Responsible Personalised Medicine

Exploring the Ethical, Legal, Social, Political and Economic Issues of Manufacturing, Distribution, Access and Reimbursement.

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About this report

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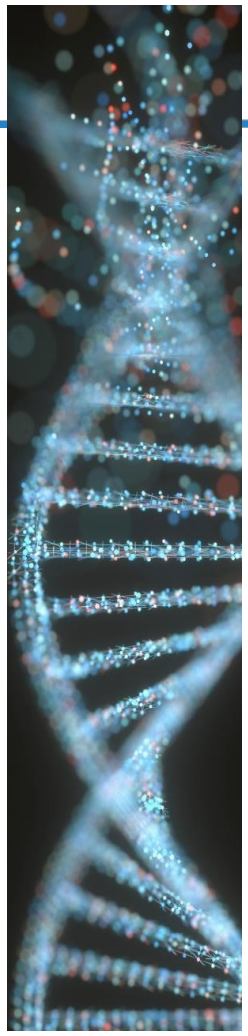

Executive Summary

This report provides an overview of the ethical, legal, social, political and economic (ELSPE) issues underpinning the "manufacturing, business and regulatory challenges" that confront the development and delivery of affordable and accessible new targeted biological medicines.

We specifically focus on the evolving **definitions and its implication for the public understanding** of personalised medicine (section 1), issues of **manufacturing and distribution** of Personalised Therapies (section 2) and **institutional readiness** (section 3) specifically focusing on emerging regulatory and reimbursement pathways (section 3.2) and how these are shaping or being shaped by 'real world evidence' (section 3.3). This is followed by our reflection on the implications of and for the entangled, complex and contingent interrelationships between **personalised medicine, society and responsibility** (section 4). Finally we conclude with discussion of the **gaps and priorities for future ELSPE research on manufacturing of advanced biotherapeutics** in terms of access, reimbursement, skills and infrastructure, regulation, responsible research and innovation (RRI) and the international political economy of emerging personalised medicine markets (section 5).

This is a necessarily narrower review of the spectrum of ELSPE issues that attend personalised medicine activities and reflects this report's aims to focus on those aspects of personalised medicine addressed by the UCL's Future Targeted Manufacturing in Healthcare Hub.

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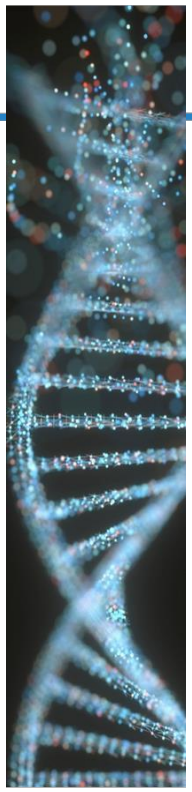

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Introduction

This report provides an overview of the ethical, legal, social, political and economic (ELSPE) issues underpinning the "manufacturing, business and regulatory challenges" that confront the development and delivery of affordable and accessible new targeted biological medicines.

As such, the evolution of 'personalisation' in medicine and the various terms and interpretations that have co-evolved with some inter- and intra-jurisdictional variations is less than tidy. A discussion of these **definitional elements (and ambiguities) of 'personalisation'** is considered useful for our purposes here and is presented next (section 1.1). This is followed by a review of the specific ELSPE aspects of data governance applicable to 'personalisation' in medicine (Section 1.2). However, we do not include a general discussion of the wider issues of data governance such as those related to privacy, anonymisation, algorithmic accountability etc. as these are not specific to advanced biotherapeutics and are discussed in depth elsewhere.

This is in keeping with the report's aims to focus on those aspects of Personalised medicine that reflect the priorities of UCL's Future Targeted Manufacturing in Healthcare Hub, which is necessarily narrower than a review of the ELSPE issues that attend the spectrum of personalised medicine activities and extensively studied elsewhere (3,4,5). In particular, a discussion of the ELSPE issues around the access and (mis)use of human tissue[1] is beyond the remit of this report as these are not unique to manufacturing of advanced therapies in particular but applicable to scientific and medical activities in general (e.g., laboratory research, biobanking, blood and organ donation and transfusion/transplantation). The issues of interest for our purposes here are those concerned with challenges and opportunities of **Manufacturing and Distribution** of Personalised Therapies (section 2), **Institutional Readiness** (section 3) with a focus on emerging regulatory and reimbursement pathways (section 3.2) and how these are shaping or being shaped by 'real world evidence' (section 3.3). Finally, we conclude with our reflection on the implications of and for the entangled, complex and contingent interrelationships between **personalised medicine, society and responsibility** (section 4). A last section identifying **gaps and priorities for future ELSPE research on manufacturing of advanced biotherapeutics** in various strands of examination from access, reimbursement, skills and infrastructure, regulation, responsible research and innovation (RRI) to the international political economy of emerging personalised medicine markets is provided (section 5).

[1] Tissue ownership, intellectual property rights, extraction of genetic information, adequacy of consent, donor (non)payment exploitative oocyte donation and organ trafficking practices, biopiracy, etc.

Section 1
Data Driven Personalisation in Medicine: Definitions and Issues

1.1 Definitions and public understanding of personalised medicine

Often interchangeably referred as 'stratified' or 'precision' medicine, the term PM has come to describe an ever-expanding repertoire of targeted medical interventions ranging from pharmacogenomics and data-driven healthcare using machine learning based algorithmic prediction to wellness activities such as self-tracking.

In general, personalised medicine evokes the idea of matching treatments to the biology of individual patients. This 'matching' in turn draws on the notion of precise measurement of a variety of physical, biological and behavioural data points that can be used to characterise, or situate, each patient in terms of a particular set of correlations derived from a large, ideally population wide, data set (1). In this sense, 'personalisation' in 'personalised medicine' involves an idea of detailed and precise measurement as a necessary precursor to narrower and more stratified ('more accurate') diagnosis, prognosis and treatment categories. Importantly, while a range of technologies from whole genome sequencing to big data are currently considered as tools for 'personalised medicine', the majority of applications involve classification and stratification of patients for diagnostic purposes as well as for risk-based predictions of future (ill) health.

Advanced biotherapeutics, especially cell and tissue-based therapies offer something different, as they provide, at least prospectively, the hope for *matched therapies*. Autologous cell therapies using cells derived from the patient's body (and usually modified or processed in some way) are one of the oldest and most established types of regenerative medicine therapies. These include early tissue engineering products such as skin and cartilage replacement products, haematopoietic (bone-marrow derived) stem cell treatments for leukaemia (2), as well as the more recent advent of Chimeric Antigen Receptor T-cell (CAR-T) therapies for blood-born cancers. In this sense, autologous therapies are 'personalised' as each batch can only be administered to the patient from whose body the biological material of the therapy was originally derived. However, cell and tissue-based therapies and even allogeneic therapies (where the cell donor is different than the patient) are also *targeted therapies* in the sense that they treat a medical condition by targeting a specific site for intervention in the body (such as an organ or tissue). A germane example is 3D bioprinting where a significant part of the appeal is the aspiration of producing tissues and even whole organs for transplant matched to the size and shape needed by a specific patient. This is seen as having particular utility for paediatric organ transplants where the shortage of donor organs of a suitable size is especially acute.

In the UK and much of the EU, PM is generally seen as the preferred term while 'precision medicine' is more commonly used in the US (for example in relation to the 'All of US' National Precision Medicine programme) (6). 'Stratified Medicine' is arguably the most accurate term to describe what is typically encompassed by much of 'personalised medicine' and has been championed by the World Health Organisation for this reason (7). In the UK, 'stratified' was also initially advocated as the more accurate term by the Association of Medical Sciences (AMS), but this was ultimately considered inappropriate after further research from Innovate UK demonstrated that the term was mainly associated with social divisions (8,9). Similarly in

the US, ‘stratification’ was seen as implying ‘racial and income stratification, genetic and healthcare discrimination and [raising issues of] social justice’ (6).

Despite this definitional ambiguity, the term PM can be interpreted flexibly (1,1011). In some contexts, the term ‘personalisation’, is part of a 4P-Medicine (180) that seeks to empower patients in ‘taking responsibility over [their own] health’, while for patients, and patient associations and charities it can also be understood as advocating more holistic, patient-centred approaches to care (1,12,13) and for scientists and clinicians the meaning is typically the aspiration for more accurate diagnosis along with fewer side effects (1,6).

