BIOMODIFYING TECHNOLOGIES

Organisational & Regulatory Implications for the Translation & Valuation of Health Research

Trends in customisation and personalisation of advanced therapies

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Overview

- This Policy Brief examines the options for customisation and personalisation in therapeutic applications of biomodifying technologies.
- Customisation and personalisation involve tailoring some part of a product or process to a specific situation and context, which in medicine is often done to meet the requirements of an individual patient.
- Truly personalised 'bespoke' treatments are likely to be restricted to a small number of hospital exemptions.
- Commercial activity is likely to focus on provider-led customisation where a degree of adaptability is built into the design of the product or to the manufacturing process.
- Cell-based therapies using a patient's own cells operate a form of 'mass customisation', where a standardised process being is applied to a patient-specific starting material, to give a defined product.
- Additive manufacturing adds new flexibilities, offering mass customisation and distributed manufacturing, but presently faces considerable regulatory hurdles.
- Procedural standards are an important part of the process, from starting material to delivery and aftercare, of involved in producing biomodifying therapies but will need to adapt to the requirements of both clinicians and patients, as patient input looks set to form an increasingly important regulatory tool.

Background

This Policy Brief reports findings from the *Biomodifying technologies* project (2017-2020), an interdisciplinary analysis of the social, organisational and legal implications of biomedical innovation in the 21st century. The project focuses on three case studies: gene-editing, induced pluripotent stem cells (iPSC) and 3D bioprinting - technologies that enable the modification of living biological tissue in novel ways.

This study is concerned with human, clinical applications. In the healthcare context they may be both 'transformative technologies' of the sort recognised by the 2016 Accelerated Access Review, capable of delivering significant benefits in terms of patient outcomes, and 'disruptive technologies' in that their development is likely to challenge existing translational and regulatory pathways.

The project is a collaboration between researchers at the universities of Oxford, Sussex and York and is funded by the UK Economic and Social Research Council. The aims are:

1. To characterise the 'experimental space' where clinical applications of gene editing, iPSC and bioprinting are developed, focusing on the UK but situating it in a global context.
2. To understand what makes a promising application and how this is shaped over the course of the translational pathway from bench to bedside.
3. To identify the particular challenges and risks posed by these technologies for existing organisational, regulatory and governance regimes and how these regimes in turn affect the development of our case study technologies.
4. To consider the role of patients and patient groups in engaging with or helping to define risks, possible governance options (e.g. patient registries), and the role of patient-centred care in assessing value.
5. To deliver an informed and constructively critical social science approach that can make recommendations aimed at supporting responsible research and innovation in this field.

Multiple research methods were used, including interviews with diverse stakeholders, review of scientific articles, mapping of patents and publications, and updates of research and clinical developments.

The Experimental Space

Gene editing, bioprinting and iPSC technologies are versatile. It is not only that they have many potential applications, but that as tools for laboratory research they can be modified to have new and altered functionalities and properties. Gene editing, especially using CRISPR/cas9, can be said to facilitate 'tinkering'; it is relatively easy to make changes to the structure of the tool, to test these to see what effect they have on its functioning, and to see how and why the changes produced this effect. This allows open-ended experimentation with the properties of the tool itself, to explore novel possibilities and to customise CRISPR constructs for new functions and applications. This is evidenced by the high number of modified CRISPR variants developed since 2012; such as base or RNA editors.

The variety of techniques and of components involved in 3D bioprinting also means there is large potential for experimentation. Academic research teams 'tinker' with the design of printers and components such as nozzles, the composition of bioinks and surfaces onto which bioinks are printed, and even custom-made or modified open source software for the computer aided design of bioprinted constructs.

The prolonged, labour-intensive process of reprogramming cells to an induced pluripotent state means that there is less scope for customising the production of iPSC in ways that affect functionality,

although work has been done on refining and improving the efficiency of reprogramming. The growing number of research grade human iPSC available from biobanks such as HipSci and the European Bank for induced pluripotent Stem Cells means that 'ready-made' iPSC are more accessible as a starting point for laboratory experimentation. In this regard iPSC are amenable to modification and exploratory tinkering using gene editing and other tools. IPSC are also capable of being 'personalised' in the sense that cells can be reprogrammed from a particular donor- for example a patient - to produce an iPSC line with the same genetic background as the donor; creating a patient-specific tool for disease modelling and research.

This malleability and the potential for tinkering and exploratory investigation is one of the features that make biomodifying technologies valuable as research tools. The main aim of this briefing is to consider how this potential for modification and tailoring is affected as biomodifying technologies enter the process of translation into clinical applications.

