ATMPs AND EQUITY OF ACCESS

Evidence review, roundtable and calls for action

GENETIC ALLIANCE UK

ATMP engage Public & Patient Involvement Working Group

ATTC Advanced Therapy Treatment Centres

Coordinated by CATAPULT Cell and Gene Therapy

ABOUT GENETIC ALLIANCE UK

Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 200 patient organisations.

Rare Disease UK is a multi – stakeholder campaign run by Genetic Alliance UK, working with the rare disease community and the UK's health departments to effectively implement the UK Strategy for Rare Diseases

SWAN UK (syndromes without a name) is a patient and family support service run by Genetic Alliance UK. SWAN UK offers support and information to families of children with undiagnosed genetic conditions.

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FOREWORD

Advanced Therapy Medicinal Products (ATMPs) command a high profile both for their potential and their cost. In oncology and for rare conditions, cell and gene therapies (both of which are forms of ATMP) offer new paradigms for addressing unmet health need. With such potential, and so much investment, we must be fair and equitable with the delivery of ATMPs in the UK.

One reason for this imperative is that research, innovation and healthcare delivery has not been fair and equitable to date. This means many of the tools and infrastructure we would rely on to deliver ATMPs might be already intrinsically unfair or inequitable. The All-Party Parliamentary Group on Sickle Cell and Thalassaemia's report No One's Listening (November 2021)[1] describes the context into which ATMPs for these conditions are arriving. Communities are angry and frustrated with the NHS for decades of failings and inaction, and point to massive disparities in progress to treat similar genetic conditions affecting predominantly Caucasian populations.

ATMPs have particular characteristics that warrant concern that they are equitably accessed. Decisions to participate in clinical trials or take an ATMP are intrinsically more complicated than the same decisions for conventional medicines because of their irreversible, one-off nature. Delivery routes, complex modes of action, manipulation of cells or genes, and technical terminology are all potential barriers to comprehension, consent and uptake. Treatment must be delivered at specialist centres and lives must be arranged around weeks or months of treatment. We need to understand whether there are cultural and other types of barriers or concerns that must be engaged with, and be alert to where these factors might combine and lead to a very high risk of some groups of people being excluded.

ATMP Engage[2] is a coalition of the willing, supported by the Cell and Gene Therapy Catapult[3] and EuroGCT[4] - members of the group attend because of their conviction that patient and public involvement and engagement is an important element of the delivery of ATMPs and their desire to contribute their time and energy. This report and the work it describes are the result of an examination by ATMP Engage members into equity of access to ATMPs, and public and patient involvement/engagement (PPIE) for ATMPs and forms a crucial strand of work for the group.

As co-chairs of ATMP Engage, we welcome this report as a validation of the potential of the group to drive progress, but more importantly as a first step to setting out and addressing the challenges that we face if we are to successfully deliver ATMPs equitably in the UK. Because they are relatively new and many more people will potentially have access to ATMPs in the future, progress in equitable access will need to be reviewed regularly over time. We are struck by how many of the wider activities of the members of ATMP Engage, such as in NHS post-treatment pathways and engagement and information materials, are crucial to equitable delivery of ATMPs. Communicating this shared potential to deliver fair and equitable access in the future will be a crucial element of maintaining the momentum we have developed with this work.

Nick Meade, Director of Policy
Genetic Alliance UK

Finn Willingham, Head of ATTC Network Coordination, Cell and Gene Therapy Catapult

Co-Chairs of ATMP Engage

[1] sicklecellsociety.org/wp-content/uploads/2021/11/No-Ones-Listening-Final.pdf
[2] eurogct.org/atmp-engage
[3] ct.catapult.org.uk
[4] eurogct.org

EXECUTIVE SUMMARY

- Given their relative novelty, it may not be surprising that there are large evidence gaps in what we know about equity of access for people with specific characteristics and ATMPs – through the development pipeline, in clinical application or in terms of their inherent acceptability as treatments.

- In a recent literature review, for example, few studies were found which address equity of access and the characteristics of disability, pregnancy/maternity, sex, or sexual orientation. The impact of geographical location on access to research trials has not been well studied. Very few studies look at equity of access during research and development outside of the clinical trial phase.

- We held a roundtable discussion to identify potential risks to equity of access to ATMPs, drawing on the expertise and opinions of people with lived experience, patient advocates, academics working in health inequalities, policy makers and clinicians and others with ATMP knowledge.

- The contributors were asked to focus on potential risks specific to ATMPs - or existing inequalities that could be magnified in the context of ATMPs.