The various terms to describe personalised medicine and the debates as to which one should be used for public acceptance of the technology is reminiscent of what King and Lyall refer to as ‘narrative priming’, an idea first developed by Ferguson et al (14,15). Initially discussed in Ferguson’s study as a way of identifying accepted terms for blood substitutes, whereby the public perception for ‘substitute’ also tends to be associated with ‘substandard’ and therefore stalls further development of a technology labelled as such, narrative priming essentially demonstrates how the framing of technologies and the terms used to describe them can have a substantive impact in their uptake and success. (6,8,9,16-20). In a similar way, the term used to describe any technology has a serious impact on whether it is considered as discriminatory (‘stratified medicine’) or participatory and a way of democratising medicine (as the use of the most accepted ‘personalised’ has demonstrated). With regards to the latter, ELSPE scholars have noted the potential for the term ‘personalised medicine’ to foster ‘overly optimistic associations’ and thereby mislead or generate unfounded expectations amongst patients and the public (6,17,21,22). Caution is therefore warranted to avoid hyperbole in promoting personalised medicine and care needed to ensure the meaning of personalised medicine in a given context, such as the Hub, is accurately and realistically convened to lay audiences.

For the purposes of this report and in accordance with the Hub’s remit, we describe PM as emerging biotherapeutics tailored to the biology of an individual (a bespoke, or mass customised autologous therapy) or to a comparatively narrow, well characterised patient population (stratified medicine). ELSPE issues of data, algorithms, patient experiences, mobile health which command an extensive and exhaustive scholarship (13,23-29) are undeniably intertwined within this description and discussion of these within the context of the manufacture and delivery of targeted biotherapeutics are provided later.

1.2 ELSPE of Data-driven personalisation in medicine

In the digital era, personalisation ‘appears as the data-intense characterization of individuals at different stages of health and disease in the course of their lifetime’ and requires molecular and non-molecular data, with a growing portion of the latter quite often coming from ‘non biomedical research contexts’ (25). This increases in complexity as boundaries between ‘health data’ and ‘non-health data’ become increasingly blurred by wearables, mobile apps and interactive devices that not only collect data across myriad types of everyday activity (e.g., walking, running) but also across diverse data sources from social media posts to voice commands recorded by emerging audio-enabled devices (30). Data driven PM raises well known, though not always well-addressed ELSPE considerations of privacy, cybersecurity and informed consent for data collection and processing. The potential for ‘context transgressions’ (31) when data passes between medical, social and commercial contexts is also considerable and adds a further layer of complexity when deciding which data *should (not) be* included in ‘personalisation’.

Issues of multiple and diverse data sources are likely to be exacerbated as the global popularity of personal 'health' tracking encourages a simultaneous rapid global expansion of diverse health and wellness offerings by global "Big Tech" firms such as Google Apple, Facebook, Amazon, Microsoft, and IBM (32) and their regional counterparts Baidu, Alibaba, and Tencent (33). The rapid penetration of private sector entities in the health and wellness data-generation space adds further complexities; A germane example are the challenges of transferring or (re)securing consent from the data subject when primary data-owning companies are liquidated or sold and data-ownership is transferred to third parties (see 'third party consent' in (30) pp 33).

In many instances users contributing data are not adequately informed as to how their data will be used, or which companies have or will acquire them. Prainsack (25) has warned of a triple threat of 'hypercollection', where organisations collect data on of consumers simply because it is available, 'harm' when collected data is primarily used as a means of increasing revenues, and 'humiliation' arising from consumers 'having to trade their privacy for something they cannot otherwise afford'. Some critics have cautioned that this kind of indiscriminate data collection, as a means of measuring long-term outcomes in the context of personalised medicine, can create a 'digital panopticon', in which individuals are essentially defined by their data (6,34). Research suggests that in the public, sharing health data with commercial companies can find support if there is clear benefit to patients or the public such as better diagnosis and treatment. However, sharing of data primarily for purposes such as marketing or insurance, may also lead to reduced rates of participation and reduced willingness for broad data sharing (35,36).

Public-private partnerships for co-producing data-driven health offerings have also attracted both public concern and scrutiny after a number of high-profile collaborations such as that between the UK's NHS Trust and Google's Deepmind. Powles and Hodgson (37) revealed gaps in the informed consent required for collection and transfer of UK citizens' sensitive medical data from the NHS to third-party data brokers (38). Similar outcomes elsewhere such as the Project Nightingale in the US and DAMID in Denmark (39) have further eroded public trust. With Prainsack (25) finding that even data collected by non-profit entities, while seemingly innocuous, can very easily become 'collected for profit' if these companies are acquired by larger conglomerates that see value in using or selling data.

Arguably, not all of these considerations are directly relevant to advanced biotherapeutics e.g., those related to wearable devices. However, advanced biomanufacturing used in the development of therapies targeted to patient sub-populations is still implicated in the wider processes and systems used to generate and process that data, even if these actions were not the direct result of the manufacturer. Using outputs of systems that are unethical or violate public trust should be scrutinised and subjected to rigorous oversight if used for personalisation or stratification of patient populations. This is illustrated in our case study of artificial intelligence (AI).

CASE STUDY 1

Artificial Intelligence: *issues of fairness, bias and discrimination*

Artificial Intelligence (AI) based health(care) applications under development are widely expected to **be** used for a range of use cases in both clinical settings (for diagnostics, clinical prediction) and non-clinical purposes (billing systems, scanning global databases of active pharmaceutical ingredients to match compounds with targets etc.). Our concern here is with the ELSPE issues surrounding the former set of applications in PM, and specifically the manufacturing-related use cases. Of particular concern are the processes and practices of stratifying patient sub-populations using genomics and other biomarkers for development and manufacturing of cell therapies as below:

- **bias in training datasets** used for (un)supervised machine learning (40) weakens commitment to fair and equitable use of health data (41-43). This is because contextual factors such as political agendas, commercialisation, personal interest, gender, class, age and race and various traditionally discriminatory practices and policies embedded in training datasets are reiterated in algorithmic functioning, becoming embedded in the technologies thus developed. As a result, AI -based application replicate and oftentimes amplify traditional biases across gender (e.g., stigmatising women (44,45) ethnicity, demographics, geography (46-48) and socioeconomic diversity (49). For instance, Benjamin's (2019) work shows how existing institutionalised racist structures are essentially replicated and amplified further by AI - the same technology that is thought as being the solution to this problem – or what she calls the 'automation of racial discrimination (50). Likewise, data-driven technologies can exacerbate traditional biases by 'render[ing] some things visible at the expense of others' (51). For instance, Nike's FuelBand, marketed as a lifestyle and wellness tracker for both genders, reinforce gender biases by tracking male-centric activities at the expense of activities traditionally associated with females (such as nursing or gardening) that are considered 'inactive' periods (25).
- **algorithmic inscrutability** (52-54) and the extent to which it enhances or hinders '**explainability' of outcomes** (55-58) have profound implications for **transparency of and public trust in AI** (59-66). Trust is defined as a 'three-place relationship' between a trustor who 'places her or himself in a relationship of dependency on [a trustee] with regard to a particular range of action' while the trustee in this case can be 'a person, a social group, institutions, set of data, operating system' (59). It also inevitably entails vulnerability and risk (60,61). In the context of AI-enabled health technologies and trust, there is a distinction between 'epistemic trust' (which is concerned with trusting expertise such as 'trusting the clinician') and 'moral trust' (which is concerned with public willingness 'to accept knowledge and information provided by scientific or diagnostic devices, social media, or intelligent systems such as AI is accurate, reliable and can be used as a basis for learning and decision making' [62,63]).
- In turn, **public (specifically clinician's) trust in the explainability and transparency of outcomes** delivered by AI-enabled PM is key to its implementation in clinical settings (67-69) As such, "acceptance of scientific innovation reflects in large part the confidence that the administering clinician has in the use of an innovative technology in clinical settings" (59). Another key issue that plays a significant role in clinician's willingness to implement AI-enabled PM in clinical practice is their trust that these technologies will 'assist' rather than 'replace' their

experience and tacit knowledge in clinical decision-making (51,65). 'Clinician's trust' is gained through collaboration between clinicians and developers over 'time and space to forge interpersonal-clinician trust relationship necessary to create bridges across the researcher-clinician divide' to develop 'affordable real world service models' that improve trust among users (patients, clinicians) and result in technology adoption, rather than abandonment (51). Thus, improving implementation rates of AI-enabled PM depends not only on improving trust in the technology but also improving confidence in the aims and functioning of AI among stakeholders from researchers, clinicians and patients to regulators.