Terms such as 'personalisation' and 'customisation' are often used interchangeably in the literature so the following table clarifies how the terms are used in this briefing:

TERM	MEANING
Customisation (provider-led)	A degree of adaptability is built into the design of the product or to the manufacturing process.
Customisation (user-led)	Occurs when a standard product is modified on an ad-hoc basis by a user. In the medical context a user could be a clinician or a patient.
Personalisation (custom-made)	Production of truly 'bespoke' therapeutic product for a single patient, usually on a one-off basis.
Precision medicine	Stratifying large patient populations into smaller groups based on genetic/genomic information or other biomarkers

Table 1.0: Definitions of relevant terminology used in this report

Customisation can occur in multiple ways. However, it is by no means inevitable, nor is it yet clear what form or forms it may take. The remaining sections of this Policy Brief reports how customisation can be seen in each of the three case study technologies.

Customisation: therapies

All autologous cell therapies have some degree of provider-led customisation, with each batch being necessarily patient-specific. However, as existing CAR-T therapies demonstrate, manufacturing of autologous therapies can operate more like a 'mass customisation'[1] approach with a standardised process being applied to a patient-specific starting material, to give a defined product. While each batch is patient-specific, it is not a new or unique product in regulatory terms.

Several developers are working on next generation allogeneic CAR-T therapies, including iPSC-derived or gene-edited CAR-T products. Other iPSC therapies may follow a similar route, with initial autologous products seen as a 'stepping stone' to fully allogenic 'off the shelf' products. Allogeneic iPSC and bioprinted treatments where each company develops its own clinical grade product from a private seed stock of clinical grade material is closest to the model of conventional pharmaceutical development and involves neither customisation nor personalisation. An alternative vision of delivering allogenic iPSC involves creating 'seed stock' banks of clinical grade iPSC from a range of donors selected to provide wide coverage of different human immune system markers, known as human leukocyte antigens (HLA) types, allowing lines to be selected to manufacture a desired cell type with an immune profile that matches that of the donor. This should reduce the need for immune suppression and reduce the likelihood of rejection.

It may be that any future global supply of allogenic iPSC would operate through networks of national or regional banks exchanging units of cellular material in a similar fashion to the way cord blood banks currently operate.[2] The degree of customisation involved is similar to that of 'assemble to order' manufacturing in other sectors, where options are selected from a range of pre-defined components and then assembled to produce a product that works for the particular 'customer'. The degree of 'assembly' is much more complex in manufacturing an iPSC therapy than in most other sectors. If this model were to be realised, iPSC therapy development could effectively operate through a public-private partnership: National governments would fund and curate haplotype banks of human iPSC lines matched to each population. This would be the official, regulator-approved starting material for all nationally-approved iPSC therapies in that territory. Individual commercial companies would then claim the model of differentiating the cells and making and delivering the end product as the commercially sensitive, IP-protected part of the process, and the part that generates revenue for them.

Several academic projects are also underway to try and develop genuinely 'universal' clinical grade iPSC using gene editing to remove key molecular markers of immunogenicity. In gene editing more broadly, the emphasis is very much on developing gene editing constructs that can work in whole patient populations, not in individual patients. However, given that many early applications of gene editing focus on rare disease

(see Briefing 1#), the small patient population means specific, often tailored, treatment and monitoring need to be provided at a limited number of specialist centres rather than a mass roll-out of the therapy to routine hospital care.

Elsewhere, precision medicine based stratification of populations into biologically-defined subsets of patients is more akin to conventional market stratification, than customisation or personalisation. User-led customisation is uncommon in the medical sector, but both clinician and patient-led tailoring modification does happen; for example some patients with type 1 diabetes use open source software to integrate continuous glucose monitors and insulin pumps into a DIY customised 'closed loop' insulin delivery system.[3] The complexity of cell and gene based therapies is such that patient-led customisation is highly unlikely.

Customisation: manufacturing

Most biomodifying therapies are produced by a process, the specificities of which are unique to that product, and indeed give that product its precise attributes and functionality. In this sense each product requires a tailored production process:

> **[I]f you deal with an advanced therapy, all of a sudden you have to deal with very divergent technologies from immunology to viral vector technology to vector analytics that speaks about the standardisation. There are no standards out there, and process innovation and you have to do all of that with a focus of one therapy (Gene therapy/gene editing company interview 3#).**

There is evidence of some manufacturers providing custom (i.e. made to order) supplies of reagents, so that one vial provides the exact amount of material needed for a particular protocol and avoids pipetting (a source of variability) or waste. Similarly closed or semi-closed automated systems for manufacturing advanced therapies tend to be modular so that specific steps can be carried out in different orders or with different timing to produce various products using the same machine. Contract Development and Manufacturing Organisations (CDMOs) also necessarily have some flexibility to adapt their basic processes to the demands of different therapies. This tends to involve a mixture of standard steps (e.g. mycoplasma testing of batches) with customised steps such as assays tailored to the requirements of that particular product.

