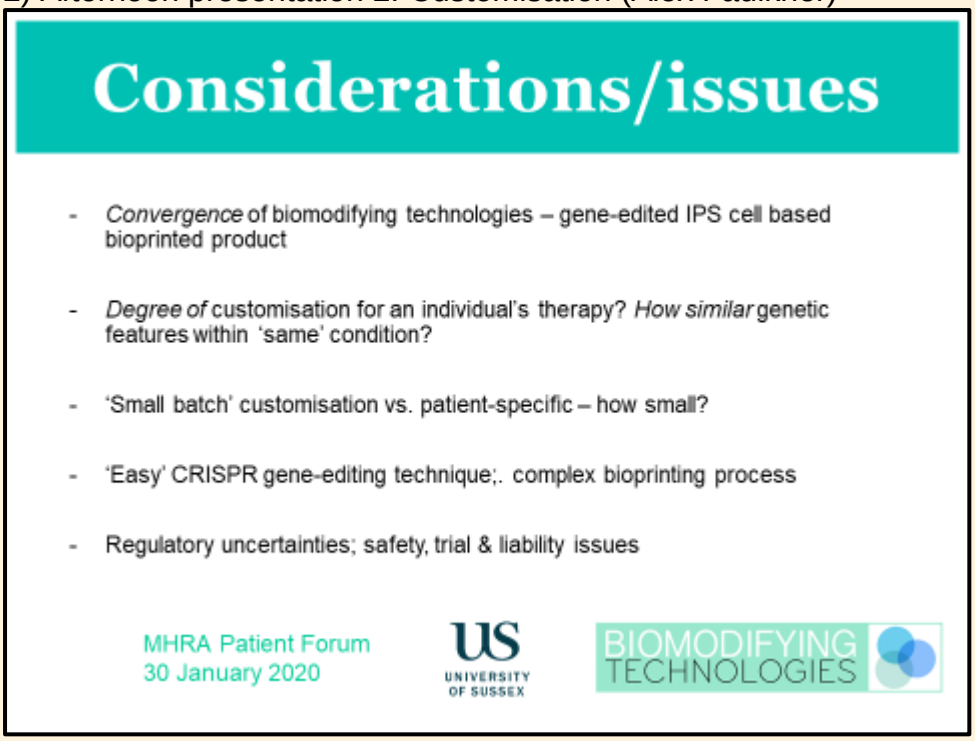
Other Organisations
UK Cell and Gene Therapy Catapult

APPENDIX 2: QUESTIONS FOR GROUP DISCUSSION FROM EACH PRESENTATION IN THE AFTERNOON SESSION

1) Afternoon presentation 1:Risk and Uncertainty (Michael Morrison)



2) Afternoon presentation 2: Customisation (Alex Faulkner)



3) Afternoon presentation 3: Data Registries: Pros, Cons and Questions (Miranda Mourby)