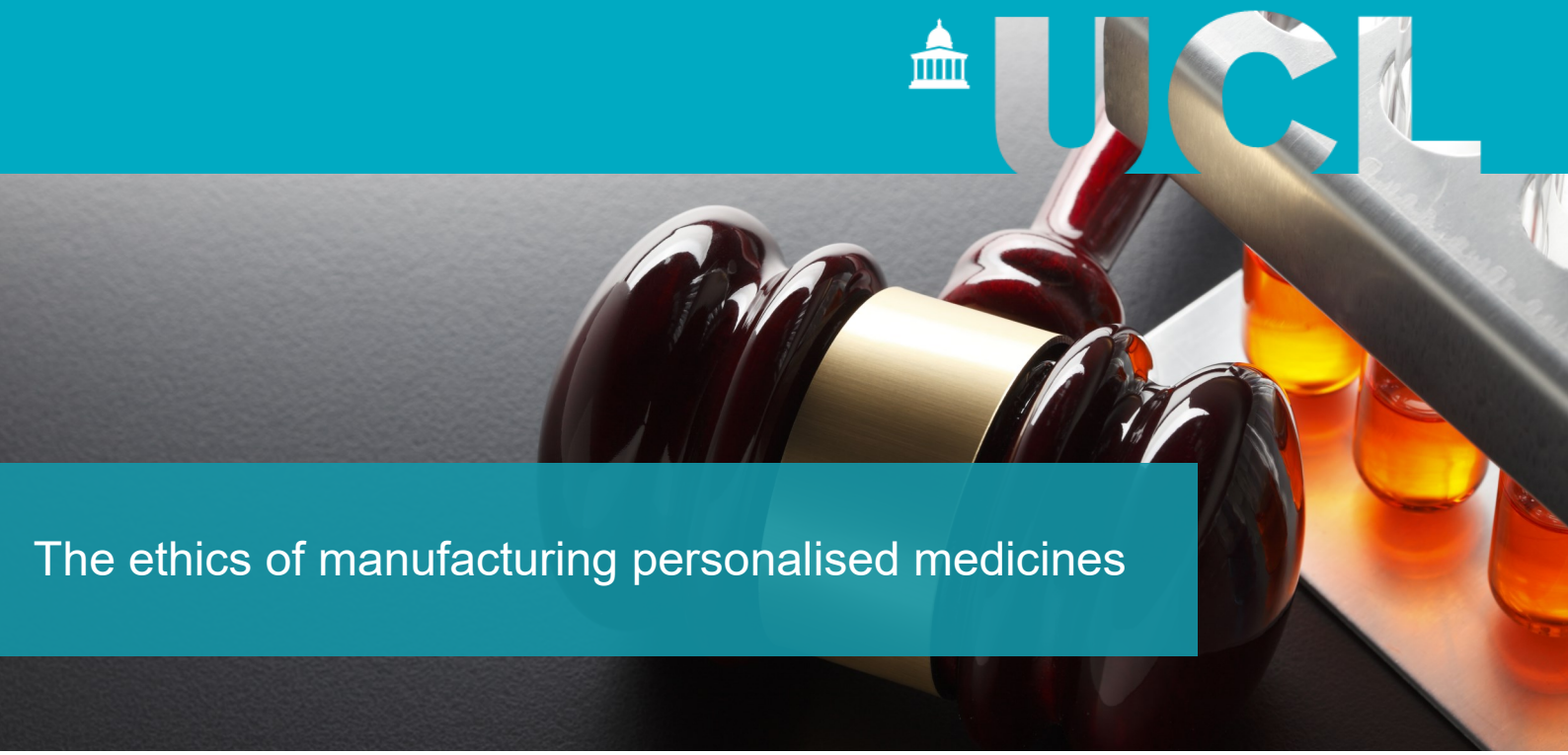

The ethics of manufacturing personalised medicines

The current "one-size-fits-all" approach to drug development is being challenged by the growing ability to create medicines targeted to specific sub-populations and even individuals. However, increased personalisation raises ethical questions around use of patient data, and the high price tag of personalised medicines to-date threatens to leave many populations behind. On 23 September 2021, UCL's Future Targeted Healthcare Manufacturing Hub (the 'Hub') held an online workshop to uncover ethical issues related to the manufacture and use of personalised medicines and identify areas for further investigation to ensure that ethical principles are "baked-in" to in the development of new manufacturing technologies for personalised medicines.

The online workshop brought together the Hub team with a range of sociologists, philosophers, ethicists, industry representatives, and policy makers to scope out the key ethical questions in personalised medicines manufacture, and to lay the ground for future research partnerships in this space. The workshop was delivered in two parts. Firstly, all participants explored the general ethical challenges that arise in the clinical development, manufacture and delivery of personalised treatments through a series of talks and focussed discussions.

In the second part of the workshop, participants were divided into two groups to focus on two themes in more detail. These were:

- Data, AI and privacy for personalised/stratified medicines.
- Global health equity and access for personalised/stratified medicines

This report summarises ethical issues and questions that were identified during the workshop.