Moreover, the product specifications- and therefore the manufacturing specifications- can also be modified during the clinical trial phase:

> **With gene therapy, because we can change promoters, we can manufacture more vector, less vector, we can adjust these parameters and I think most gene therapy products have had to go through a round of clinical testing followed by the next round, and it may be your delivery method is different […] so these parameters can only really be optimised in following data from patients (Gene therapy/gene editing company interview 6#).**

This 'tinkering' with the production process is often necessary, but can add to the time pressure for getting a workable manufacturing solution and supply chain (including full traceability) in place during the already compressed clinical trial phase of R&D (see Briefing 2#).

The most disruptive forms of customisation in manufacturing comes through 3D bioprinting. Bioprinting, like other 3D printing is a form of additive manufacture that builds complex structures through repeat layering to generate a three-dimensional form. Additive manufacturing is a flexible production technology that embeds customisability in the design process and is geared towards cost-effective, low volume manufacturing of complex 3D products tailored to small group or individual spatial (geometric) requirements. Non-invasive medical devices such as orthopaedic supports, in-ear hearing aids, and orthodontic aligners are already produced using 3D printing of plastic or metal, where the standard product is adapted to the contours of a specific patient's body shape. This can be done rapidly because 3D scans or casts of body parts can be readily converted to Computer Aided Design (CAD) files which can then be designed and sent to a 3D printer for automated production. For the purposes of EU medical devices regulation, these are not considered 'custom-made' (i.e. bespoke, personalised) medical devices.

This model of provider-led mass customisation has been termed 'standardised individualisation'[4] because the process of customisation is made routine (through the scans) and built into the production system rather than involving manual 'craft' production of a tailored item. Applied to bioprinting this could enable routinely customised tissue implants to be created. The viability of this approach may depend on whether the intended function of the implanted tissue is primarily mechanical, where customisation in term of shape and size is the main concern, or if the cells are intended to produce a biological action as well, in which case customisation starts to look more like *personalisation* of molecular compatibility between patient and product, which is more complex in both technical and regulatory terms.

3D bioprinting as a manufacturing technology can also enable redistributed manufacturing of cell and tissue based products. For standardised products, whether allogeneic or autologous therapies where each sample is processed in a comparable way— it makes logistical and economic sense to keep manufacturing as

centralised as possible. This keeps the cost of equipment and facilities down and allows centralised quality management, batch control and sign- off by qualified persons (QP) and is favoured by many commercial manufactures including large pharmaceutical companies. There are two ways bioprinting could be deployed:

1) Bioprinting could facilitate highly localised, 'surgeon-led' 3D printing of customised cellular constructs. This would allow very near-patient manufacturing, which can be important for products with a very short shelf life or which are not amenable to the freezing and thawing cycles needed for more centralised manufacturing strategies.
2) Alternatively scans could be transmitted to a centralised facility, NHS or commercial, where each implant is designed, then transmitted to bioprinters at local sites. This looks more like conventional manufacturing in terms of scalability and manufacturing site costs, but raises issues of the security of transmitted patient-specific CAD information, which is unavoidably confidential, and about the distribution of liability among the various computer engineers, bioprinter operators, Qualified Persons, surgeons and manufacturers of components such as bioinks and scaffolds that may be utilised to create the final implant. Here, it is not the bioprinted construct that is commercialised but the equipment, protocols and capacity to produce the implant, which is a rather different business model.

The feasibility of both options depends a great deal on the skill sets, equipment, and GMP-compliant facilities at hospital sites to deliver cell-based products.

Regulatory considerations

At the present time truly patient-specific, biomodifying therapies are only likely to occur as one-off exceptional interventions, delivered through the regulatory pathways for hospital exemptions or hospital specials. The hospital exemptions route of the EU ATMP Regulation has been controversial from its inception. Data suggest it has seen only limited application to deliver advanced therapies in the UK. This may also reflect the fact that the MHRA takes a tougher stance than some other European national regulators, on what counts as 'non-routine' use. Preliminary evidence from an MHRA Patient Group Consultative Forum on biomodifying technologies also suggests that patients are not enthusiastic about truly bespoke therapies, preferring interventions that come with the evidence base from testing and evaluation in a relevant patient population. This insight produces not only medical evidence but experience-based knowledge of how to navigate care pathways and cope with treatment regimens that patients can share with each other as a source of peer support.

If bioprinting were to be considered in regulatory terms as only a minimal manipulation of the cells, then a bioprinted construct might be regarded as a transplant, and its products as the 'practice of medicine', but it is more probable that regulators will regard the construct as a product under the ATMP regulations (most likely either as 'tissue engineered medicines' or 'combined ATMPs' including a medical device component). At present there are still significant regulatory and logistical obstacles to redistributed bioprinting, but it remains to be seen whether post-Brexit regulatory changes will have any effect on this situation.