These issues and implications of 'trust' in the development and use of AI are reflected in the European Commission's guidelines on what trustworthy AI should be (70). Alongside compliance with regulations and technical robustness, the EC's 'trustworthy AI' guidelines highlight the importance of respecting and strengthening democratic values and respect for human rights (59).This must necessarily go beyond 'ethics washing' (188-190) to meaningful engagement with the 'principles' and codes of ethical conduct to include concrete and assessable practices of engagement, harm mitigation and a commitment to ameliorating, changing, or replacing AI tools and practices that are unfair, unjust or discriminatory[2]. Various processes for improving transparency and (thereby) public trust in AI-enabled technologies have also been recommended. For instance, the Ada Lovelace Foundation's Algorithmic Impact Assessments (AIAs), a method first used in Canada (71) proposes a participatory consensus-building process whereby publics have the opportunity to debate the harms and benefits of implementing AI technologies in specific scenarios. AIA uses a 'citizen jury' methodology (72) whereby participants are ideally not only patients (the users) themselves but also represent stakeholders likely to be bear the (adverse) consequences of algorithmic implementation.

CASE STUDY 2

Algorithmic 'Trade Offs'?

No technology is, or can be, perfect or risk free and there will always be uncertainties and ambiguities about how best to proceed (73). Implementation is a matter of judgement, of finding an acceptable balance, not only between risks and harms, but also between competing goods. For example, many citizens would agree that faster and more accurate diagnosis of disease is desirable, but if it requires sharing large amounts of sensitive medical data with private developers, then the question becomes how to balance the competing 'goods' of health and privacy (74). Key trade-offs include:

- Accuracy versus explainability: explainability (the ability for a human to be able to understand and assess the manner in which an AI functions and why particular inputs result in particular outputs) increases understanding and accountability but may produce less sophisticated algorithms that may be less accurate.
- Transparency versus usability: a related quandary is the question of what the desirable balance between is providing information to show the calculations leading to each decision by an AI and keeping particular doctor-patient interactions timely and functional (i.e. not overburdened by complexity)

[2] Indeed the EC guidelines have themselves been the subject of substantial criticism for being tokenistic, unenforceable and potentially contributing to 'ethics washing' by AI developers (188-190).

- Performance versus security: AI systems work better with more data but enabling access for AI and ML tools may make sensitive personal medical data more vulnerable to unauthorised access and more available for genuine but oblique secondary research purposes.
- Performance versus privacy: Similarly, accessing more data can also extend the reach of AI systems into ever-greater aspects of a person's life; confidential medical notes, audio recordings, conversations with 'chatbots', visual data (for facial recognition), mental health and behavioural data. Is there a point at which participants judge that improved AI function is not worth the loss of privacy required to generate it?
- Security and privacy: This is of particular salience when private companies are involved in accessing or safeguarding personal data and when the AI's activity may generate secondary information that is itself commercially valuable. Privacy and security concerns can also be inverted in the commercial case as companies have an interest in protecting their intellectual property in the functioning of an AI through secrecy, which must be balanced against explainability and transparency.
- Speed of implementation versus fairness: AI systems that make predictions based on historic data sets are vulnerable to replicating racial, gendered, socio-economic and other biases inherent in that historical data (75). There is therefore a trade-off between getting new AI systems up and running, and potentially delivering patient benefit, and rigorously testing the AI performance for any signs of bias before deploying it.
- Efficiency versus patient and physician autonomy: Does there need to be a 'human in the loop' even if this slows the AI system down and makes it less efficient? Do decisions made by an AI system need to be verified by a physician before they are actioned? (76). And do patients have the right to dispute AI findings or opt-out of AI services, even if lower participant rates reduce the accuracy and efficiency of the system?
- Performance versus affordability and accessibility: AI technology can be expensive to produce and maintain, as well as to train staff to use with sufficient understanding and certainty. High-powered AI systems may not be accessible to rural or smaller healthcare facilities. AI systems may also produce efficiencies in care but impose significant financial and resource burdens on hospitals.

Trade-offs can also involve balancing competing harms as well as goods. As a statistical tool, machine learning cannot have complete accuracy (even if accuracy can be extremely high). Instead, there is an unavoidable choice to be made as to whether to optimize false positive results (detecting disease where none is present) or false negative results (failing to detect disease where it is present).

Section 2
Manufacturing and Distribution: Challenges and Opportunities

In this section, we review the different manufacturing options posited for advanced biotherapeutics and summarise general ethical, legal, social, political and economic (ELSPE) issues arising from each or all of the different manufacturing options. A case study of 3D bioprinting and biofabrication will provide a more detailed look at issues associated with fully redistributed, co-located manufacturing of advanced biotherapeutics.

2.1 ELSPE of Manufacturing Models

Fully Centralised Manufacturing Model: this is the traditional pharmaceutical model where manufacturing takes place in a centralised facility with distribution to a large number of clinical facilities over a large, often international area. This is the most widely used model outside advanced therapies and is a very successful and well established one in healthcare as its economies of scale supports the 'blockbuster' pharmaceutical model which is the antithesis of personalised therapeutics (77). It is potentially applicable to allogeneic cell therapies, provided the product is amenable to cryopreservation and transport. However, advanced therapies often have very limited shelf life and require a high level of care specialisation and co-ordination to deliver successfully. For example, autologous keratinocyte-based engineered skin should be transplanted within 24h of leaving the manufacturing facility, but if a patient's condition deteriorates during the transit period such that surgery is not possible within that window, the patient's skin, the company's resources, and critical time for healing are all wasted (78). Autologous therapies also require a more careful chain of custody management that is challenging to achieve with centralised models. As a result, some commentators have advised that the fully centralised model is the least appropriate manufacturing strategy for autologous therapies (see e.g., (79), pp 571-572).

Hybrid/partially distributed Manufacturing Model. Several options exist from partially distributed manufacturing models which also support different degrees of personalisation. The **hub and spoke model** uses a single manufacturing centre serving multiple clinical sites within a defined geographical locus (usually local or regional) (77). For autologous cell therapies, such as a number of existing CAR-T products, this permits a degree of "mass customisation" with a standardised process being applied to a patient-specific starting material, to give a defined product (80). While each batch is patient-specific, it is not a new or unique product in regulatory terms. Alternatively, with induced pluripotent stem cells, it may be possible to generate banks of clinical grade cells covering the major HLA types for a given population or region (81-83) Such banks may be state-run and could operate as a different kind of 'hub' supplying different companies within that country or region each applying their own manufacturing process to generate a specific product. 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 predefined components and then assembled to produce a product that works for the particular 'customer' (80). Lastly, single sites within the EU where manufacturing and clinical care are collocated may be able to operate a franchise model where the manufacturing process and associated IP is franchised out to a comparable centre in another Member State, as the marketing authorisation and approval obtained from the EMA would still apply (77).

Fully (re)distributed Manufacturing Model (RDM): this model is also known as 'point of care manufacturing' or 'single centre co-located manufacturing model' (77,84). Here, the clinical facility is also the site of manufacturing. This model is the best fit for truly bespoke personalised (individual) therapies and facilitates near-patent manufacturing of small batches of biotherapeutics for stratified patient populations. Closed, automated or semi-automated processing systems, especially 'desktop' cell processing units can support this kind of approach, although some level of GMP clean room is still required and not all clinical sites have sufficient patient numbers for relevant conditions for this to justify the investment (77-79). An extreme model is to have a single clinical/manufacturing site for an entire geographic region such as Europe or North America, and to have the patient population travel to the centre to receive care. 3D bioprinting is another technology that supports fully distributed manufacturing and raises several specific issues that are considered in more detail below.