Main session: The ethical issues of manufacturing personalised medicines

Participants identified a number of ethical challenges during discussions and recorded these in an online whiteboard. These have been grouped into the following five themes and the key questions outlined (note, this list does not contain those questions

Workshop aim

To identify the ethical issues related to manufacturing personalised medicines and formulate specific research questions on ethical issues related to the use of data and AI, and on access to medicines in resource limited settings. Additionally, the Hub team had the aim to identify those with research experience and expertise in ethics and create the opportunity for collaboration via short, funded feasibility studies, which will be informed by the findings of this workshop.

"When you see something that is technically sweet, you go ahead and do it and you argue about what to do about it only after you've had your technical success…this is the way it was with the atomic bomb."

J. Robert Oppenheimer cited by Day MA in The hope and vision of J Robert Oppenheimer p105 World Scientific Publishing Company 2019.

The Future Targeted Healthcare Manufacturing Hub (the 'Hub')

The Hub is addressing the manufacturing, business and regulatory challenges to ensure that new targeted biological medicines, including cell and gene therapies, and stratified proteins, can be developed quickly and manufactured cost-effectively. With over 40 partnering organisations, the Hub has huge convening power which it uses to drive forward the agenda for research and innovation in targeted biological medicines.

Table 1. Typical biologics treatment costs per pa-

Antibody-based treatments. There are many different antibody treatments available which are used to treat a wide range of diseases. The price for antibody treatments in the US ranges from approximately **$15,000-$200,000 a year,** potentially over many years.
Gene therapy. Since this type of therapy is often used to treat rare diseases, costs can run into the millions. For example, the gene therapy Zolgensma (Novartis) costs **$2.1 million for a one off treatment.**
Chimeric antigen receptor T-cell (CAR-T) therapy, which is used to treat certain types of blood cancer. For example list prices for the CAR T-cell therapy Kymriah (Novartis) are **$475,000 for a one-off treatment.**

relating to issues of data and privacy, and access to medicines, which will be covered in detail in the next section):

1. Affordability and health budget constraints

- Given the very high cost of personalised medicines (see Table 1), is it ethical to develop medicines and test these in clinical trials if there is limited scope to reduce these costs?

2. R&D investment priorities

- For personalised medicines in general: should we spend money on this type of research that only a few may be able to access?
- For cell therapies: is it ethical to develop personalised (autologous) treatments which use a patient's own cells, or should we invest more in universal (allogeneic) therapies that use donor cells and could be more widely accessible and cheaper (albeit with higher risks of rejection)?
- How are financial risks and benefits distributed? A concern was raised that risks may be shared with the public, while the benefits may all accrue to the private sector.
- Is it ethical for medical infrastructure to be driven by commercial goals in order to cover R&D costs?

3. Liability and legal considerations for manufacturing

Given their novelty and high cost, personalised medicines are often used as a last-line treatment. For example, in the case of CAR T-cell therapies, patients will have undergone several rounds of chemotherapy before their cells are collected for processing

- What happens if manufacturing fails due to compromised patient material and who is liable?

4. Which treatments should be offered and in which order?

- What are the ethics of pursuing chemotherapy and other current treatments ahead of ATMPs, which could potentially be curative?
- To provide the highest chances of success for therapies which rely on patient material, this would ideally be collected before patients are unwell. What are the ethical issues of collecting patient material from birth and storing this in biobanks in case of illness later in life?

5. Sustainability

Current manufacturing processes for many personalised medicines involve shipping patient material across great distances for processing in specialised centres.

- Do we have an accurate estimate of the carbon footprint of personalised medicines?
- What are the environmental, financial, and social impacts of personalised medicines and how do these weigh with their benefits?

6. Engaging with patients and public

- How do we engage the public and get their support for personalised medicines? Is this what the public wants?
- When using personalised approaches and treating rare diseases with high cost therapies, how can we be sure that patients understand "why me" (and "not them")?

Parallel sessions on AI/data/privacy and equitable access

In two separate groups, participants were asked to consider (a) the ethical issues specific to the use of data and AI and (b) the implications on privacy that this might have, and the ethical issues for developing personalised medicines which are both expensive and reliant on significant infrastructure, and the implications that this may have for their applicability in low and middle-income countries (LMICs) where resources are limited. Participants considered the needs from the perspectives of patients and manufacturers and the different ethical implications for these stakeholders. The questions raised under the two themes are set out below:

Data, AI and privacy for personalised/stratified medicines

1. Data sharing

- Who should have access to data? Clinicians will always have more data than is available to manufacturers. If they only share 'essential' data, can we define what might be considered to be 'essential'? Who should decide this? Where can anonymised data be used?
- Is there a way within the biotech industry that we can standardise data formatting to: (a) use the least and non-identifiable data and (b) be collected and processed in a standard way to help with sharing cross-platform utilisation?
- How can data sharing considerations be better built into clinical trials to ensure correct consents are obtained up-front and patients have the information that they need to make informed decisions on use of their data? (sometimes it is necessary to go back to people at a later stage to ask for permission)

2. Data security, liability and protection against misuse

- In connected systems, where does responsibility fall if there is a data breach? There are various different stakeholders involved in the "needle-to-needle" processing of cell and gene therapies, including shipping companies, manufacturers, hospitals, leukapheresis centres; since all elements are connected, will it be hard to determine where liability lies in the case of a data breach?
- How do we ensure justice for patients in cases where people are harmed though use of their data, but where no laws have been broken, or where it is not possible to prove that someone caused the harm? Could harm mitigation bodies be used in these cases?
- Could metadata be used to mine personal information even though individual data is anonymised?