The regulatory requirement to verify the safety and quality of patient-specific batches of therapies is one of the major limiting factors of customised or personalised therapies in terms of time (see Briefing 2#) and cost. CAR-T cells for non-solid tumours have an advantage here in that, as a treatment of last resort, even batches that are 'out-of-specification' in terms of quality manufacturing standards may still be administered to the patient because there are no other therapeutic options. However, therapies for non-fatal conditions will not benefit from this leeway. Agreeing procedural standards is especially important in managing and de-risking the inherent variability of many biomodifying technologies. The Joint Accreditation Committee of the International Society for Cell and Gene Therapy's European arm (ISCT-Europe) and the European Society for Blood and Marrow Transplantation (JACIE) now provide accreditation for clinical facilities providing cell therapy, covering the clinical steps from collection of the starting material through to patient follow-up.

The drive towards more patient-centred medicine also means that performance standards for biomodifying therapies will likely include both technical measures of safety and efficacy, and measures that capture the qualitative experience of therapy such as patient-reported outcomes measures (PROMs). This stance is echoed in the recent *Cumberlege report* into the post-marketing surveillance of implanted medical devices, which found that patient-reported experiences of interventions should be given more importance in evaluations of implantable medical devices, and in recent statements from the MHRA which have emphasised the importance of "putting the patient voice at the heart of regulation".

A considerable body of sociological evidence also shows that clinicians adapt, tinker with, and modify procedural standards, or choose flexibly between competing standards, in order to make them work for the needs of specific patients. Both patient and healthcare professional experiences of 'what works' are therefore going to feed back into the development and refinement of procedural standards for administering and following up biomodifying therapies.

Priorities for policy

- **It is important to find the balance between having sufficient flexibility to allow customisation to operate alongside mass manufacture**, **while maintaining quality and protecting patient safety**. Mass production of therapies for certain conditions will remain the most commercially attractive option, while others could benefit from one or more of the forms of customisation presented here.
- **Post-Brexit reforms need to decide whether to support one or multiple production strategies**: mass production, mass customisation, and redistributed manufacturing need different organisational structures and require different skill sets from the workforce, and face different logistical and regulatory hurdles to viability. Future policy developments, especially in view of the UK's departure from the European Union, need to evaluate whether to support one or several forms of manufacturing within the UK healthcare sector, as each requires different forms of support.
- **Procedural and performance standards need to be capable of evolving over time**: ATMP pharmacovigilance, whether one-off studies or registries, should incorporate evaluations from patients and clinicians in addition to standard measures of efficacy and reporting of adverse events. The combination of precision medicine and patient-centred medicine supports ongoing evaluation of the outcomes of treatments which creates a feedback loop into procedural and performance standards for biomodifying therapies. The three UK Advanced Therapy Treatment Centres should identify workflows across companies and hospitals that support this ongoing refinement of the entire 'pathway to the patient'.
- **Users, both patients and clinicians have an important role to play in the design, development and evaluation of biomodifying therapies.** This is especially pertinent when considering the evaluation of conditionally-approved therapies where multiple types of data (observational, registry, patient record, PROMs) could be integrated.
- **Design 'supporting technologies' for biomodifying therapies to support tinkering**. Designers of technologies that enable the production, testing, storage or administration of biomodifying therapies should consider whether their products support local 'tinkering' adjustments and customisation by skilled technicians, as this practice-based learning is a valuable source of innovation and process improvement.
- **It is important to avoid premature 'lock-in' to design standards:** Design standards for components (clinical grade cell lines, bioinks, gene editing constructs, bioreactors, bioprinters) are necessarily less flexible than procedural standards, but as product and process are so closely linked in biomodifying technologies, design standards will need to be revisited and reviewed periodically to ensure they do not inhibit positive improvements in how treatments are stored, administered or otherwise tailored to patient needs.
- **Opportunities for strategic standardisation at NHS level to avoid excessive customisation:** A proliferation of product-specific collection, storage and administration protocols could overload the capacity of even specialist clinical centres. As the UK's primary provider of healthcare services, the NHS is in a position to develop standards for some procedures relating to biomodifying therapies, such as protocols for harvesting of biological material as a starting material, data standards and tools (software) for reporting data on storage and administration of biomodifying therapies, patient aftercare, and 'real world evidence' of outcomes. Diverse providers would be incentivised to meet these standards in order to access the UK healthcare market.
- **Tailoring of treatment can also occur after marketing approval:** Policy briefing 1# identified that for some conditions multiple biomodifying therapies are in development. If several products are approved this could allow pragmatic trials and n-of-1 trials, aimed at finding the optimal therapy for small groups of individual patients.

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