Some generic ELSPE concerns have been identified with fully or partially redistributed manufacturing:

- The geographical location of hub-and-spoke or franchised clinics raises access issues. Not all locations will have adequate infrastructure to support these manufacturing facilities which implications for access by patient populations outside large metropolitan centres. This is exacerbated if international travel is required and not all healthcare systems and payers will support the costs of international travel and accommodation needed for this model.
- 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 of mass production, mass customisation, and fully redistributed manufacturing need different organisational structures and require different skill sets from the workforce, and face different logistical and regulatory hurdles to viability.
- 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 advanced therapies. 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, although more work is needed on how to operationalise this in practice.
- Sociological research on public and patient attitudes suggest that at least for some allogeneic cell therapies, such as iPSC-derived blood products, they are likely to occupy a 'liminal space' between donated blood (which is often seen as natural and relatively safe by blood donors, transplant recipients, and members of the public) and synthetic blood products, which either use animal derived material or acellular chemical compounds like perfluorocarbons to transport oxygen round the body, and are often regarded as unnatural, substandard, or more risky by the public (15).
- Where allogeneic cell therapies aim to replace existing autologous donated materials (blood, corneas, oocytes, etc), they also change the social meaning and experience of donation, from an altruistic act of solidarity, based on need and the common good, to consent to create a potentially lucrative and/or exclusive commercial product (19,85). Using iPSC-derived blood products as an illustrative example, such donors could be asked to show solidarity with a biological (and in the case of thalassemia and sickle cell disease, often racially or ethnically defined) population rather than to a broader communal good. This change in the organisation of donation has the potential to disrupt longstanding ideas of the donor-recipient relationship (86,87).

- Truly personalised therapies may be unappealing to patients as they may involve a unique or hard to quantify level of risk. Patients can draw reassurance from knowing that other people have undergone a particular treatment or used a medical device. This shared experience provides a shared pool of knowledge and know-how, which individual patients can draw on to make informed decisions (88).
- Personalisation or stratification of treatment can also create a plethora of treatment pathways (as seen to an extent in personalised cancer treatment regimens), which inhibit the sharing of patient experience sharing and the sense of solidarity this can foster, as well as sometimes entailing the stratification of service provision amongst a greater diversity of public and private groups, which again makes it harder for patients to understand the care pathways in which they are involved (89).

CASE STUDY 3

3D Bioprinting: *An emerging tool for distributed manufacturing.*

3D Bioprinting is a novel technology that aims to producing 'structures approximating body parts', the 'production of bioactive structures in layer-by-layer deposition of cells, with the use of devices called bioprinters' (96,106). It is a form of additive manufacturing, where complex three-dimensional constructs are produced by depositing fine layers of material one on top of the other. Bioprinting adapts this technique by replacing plastic or metal as the material to be 3D printed with gel-like suspensions containing living cells, polymers and signalling molecules (such as growth factors), known as 'bioinks'. The goal is to "transfer the precision, flexibility, speed and agility offered by 3D printers to clinical applications in order to recreate highly complex and heterogeneous structures" (90).

The process, otherwise described as 'biofabrication' has two phases, bioprinting and bioassembly. The bioprinting phase uses a bioprinter, bioink, and accompanying software. The software includes Computer Aided Design programmes that allow the modelling of three-dimensional constructs, Computer Aided Manufacturing software, which translates the design files into digital instructions that a bioprinter can interpret, and potentially also software to support quality analysis of the printed cells in culture. Bioassembly is essentially the additional methods used (weaving or knitting) to allow the integration of building blocks of bioprinted material (91). It has been argued that bioprinting entails a convergence of technologies, bringing together diverse elements; printing devices, bioinks and software, as a means of producing advanced therapies (84,90,92,93).

Much of the ELSPE work pertaining to bioprinting has focused on the regulatory issues raised by the technology. As with advanced therapies more generally, there is a variety of different regulatory pathways and classifications applicable to 3D bioprinted constructs in different jurisdictions around the world (92,94 for overviews). The complexity and many components involved in bioprinting mean that the production and application of a bioprinted construct could potentially fall under the ATMP regulations (for the cells), the Medical Device Regulation (for the software), the Machinery Directive (for the bioprinter itself), and the Computer Aided Design (CAD) file might also contain sensitive personal data as defined by the GDPR if it matches features of the patient's biology and/or anatomy (84,92,95,96). Bioprinted constructs themselves will either qualify as Advanced Therapy Medicinal Products or transplants depending on the degree of manipulation of the cells. Bioprinted implants also have the potential to be tailored to the specificities of individual patients. It has been noted that bioprinting of whole organs, if successful could alleviate the especially acute shortage of paediatric organs for transplant. This does not necessarily mean that bioprinted

constructs will be considered ‘custom’ or ‘patient-matched’ devices in regulatory terms. The Medical Devices regulation allows custom-made divides intended to treat a specific patient to be exempt from many of its provisions. However, “products that are ‘mass produced’ and adapted, or mass produced using ‘industrial manufacturing processes’, will *not* be classified as custom-made devices [which] would appear to limit the applicability of the exemption to many bioprinted products depending on how the terms ‘mass-produced’ and ‘industrial manufacturing processes’ are interpreted” (92). The US Food and Drug Administration has indicated that as a rule bioprinted constructs will not be eligible to be treated as ‘patient matched’ devices under US regulation.

Bioprinting also raises several legal issues relating to product liability. There is a need to define what constitutes ‘product’ in bioprinting (whether it is the 3D bioprinted material; the bioink) and who the producer is (the patient from who cells are harvested; the laboratory technician generating the 3D bioprinting; the hospital/treatment facility itself) (84,96-99) as it is the nominated producer who assumes manufacturing liability in law. There are also questions concerning the software and Computer Aided Design files used for 3D Bioprinting and whether they should be considered as ‘products’ themselves, particularly when it comes to liability legislation (96). The use of software is of particular interest as it highlights some of the complexities of this technology. Currently, only a limited number of dedicated software packages specifically for bioprinting exist. Instead, the process often relies on other ‘packages that happen to be useful for bioprinting work’ (84). Bioprinting projects use a mixture of proprietary or open-source software, but in both cases the majority of software licences or terms and conditions explicitly disavow clinical use and any liability that might result from use to create a clinical product, leaving academics and SMEs with the liability for errors, bugs or inherent flaws in the software code itself if used to 3D print a cellular construct (84).

The lack of dedicated, holistic 3D bioprinting software can also result in the purchase of different licences for the various different software packages involved, which in turn increases software costs for those clinics/facilities that use it. Because of this, those involved in bioprinting resort to open software as the best available solution, as this has the advantage of being maintained by large communities that quite often are quick to pick up and rectify software bugs (100). This also points toward a lack of harmonised standards which again poses difficulties for translation to clinical applications (94). The use of software, as with any other digital device, additionally raises questions of data privacy, security and processing and intellectual property rights. In a ‘hub and spokes’ model of bioprinting any transfer of digital product files from the hub design centre to the clinical spokes would count as both transfer of sensitive personal data under data protection laws and data critical to the quality of the final product in quality management terms and so would have to be exceptionally secure against the possibility of outside agents intercepting or editing the data during transfer. Quite apart from the use of software itself, a common practice in 3D bioprinting is collecting additional data from patients, alongside the biomaterial harvested, to enable better and faster processing, and as a result there is an additional layer of data privacy and collection related to this (84,101).

The very existence of bioprinted organs also raises intellectual property rights questions. Natural occurring human organs are not eligible for patent protection as they are ‘products of nature’. A review of the existing case law pertinent to bioprinting concluded that “3D bioprinted human organs may be excluded [from patent eligibility] if it is a claim for a method of treatment by surgery, diagnosis or therapy in the United Kingdom and New Zealand, where legislation provides for an explicit medical treatment exception (102). However, if a method claim is construed under the non-surgical aspect of making and printing of a 3D

bioprinted human organ, (in contrast with the surgical implantation of a 3D bioprinted organ) it could be patentable and not fall under the medical treatment exclusion". Whether or not a bioprinted organ that was identical to a naturally occurring organ would be patentable will be for the patent office, and potentially ultimately the courts to decide in each jurisdiction but there are several precedents that would suggest that a product claim or composition of matter claim on the organ itself would not be valid. As the field develops it will be worth conducting further legal analysis to assess i) if a lack of patentability would deter investment in the field, ii) what the social and ethical impacts of allowing patentability on bioprinted organs might be, and iii) whether bioprinted constructs that were sufficiently distinct in legal and biological terms from naturally occurring human organs might be viable and desirable.