3. Use of AI/machine learning technologies

- How can we ensure accessibility for patients regardless of where they live, which might require everyone across the whole supply chain to have access to the same infrastructure (NHS, manufacturers etc.)?
- Who is responsible if AI makes a bad decision? If machine learning and AI are used for decision-making, what happens if decisions are sub-optimal and who is liable for this?
- What are the wider impacts of an automated future on the environment (energy, materials), labour, and communities?

Workshop speakers

- **Professor Paul Dalby,** Professor of Biochemical Engineering and Biotechnology at UCL, and Co-Director of the Hub
- **Professor Suzy Farid,** Professor of Bioprocess Systems Engineering, UCL Biochemical Engineering and Co-Director of the Hub
- **Dr Qasim Rafiq,** Hub co-investigator who specialises in manufacture of personalised medicines including CAR T-cell therapies;
- **Dr Jonathan Appleby,** Chief Scientific Officer at the Cell and Gene Therapy Catapult, whose previous experience includes the EU submission of the gene therapy Strimvelis whilst in the role of Chief Scientific officer at GSK
- **Professor Nina Hallowell** specialises in the ethical aspects of genomics in the Nuffield Department of Population Health at the University of Oxford.
- **Professor Barbara Prainsack,** specialises in the regulatory, social and ethical dimensions of bioscience, biomedicine and forensics in Department of Political Science at the University of Vienna, and at the Department of Global Health & Social Medicine at King's College London.

Feasibility Study Call

UKRI-eligible academic researchers are invited to submit proposals for feasibility studies to build on findings from the workshop an outline current and future priorities in ethics research relating to the manufacturing and use of personalised medicines. The Hub will provide £20-45k to support projects of 3 to 6 months in duration.

On conclusion, each study will provide a high-level report to the Hub consortium outlining the potential of the approach that has been investigated, and briefly outline the plan for future development.

Ethics Feasibility Studies are awarded competitively. The application form is designed to be simple and straightforward to complete, and can be found on the Hub's website at:

https://www.ucl.ac.uk/biochemical-engineering/research/research-and-training-centres/future-targeted-healthcare-manufacturing-hub/hub-ethics

Key dates:

- Application deadline: 08 December 2021, 17:00 UK time
- Review and decisions by Hub panel: w/c 10 January 2022
- Projects can begin from 01 February 2022

Global health equity and access for personalised/stratified medicines

1. IP, commercialisation and marketing of personalised medicines

- Is intellectual property a factor in reducing access to personalised medicines in resource-poor settings and what mechanisms for IP sharing might be put in place to facilitate access? (For example the WHO's COVID-19 Technology Access Pool , C-TAP).
- Is marketization of healthcare ethical and if so could we create a global marketplace which is sensitive to regional needs?
- What reimbursement mechanisms might need to be in place to facilitate access to personalised medicines? Should originators supply at cost to resource-limited countries?
- Fairness, inclusivity and access to personalised medicines across diverse communities begins with the clinical trial design as treatments will be optimised toward those populations.. Are these factors currently considered at an early stage, and do some benefit more than others?

2. Infrastructure demands of personalised medicines

- Is it ethical to pursue high cost therapies with high infrastructure demands in resource-limited settings? How can investments be balanced with other health priorities?
- Is providing personalised medicines at cost to LMICs sufficient to deliver health equity? (for example access to COVID-19 vaccines has been weighted to high-income countries during the pandemic). Should we instead work towards building local production capacity?

3. How 'personal' should personalised medicines be to provide the greatest benefit?

- Is personalisation and stratification of medicines desirable, or will this just amplify biases that already exist in terms of access?
- If we instead consider 'universal' treatments, are they really equally accessible – if they are found to be less effective for certain groups of people, might they be excluded?

Conclusion and next steps

Accepting the transformative potential for patient outcomes using personalised treatments, there remain many unanswered questions in the realm of personalised medicine development and manufacture. To ensure justice for all patients, both nationally and internationally, consideration of the potential ethical challenges and pitfalls is vital at the outset of product development. We hope to work with others via funded feasibility studies to further investigate the ideas gathered during this short workshop and begin grappling with some of the ethical challenges and providing practical solutions for patients, clinicians and manufacturers.

Our research

This report was produced in partnership with UCL STEaPP's Policy Impact Unit (PIU) as part of the work carried out by the Future Targeted Healthcare Manufacturing Hub (the 'Hub'). Funding from the UK Engineering & Physical Sciences Research Council (EPSRC) for the Hub hosted at University College London with UK university partners is gratefully acknowledged (Grant Reference: EP/P006485/1). Financial and in-kind support from the consortium of industrial users and sector organisations is also acknowledged.

To find out more about the Hub, please visit: www.ucl.ac.uk/biochemeng/hub

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