There is also debate among legal scholars about the appropriate focus of regulation. Li et al (96) propose a transitional model whereby "processual 'process-based' approach to bioprinting, facilitated by the co-regulation model, is best fit for purpose during the early development phase of bioprinting. The provisional 'process-based' approach will serve as a safety valve to temper the tension between innovation and safety. After the risk profile of the technologies is complete, and standardisation of the industry is well developed, regulators, intermediaries, industries, and participating stakeholders could make an informed decision as to whether, when and how to transit to a 'product-based' regime" (2020, p28). However, Nielsen et al (92) reviewing the EU, US and Australian regulatory landscape for 3DP found that studying details of process-based and product-based regulations both reveal the inadequacy of regulatory systems when it comes to novel technologies, by offering only a binary approach to technologies that cannot fit into this type of regulatory analysis.

Lastly, bioethical analysis has suggested that bioprinting of organs, if it can be achieved, would be more ethically acceptable than alternative such as xenotransplantation or gene editing animal-human hybrid organs, a sentiment that a limited number of surveys of public attitudes appear to confirm (103). Several studies have also noted that the current 'biotechnology industry' model of strong intellectual property rights as a basis for commercialisation of bioprinting could lead to a 'stratification of access' with "those who can afford to pay for self (i.e. bioprinted, autologous) organs living longer; perhaps enjoying a significantly high quality of life avoiding the negative physical consequences of taking immune-suppressant drugs, [w]hile others will wait until a human organ donor becomes available and then have to undertake a punishing drug regime for the rest of their lives to prevent episodes of rejection of the transplanted organ" and it has been questioned whether property rights over bioprinted organs per se would be socially desirable (102-105). Given these factors, 3D bioprinting remains currently in a pre-clinical experimental state (84,106).

Section 3
Institutional Readiness: Challenges and Opportunities

This section (3.0) reviews 'institutional readiness' (IR) a model of adoption of innovative health technology developed by UK social scientists studying the specific case of regenerative medicine. 'Readiness' has gained traction internationally (103) and has also been used to inform tools for assessing readiness for cell and gene therapies by the Northern Alliance ATTC and hospital pharmacy readiness for covid-19 vaccines. (107-109).

The ethical, legal, social, political, and economic (ELSPE) issues of novel reimbursement schemes and the economics of advanced therapies are also included as issues of space, speed, cost and quality are typically interdependent (110) in the manufacturing of advanced therapies. The design and operation of any one element, whether manufacturing models, business models, reimbursement models, the degree of personalisation or customisation of therapies, or clinical delivery, each affects the others, and therefore it is appropriate, indeed necessary, to consider them in concert (78).

Section 3.2 deals with novel reimbursement strategies, primarily involving some form of payment by instalments or payment by results, the proliferation of adaptive regulatory pathways for advanced therapies (expedited access, conditional approvals, compassionate use etc), while Section 3.3 addresses ELSPE associated with the use of Real World Evidence (RWE) as one tool which can support expedited access and post-market surveillance of advanced biotherapeutics. A third case study focuses on the phenomenon of so-called 'stem cell tourism' and the challenge of differentiating unproven, dangerous cell therapies from legitimate clinical innovation, as this is an area where there has been, and continues to be a proliferation of ELSPE scholarship.

3.1 Institutional Readiness for Advanced Biotherapies

Traditional understandings of healthcare innovation frame translation as a linear progression through a sequence of hierarchical "technology readiness levels" (TRLs), where the product is subject to varying degrees of 'science push' and 'market pull'. These accounts neglect organisational and systemic enablers of adoption. However, the unique, and potentially disruptive features of advanced therapies (especially in conjunction with personalised medicine and/or redistributed manufacturing) accentuate the importance of receptive environments with sufficient capacity to adopt novel health technologies in making clinical delivery a reality. The concept of Institutional readiness (IR) was developed to address just this issue and focuses on the degree to which a clinical site needs to *adapt* to successfully *adopt* advanced therapies, and the extent to which these changes have been implemented (111-113). For example, hospitals need the capacity to cope with the requirements of these new therapeutic modalities: from appropriate staff training; ensuring access to a GMP-licensed facility; to putting appropriate systems in place to monitor outcomes and costs (111). While TRLs deal with whether technologies 'work' in terms of internal function, IR places these technologies in the context of 'real world' organisational environments within which they must operate to be workable. The use of the term 'institutional' also recognises that responsibility does not only lie with specific clinical sites but extends to the full pathway of organisations involved in the production of advanced therapies, from couriers to manufacturers and Contract Development and Manufacturing Organisations, supply chain firms, quality managers and

others. Coordination and collaboration across organisational boundaries is integral to IR. The concept has been operationalised by the Northern Alliance Advanced Therapy Treatment Centre (NAATTC), one of the UK's network of Advanced Therapy Treatment Centres (ATTCs) which bring together NHS hospitals, universities, and SMEs to enable the clinical delivery of regenerative therapies. The NAATTC used IR to inform the design of a tool to assess and compare readiness across product types and clinical sites (107), that is now being rolled out to other NHS sites beyond the ATTC network (114).

The concept of 'readiness' has also begun to be considered with specific reference to the role of digital technologies in the production and delivery of advanced therapies, and at the level of national strategies to support advanced therapies (115-118). However, there is still scope for considerable further comparative analysis of national and local adaptations to facilitate readiness for advanced therapies in different territories, and to extend analysis of readiness (digital and otherwise) to encompass the development of artificial intelligence and machine learning in the manufacturing of advanced therapies, as being developed, for example by the EU Horizon 2020 AIDPATH project (119). Fully redistributed manufacturing of advanced therapies also raises specific issues for institutional readiness (181-182). For example, one component of IR assessment is the appreciate staff skill sets and infrastructure to deliver the therapy in question (111). Redistributed manufacturing may require a Qualified Person (QP) to sign off on each batch of product made at a site, which raises questions about the number and affordability of the requisite number of adequately trained QPs. Similarly, redistributed manufacturing will require a particular 'physical, material and temporal infrastructure' to be in place at a clinical site that will almost certainly be different from that needed to store and deliver allogeneic cell therapies or Tissue Engineered Medicines (78).

3.2 Regulatory Pathways and Reimbursement

A key component of IR is institutional capacity to reimburse the high costs of PM and especially given the limited scalability of current manufacturing techniques. This in turn, has prompted calls for novel reimbursement schemes and global regulatory experimentation with alternative pathways to get therapies to patients faster. Adaptive licensing and regulatory pathways which are available to advanced therapies (though not necessarily exclusive to them) including expedited access 'fast track' pathways, conditional approvals, hospital exemptions, the UK 'manufacturers specials' pathway, compassionate use schemes, and others (4,120-123).[3]

Japan has been particularly active in regulatory innovation, having developed both a form of conditional approval which allows advanced therapies in phase II clinical trials to be offered for sale on a named-patient basis to patients not formally included in the phase II trials, and a separate regulatory pathway for clinical innovation that is utilises data collection from experimental therapy outside formal clinical trials (at least in its early stages) (116,124). The ELSPE raised by these alternative and adaptive regulatory pathways and by novel reimbursement practices have so far received only limited scrutiny, especially with regards to how they operate in real world settings. It is also not clear from research to date how the ELSPE of expedited or accelerated access pathways interacts with different manufacturing strategies for advanced biotherapeutics described in Section 2.1.

[3] For a recent review of UK and EU pathways see Mourby et al (2022) 'Biomodifying the 'natural': from adaptive regulation to adaptive societal governance', Journal of Law and the Biosciences, Vol. 9 (1), lsac018. https://doi.org/10.1093/jlb/lsac018

Existing analysis has highlighted that competition between nation states has fostered a proliferation of different national regulatory strategies which may benefit scientists in the home country but simultaneously pose challenges for international clinical trials (4,120). ELSPE analysis has also noted the potential for 'regulatory brokerage' where the geographic location of different R&D activities is chosen based on minimising regulatory requirements, and which in turn can lead to national regulatory reform aimed at attracting investment. Whilst potentially beneficial, the risk is that such activities are "based on competition in regulatory advantage rather than on ethical and scientific values" (4). Lastly, the dynamic and fragmented regulatory landscape, and the move away from three phase randomised placebo-controlled trials as the 'gold standard' of evidence, has also highlighted the uncertainty and difficulty of effecting a clear separation between 'rogue' 'unproven' cell therapies and legitimate therapies. (125) The issue of unproven therapies and the phenomenon of 'stem cell tourism' is examined further below.

The high cost of PM (e.g., *Zolgensma* - Novartis' one-time-only gene therapy treatment for children >2 years old with spinal muscular atrophy (SMA) costs USD2.1 million for a single treatment) has motivated both national governments and pharmaceutical companies to investigate novel reimbursement schemes that stagger payment rather than utilise the transitional one-off upfront payment in advance of application model used for conventional pharmaceuticals, diagnostics and medical devices. Some EU countries have introduced novel reimbursement schemes for *Yescarta* and *Kymriah*, two CAR-T Cell therapies used for certain blood-born cancers. Reimbursement models in these cases are usually outcome-based and therefore in stages, utilising post-treatment monitoring to demonstrate efficacy at the various stages of use. Outcome-based payment requires patient follow up and data collection after treatment, which raises questions about whether there is any legal or ethical justification for making such follow-up examinations compulsory, what this might mean for patient trust, and how to deal with recipients of advanced therapies who i) move jurisdictions or ii) do not comply with follow-up appointments.

There are also questions about the long-term storage of outcome data, and whether patient-run registries or joint enterprises with hospitals or companies might have a role to play in managing this data? 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, and which it would be an oversight to ignore or dismiss. This touches on issues of patient and public trust, but also of control and custodianship of data, as it could be both a valuable tool for health research and a commercially valuable asset. The long-term sustainability of any such data resource is important. Companies undoubtedly 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.

As Jørgensen et al demonstrate in their paper on outcome-based reimbursement, there have been clear signs of willingness to adopt new reimbursement models. In some cases, the first opportunity appears to have been the implementation of *Yescarta* and *Kymriah*. Nevertheless, each country must adopt different variations of this model, as they all have unique infrastructures, with different priorities, institutional readiness levels and processes (126). Novel reimbursement schemes also mean in some cases novel healthcare funding mechanisms, as in the German model where hospitals that adopt advanced biotherapies are allowed additional funding (a similar approach to the UK Cancer Drugs Fund). Similarly, GlaxoSmithKline (GSK) proposed a novel 'money-back' reimbursement pathway strategy for *Strimvelis* – a gene therapy treatment for children diagnosed with Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID). In exchange for getting the Italian state to

reimburse *Strimvelis'* US$665,000 per treatment cost on the expectation that it would halve the state's traditional treatment-cost burden for ADA-SCID, GSK proposed a money-back guarantee if *Strimvelis*' performance fell short of expectations (79) p.571-2). Lack of consensus as to how exactly this 'performance' evaluation would work in practice severely impeded take-up of GSK's proposal. Nevertheless, as more developers target 'orphan-disease' pathways for new and emerging cell and gene therapies, finding novel strategies to reimburse the high cost from smaller patient populations has become increasingly important for firm's long-term sustainability (orphan disease populations are by definition are substantively smaller than for diseases with large global footprints which allow for blockbuster global revenue-earning potential through traditional (bio)pharmaceuticals e.g., *Humira* or *Harvoni*). Ultimately, GSK's inability to find a viable revenue-generation model for *Strimvelis* contributed to its sell-off, reiterating the salience of finding suitable reimbursement pathways (79), although there has been limited ELSPE scholarship on these novel reimbursement models to date.

The potential high cost of advanced biotherapeutics has also reignited interest in Value-based Assessment (VbA) of medicinal products. The idea of VbA is to allow a greater range of factors to count in evaluating the cost-effectiveness of new therapies, to allow pricing to better reflect the cumulative societal value of an intervention. However, consideration of VbA in the UK was shelved due to concerns in developing a workable model that did not inadvertently allocate lower value to incremental extensions to the lives of older people. There are also concerns that some forms of VbA could introduce less robust and reliable forms of evidence into pricing decisions by national healthcare providers.

3.3 Real World Evidence

Several conditional approval or expedited access pathways make use of so-called 'real world evidence'. Real World Evidence (RWE) is also used, connected to Real World Data (RWD) (78,127-130). This can include data from routine hospital care, post-marketing surveillance, experimental care administered in a clinical site, and even data generated by patients themselves (such as from wearables, mobile devises or collected from other avenues outside highly controlled clinical trials). Owing to the fact the data is produced outwith formal clinical trials, RWD is considered 'supplementary' data, with RWE essentially being generated from RWD (128). Proponents argue that RWD can enable a 'rapid, robust and responsive technology evaluation, and dynamic, living guidelines' (128) and the US in particular, has reported utilising RWE in fast-tracking therapies (78). However, serious questions remain about the quality and status of the data, and ethical and legal queries have been raised about the adequacy of protection for patient safety involved in expedited access and conditional approval, whether or not RWE is utilised; not least because evidence suggests that once a marketing authorisation and approvals issued, even conditionally, it can be very difficult to remove a product from use in practice.

One area where RWE is considered particularly beneficial is in paediatric drug safety, by providing data that can fill in gaps when it comes to safety, and additionally helping in understanding 'long-term effects of exposure to medicines in children's' development (131). This may also be a relevant concern for some advanced therapies as they are typically not tested in children unless they are being developed specifically for a paediatric or childhood-onset condition. Unsurprisingly, as is the case with every data collection method, it also raises privacy and data sharing concerns (131), as discussed in Section 1.

CASE STUDY 4

Unapproved, Unproven, Stem Cell Therapies and Tourism

'Stem cell tourism' is a phenomenon where patients, often accompanied by parents, family members and carers travel overseas to access stem cell treatments not available in their home country (132). There are similarities with the related phenomena of medical and reproductive tourism, but one important caveat is that many of these stem cell products are not approved by any regulatory authority, nor is their use generally part of a recognised clinical trial. In her article on how stem cell therapies are marketed as 'cure-alls', Jane Qiu highlights how the take-off in promoting such therapies typically and rests on the idea of 'trading on hope', with private clinics taking advantage of those desperately looking for a last resort therapy, quite often belonging to groups of desperate or vulnerable patients that turn to unproven therapies as a result (124,133-135). While the phenomenon of seeking unapproved therapies does not only relate to stem cell therapies, stem cell tourism tends to be a common reason for travel (136-146). This practice contributes to the growth of untested and unproven treatments, supporting an industry mainly provisioned by private clinics (132).

Advocates of legitimate stem cell therapies fear that reckless use of so-called 'direct to consumer' cell therapies (79) will not only fail to help patients but can, and indeed has caused new iatrogenic illness and even death in recipients. This is not only deeply undesirable from a patient safety perspective but could also damage the reputation—and commercial prospects—of advanced biotherapies, similar to the way fatalities in early gene therapy trials are believed to have affected that field. In response, the International Society for Stem Cell Research (ISSCR), a leading international academic scientific society in the SCBI field, has produced guidelines for responsible translation stating that "[g]overnment authorities and professional organizations are strongly encouraged to establish and strictly enforce regulations governing the introduction of stem cell-based medical interventions into commercial use". Responses have focused predominantly on regulatory reform and education programmes (124,135,147-150).

Initially conceived of as a problem for low- to middle-income countries which lacked adequate regulatory oversight or resources to enforce regulations, subsequent research has shown that unlicensed cell therapies are also a problem for high income nations such as US, Australia, Canada, Japan and European Union Member States (124,151-155). This, as Datta (79) argues, questions the simple assumption of weak or absent regulation, although 'regulatory brokerage' does appear to play a part (4). Instead, the 'endogenous attributes' of direct to consumer cell therapies, notably "autologous cells, personalised point-of-care delivery, short shelf lives […] raises questions of commensurability with existing regulation oriented towards (bio)pharmaceuticals with long shelf lives and process-dependant mass-scale production and distribution networks". In essence it is not poor or absent regulation, but the problem that much existing regulation is devised for mass-produced small molecule pharmaceuticals that allows direct to consumer provision of unapproved cell therapies to persist and indeed flourish. While direct to consumer cell therapies challenge existing models of regulation and clinical practice (156-158) they do highlight the limited options available through approved avenues, compared to the actual demand (136). Competition between nation states for investment and regulatory advantage has to an extent provided a counterweight to attempts to impose tight restrictions that would prohibit all DTC cell therapies.

Here it is worth noting the distinction between 'unapproved' and 'unproven' therapies. While 'unapproved' are those therapies that have not received marketing authorisation and

approval in a given jurisdiction and/or are not covered by national health insurance, but may be available through clinical innovation pathways such as the hospital exemption in the EU ATMP Regulations or the Act on the Safety of Regenerative Medicine (ASRM) in Japan, 'unproven' therapies are those that have no or inadequate 'scientific and therapeutic evidence' for their safety and/or efficacy (124,135,144). The former have potential to alleviate unmet medical need while the latter constitute a significant hazard to patient safety and wellbeing, but in practice they can be hard to distinguish (159-161).

An important legal challenge is therefore to ensure future regulatory frameworks can curtail dangerous and unapproved direct-to-consumer cell therapies without inhibiting the kinds of personalised biotherapeutics, including the option of distributed manufacturing the Hub seeks to develop.

Section 4
Personalised Medicine, Society and Responsibility

One of the connotations of the term of personalised medicine is the idea that the individual is responsible for her/his own health. 'Personalisation' in this context refers to a participatory system, to which patients, and often members of the public as well, are expected to contribute their own data for themselves and others to benefit from advanced in data-driven healthcare. One articulation of this model is that of 'P4 medicine', which aims to be 'predictive, preventive, personalised and participatory' (162). This is one of the reasons why data collection (as discussed in 1.2) in this context is often promoted as a means of "democratising medicine". However, an excessive focus on the individual as the locus of agency and responsibility for health tends to obscure the social and economic factors that play a significant role in shaping peoples' health: the social determinants of health (1,25,163). ELSPE scholars critical of 'responsibilisation' reject the idea that individual 'empowerment' through participation is sufficient to solve health inequalities, noting that factors that influence health outcomes can be anything from stress as the result of experiencing structural discrimination, uneven quality of healthcare between different areas of the same city, and conscious or unconscious bias embedded in healthcare, socioeconomic status and more (1,25).

For some groups of the population, healthy behaviours are much harder to achieve compared to others. Prainsack refers to how even within the same wealthy borough in London (Westminster) life expectancy can have a difference of as many as 9 years, while simplistic narratives of health outcomes that divide the UK into a 'wealthy South' and 'deprived North' obscure more specific analyses of causes of health inequality (25). Studies of statin use have also demonstrated that even when the initial introduction of a treatment did not appear to amplify social determinants of health, the introduction of other elements such as monitoring served to amplify the gap between affluent and disadvantaged areas in terms of health outcomes (164,165).

Personalisation of therapies and care pathways also raise questions about lay expertise. Prainsack and Buyx speak of 'solidarity' amongst people when they diagnose a 'manifestations of people's willingness to carry costs (financial, social, emotional, or otherwise) to assist others'. This is primarily created out of the similar experiences or other characteristics people share, 'facing similar risks, having shared the same experience, or working towards the same goal' (163). Lay expertise and its role in negotiating care and side effects has been cited as a particularly important aspect of treatment, with patient-led organisations informing even clinical services (88,111,166-169) as patients consistently draw reassurance from those undergoing similar treatments (79). At hospital level too, there are indications that stratified medicine promotes more fragmentation and de-personalisation of care, as it results in necessary recalibration of staff roles and 'the introduction of new roles and some external providers' which 'do not always work with the result that some patients describe care that is far from personalised' (89).

Personalisation of therapies and care pathways thus raise questions on how and where lay expertise fits within this framework. Websites such as 'PatientsLikeMe', initiated out of the need to share personal experience with specific conditions, have become an important avenue of sharing experiences and receiving support from those equally affected by the same condition (25). While it is very unlikely that personalisation of therapies will become truly personalised to the extent that each patient's experience is truly unique, stratifying patients in ever smaller groups may reduce patients' capacity for collective support through "engagement

with data and information relevant to them, [and] connecting with others who have similar experiences" (170).

Prainsack and Buyx mention three tiers on which solidarity can materialise. The first tier is the interpersonal level where individual people are willing to carry costs in order to assist others while in the second, there is a 'collective commitment to carry costs to assist others' at group level. The final tier is solidarity in its 'contractual and legal manifestations', in which those 'principles solidify not only into social norms but manifest themselves in contractual or other legal forms' (163,171). The significance of lay expertise and its manifestation in solidarity is therefore important not just for reassuring patients undergoing similar treatments and sharing their experiences, but it can result in social and legal arrangements. The structure of solidarity in three tiers indicates that the last tier of legal manifestation cannot exist without the first two - essentially, for legal and social arrangements to change in healthcare, interpersonal and collective solidarity needs to take place first (172). Excessive personalisation (in the sense of an individualisation of agency and responsibilities) therefore can break down the cycle of solidarity that leads to more structural manifestations and could not harm only patients who benefit from its first two tiers, but also the wider healthcare system which benefits from their experience (88,163,172).

Lay expertise is of particular significance when it comes to Responsible Research and Innovation (173-177). Literature on Responsible Research and Innovation (RRI) highlights the importance of public and patient involvement in the decision making not just in the implementation but also in the design of technologies, quite often also generating 'alternative ways of imagining socio-technical futures' (175,178,179). This can help reduce the risk of the public feeling disenfranchised and alienated from research and development (176).

Section 5
Gaps and priorities for future ELSPE research
(in manufacturing of advanced biotherapeutics)

5.1 Access

A significant ELSPE issue is how we might prevent patient stratification from becoming stratification of access by anything other than medical need. While ELSPE scholarship has advocated the idea of equity of access, practical approaches need to consider mechanisms and strategies for preventing discrimination in key domains as below:

- by geographical location: as different manufacturing models have varying degrees of centralisation/ de centralisation, which may mitigate against fair access by patients in rural areas or regions with no viable advanced manufacturing centre.
- In particular, different countries, and even different states within federations are likely to have different health budgets, and different legislation and policies relating to access, reflecting varying health priorities in different territories. This has further potential to exacerbate inequality of access.
- Ethnicity, gender or other protected characteristics (excepting where there are valid scientifically justified grounds for restricting access, as for example where particular treatment regimens may not be suitable for very old or very young patients[4]). This requires ensuring the mechanisms of patient stratification avoid or compensate for biases in underlying datasets and assumptions.
- Ability to access and participate in clinical trials of new advanced therapies
- Ability to pay, including the differential budgets of NHS Trusts or Integrated Care Systems (which replaced Clinical commissioning Groups in 2022) in different regions.

A persistent issue with PM is what happens to those patients who are identified as 'poor responders'. Ethical concern about this issue is well known, but practical solutions have been less forthcoming.

What role, if any, do concepts such as 'solidarity' and 'relational autonomy', which have been applied in the context of data-driven personalised medicine, play in debates about access to advanced biotherapeutics?

5.2 Reimbursement

Closely linked to access, there is scope for considerable ELSPE work on novel and alternative reimbursement mechanisms for advanced biotherapeutics. Key issues include:

- Understanding the distribution of risk and responsibilities between manufacturers and hospitals; for example, with 'fresh' products with limited shelf-life, which party or parties bear the financial cost if a therapy is made but not used because medical complications

[4] In this regard it is worth acknowledging the role of legislation such as the EU paediatric medicines Regulation (Regulation (EC) No 1901/2006) which sets out specific requirements for accessible drug development for paediatric populations. Many childhood diseases are also rare disease so this legislation is intended to work in concert with the Orphan Drug Regulation, making this overlap particularly relevant for advanced biotherapeutics.

mean the patient is not available during the window when the product is viable? Similarly, how are costs allocated if there are errors in the collection or storage of starting material prior to manufacturing that render the product Out of Scope for quality approval?

- In the latter case, liability for payment may well depend on the details of the contract between the manufacturer and the hospital and the respective insurance policies of all parties involved. Research could address how legal liability for near-patient/ point of care manufacturing is, and should be, attributed in different jurisdictions, and whether measures could be put in place to reduce the likelihood of lawsuits in cases where liability for costs is disputed between different parties.
- There is scope for both empirical analysis to understand what current practice looks like in real world settings and normative analysis to assess how fair, proportionate and equitable reimbursement should operate.
- Several novel reimbursement mechanisms call for extended post-market surveillance and collection of outcome data on patients treated with advanced therapies. It will be important to have further research on patient (and public) preferences about which organisations should have custodianship of this data, how access should be governed, whether there can or should be a role for patient charities and organisations (especially where they are involved in existing registries), and whether, if follow-up data collection is linked to payment, participations could be made compulsory and how this might affect patient trust?
    - What are the implications for the Institutional Readiness of UK clinical sites with respect to staff training and expertise, data collection infrastructures or other features that may be needed to support and facilitate novel reimbursement mechanisms?
    - How do novel reimbursement systems operate in practice, and does this change across different national healthcare systems? What are the ramifications for developers accessing UK, EU, US and other markets?
- There is also scope for interdisciplinary research to address how to ethically, legally and economically balance the high cost of advanced therapies (even if this decreases in the longer term) against other health priorities in ways that are transparent and accountable to society.
- This could also involve returning to questions of value-based assessment of medicinal products.
- It is also pertinent to note the recent adoption of EU Regulation no.2021/2282 on Health Technology Assessment. This Regulation, which is expected to come into force from January 2025, provides greater harmonisation in the requirements for the clinical components (defined as identification of a health problem and current health technology, the examination of the technical characteristics of the health technology under assessment, its relative safety, and its relative clinical effectiveness) across EU Member States (MS). ATMPs have been designated as the first category of medicines for which it will be implemented (See article 7.2.a of Regulation 2021/2282).
- ELSPE research should investigate the practical implementation of this Regulation in different MS and assess the extent of alignment/harmonisation with the data requirements of NICE in the UK.

5.3 Critical skills and Innovation Infrastructure

The clinical delivery of advanced biotherapeutics requires specific infrastructure and skills. The concept of Institutional Readiness (IR) has been developed to measure the capacity of any given clinical site to deliver different types of advanced therapy and has been adopted by the UK Advanced Therapy Treatment Centre network. Further work may be warranted in the following areas:

- Recent work is staring to assess what Institutional Readiness for distributed manufacturing looks like, (182-183) but the existing IR tools and methods may need to be adopted to make it fit for purpose for distributed manufacturing. IR is derived from empirical studies of UK hospital sites so additional empirical work on distributed manufacturing in practice would be ideally required.
- There is value in comparative analysis to understand how clinical delivery of advanced therapies is prepared for and achieved in different countries such as the US, Germany or Japan, which have different healthcare systems, different regulatory pathways for advanced therapies and different policies and networks supporting advanced therapies.
- This work could assess the links between 'local' hospital readiness, national policies and regulations, and examine different product classes of advanced biotherapeutic and/or different manufacturing strategies.

  This work could be further extended to understand the 'readiness' of various manufacturing efforts at the global level with the aim of better understanding the opportunities and risks of pooling diverse competitive advantages in skills and capacity (such as for the COVID-19 vaccine development)

A number of changes to structures and practices of preclinical research have also been proposed with a view to improving the translational success rates of personalised medicine endeavours (183-185).There is scope for ELSPE work to i) assess how these changes are being implemented in practice, ii) understand barriers to openness, reproducibility, accessibility of data et cetera, iii) evaluate the ethics of novel trial design and novel translational strategies for personalised medicines (186) and iv) assess how concepts such as 'clinical relevance' for personalised medicine are implemented in practice. It is also important to build on recent efforts to integrate insights from the social sciences and humanities into biomedical research though tools such as shared terminology (187).

5.4 Regulation

Further work is needed to clarify the legal framework around distributed manufacturing of advanced biotherapies. The existing uncertainties around distribution of liabilities is well documented, so further work will need to engage relevant stakeholders such as regulatory agencies, practicing lawyers with expertise in liability relating to medicine, manufacturing and (potentially) software, and hospital managers, to try and map out how issues will be addressed in real world situations, what impact this will have on distributed manufacturing, and consider viable legal or policy solutions for any significant limitations or roadblocks. Other priorities for future work include:

- **Patentability of Bioprinted organs:** The uncertainty concerning the patentability of bioprinted organs has been identified (see case study 2). Further work is needed to assess the social and ethical desirability of national patent offices' permitting or prohibiting the granting of intellectual property rights in bioprinted organs, including the likely impact on the advanced manufacturing industry.
- **Impact of the full range of intellectual property** rights (patents, copyright, trade secrets, legal protection of databases et cetera) on the creation of markets for advanced biotherapeutics and personalised medicine.
- **Improving access via regulatory reform:** There is scope for ELSPE scholars to consider the viability and desirability of additional or amended regulatory pathways to support i) improved access to advanced therapies, ii) clinician-led innovation involving advanced biotherapies and/or distributed manufacturing and iii) how best regulatory frameworks can support personalised biotherapeutics while also inhibiting dangerous and unapproved direct-to-consumer cell therapies. The latter could consider opportunities for post-Brexit regulatory reform though alternatives to the hospital exemption scheme.
- Given the complexity of the field ELSPE research also needs to consider the level of intervention; formal legislation, regulatory body rules, recommendations, and guidelines, and so on. It is likely that any changes will need to balance flexibility with stringency and will involve a multi-level regulatory approach using a variety of legal or quasi-legal tools.
- **Integrating Real-World Evidence in regulation:** There would be value in empirical studies of how Real-World Evidence is generated and assessed in practice to better understand its benefits and limitations, as well as the infrastructure and skills needed to utilise this approach in a scalable way.
- **Sustainability of current 'rare' diseases pathways for PM development:** Many advanced therapies are targeted at rare diseases. However, if further stratification and personalisation to therapies results in many common conditions being fragmented into different 'rare' disease categories, this raises questions about the sustainability and appropriateness of rare disease provisions such as the EMA orphan Disease designation[5], as well as the impact on patient identity and collective social movements based on diagnosis such as medical research charities and patient associations, both of which warrant further study.

5.5 Responsible Research and Innovation (RRI)

Collaborative research involving stakeholders in the earlier, 'upstream' phases of research and development could foster better anticipation of challenges, reflection on pathways to

[5] This is particularly salient for legal research as the current European legislation on orphan medicines as well as the general European legislation on medicines has entered a revision process, with proposals from the European Commission expected at the end of 2022. The revised legislation is expected to focus on "medicines for unmet medical needs", probably with orphan medicines for unmet medical needs and associated (conditional) incentives.

overcome challenges, stakeholder engagement and meaningful action in the following domains:

- The development of transparent and explainable data-driven (AI-enabled) technologies with fair and trustworthy clinical outcomes while helping bolster public trust
- Public and patient perspectives and attitudes towards personalised and/or customised therapeutics
- Improving patient and public participation in different phases of the innovation pathway for advanced biotherapeutics, and the different methods that might be appropriate in different cases (e.g., Algorithmic Impact Assessment tools, consensus building deliberative democracy exercises or participatory scenario assessments to identify ways forward on defined issues, surveys to assess more general attitudes or preferences et cetera).
- The impact and implementation of more 'patient centred' care and how this affects the development and delivery of personalised biotherapies.
- The sustainability and environmental impact of developing and using data-driven systems as well as different manufacturing options for advanced biotherapeutics
- Assessing the role of open science, including open access publishing, open data, open software, and open hardware in manufacturing advanced biotherapeutics

There is also scope for further ELSPE research to investigate the practical mechanisms for involving patients and the public in clinical, regulatory, HTA, and similar issues and to assess what weight is, and should be, given to their views, especially with regards to balancing this input with the requirements of existing institutional structures, legal provisions, scientific knowledge, commercial aims and so on. This also applies to the consultation process for adoption of legal acts (regulations, directives, guideline), where there can be a tension between the need for procedural and legal legitimacy and the real impact of "society at large" proposals.

5.6 Political Economy of Emerging Markets in Personalised Medicine

Future research should build on existing 'horizon scanning' work, by drawing on mixed methods analysis, combining qualitative and quantitative techniques for a better understanding of the (inter)national political economic imperatives and implications that help or hinder the routinisation of emerging advanced therapies. Quantitative data pertaining to various measurable market metrics (related to land, labour, capital, global/regional distribution of manufacturers, patents generated etc.) are widely available from market research companies (e.g., Statista) albeit at considerable subscription costs. What is needed is a qualitative consideration of these quantitative elements to answer key questions in the following areas:

- What are the implications of the emerging distribution of the factors of production across regions (which would ultimately relate to issue of access to therapies) and across the different stages of development from preclinical to phase III clinical trials (which would shed light on the challenges of the innovation pathway)?

- How does this compare with global funding for academic research and global distribution of intellectual property rights relating to advanced manufacturing?
- Why are some diseases conditions prioritised over others for therapeutic development and what are the implications for local and global publics? This would help future scenario planning; for example, are there some conditions where multiple competing therapies are in development, or other areas that remain underserved? Additionally, the qualitative element could also provide insights into the scientific and commercial factors driving the choice and prioritization of conditions for which advanced biotherapeutics are being developed.

Issues of privacy and security in relation to both data subjects and objects for PM-focused research raise considerable ELSPE issues. However, these were not included here as they are not specific to PM and command an expanding scholarship as already noted above.

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