- Five themes arose from the roundtable which deserve attention as ATMPs continue to move along the development pipeline into the clinic:
  - Who is taking part?
  - Support during trials and treatment
  - Health service readiness
  - Communication and information
  - Trust in medical professionals and new treatments

- Calls to action relating to each of these themes and naming specific stakeholders are presented (see page 7).

INTRODUCTION

Advanced Therapy Medicinal Products (ATMPs) are a category of novel treatment generally known as tissue, cell and gene therapies which offer hope for people with some complex diseases, genetic conditions and cancers. Rather than using the term for its precise regulatory meaning, we use it in this report as an umbrella term for these treatments. In recent years, some of these therapies have become available in the clinic, for example for rare blood conditions (sickle cell, beta-thalassaemia), immune disorders (severe combined immune deficiency (SCID)), some forms of cancer (lymphoma, leukaemia) and neurological conditions (metachromatic leukodystrophy (MLD), spinal muscular atrophy (SMA)). The pipeline of activity is growing fast.

Barriers in access to health services and treatments are an important source of health inequalities between groups of people with particular characteristics, such as sex, race, geographical region, socio-economic status or intellectual disability. Causes are varied and include discrimination, service availability and uptake, and problems with accessibility (such as unclear or insensitive language). The unique pathway of novel ATMPs through research and development, regulatory approval, and application in the clinic, must be carefully considered in order that new, specific barriers to access are not introduced and existing systemic barriers minimised.

With the support of the Cell and Gene Therapy Catapult, ATMP Engage commissioned Genetic Alliance UK to design and deliver a scoping project to examine potential inequity of access in ATMPs. The aims of the project were to examine the ATMP research and treatment pathway, and inherent attributes of ATMPs, for potential risk of inequity – either through introducing new barriers or magnifying existing inequalities (including through potential inequitable patient and public involvement and engagement).

There were two phases to the work:

Review of existing evidence. A search strategy was designed, with input from ATMP Engage members and academics with expertise in ATMPs and health inequalities, to identify relevant peer-reviewed (scientific) literature and other sources of relevant information available online. The review is summarised in this report, and the strategy and full review are published in a supplement, appended to this report. Tables illustrating evidence gaps are given in annex 1.

1. Roundtable discussion. A facilitated discussion was held with ATMP Engage equity-of-access subgroup members and other stakeholders including people with lived experience and patient group representatives, clinicians involved in ATMP trials, academics with expertise in ATMPs and in health inequalities[5], and policy makers. Two invitees were unable to attend the roundtable but discussed the same set of issues separately with the facilitator and Genetic Alliance UK staff. A summary of the discussions, the risks identified and calls for action, are detailed in this report. Annexes 2 and 3 provide demographic and biographical information about the participants.

[5] It was challenging to recruit health inequality academics to the project (to secure two academics we invited 14), which may speak to the highly specialised (and 'rare') nature of ATMPs, their low profile in the context of existing, major health inequalities and their complexity, as their specific equitable access risks may not be immediately obvious. Continuing to work across disciplines will be critical in efforts to establish equitable access as ATMPs are introduced.

EXISTING EVIDENCE

The literature review reports on existing evidence of health inequalities within the research and development pathway including regulatory approval and health technology assessment (HTA), clinical application, acceptability of the nature of ATMPs, and other issues across the whole of the treatment development pipeline. It highlights substantial evidence gaps for particular characteristics.

The literature review was based on identifying relevant research articles (via specialist sources such as the Web of Science, APA Psychinfo and Pubmed databases) as well as an internet-based search for 'grey' literature (reports and websites); this led us to nearly 70 relevant items which have been read and summarised. The search terms ranged from quite focused (e.g. 'advanced therapies' combined with 'health inequalities') to relatively broad (e.g. 'drug development' combined with 'health inequalities').

Most of the studies we found took place in the US or Europe and addressed one aspect of the treatment delivery pathway from research and development to clinical application; these tended to be quantitative studies identifying the groups who may experience inequality. We found only a few studies which focussed on aspects of the research and development pathway outside of clinical trials, such as basic research and preclinical development, local regulatory practices and HTA.

Similarly, few articles came to light on health inequalities and the acceptability of the novel nature of advanced therapies; the studies we found in this area tended to be qualitative and aimed to understand attitudes towards advanced therapies. The discussions focussed on the conflict between religious and scientific beliefs held by some groups which are relevant for some particular advanced therapies.

We have categorised the health inequalities addressed in the articles we found into those relating to:

- Protected characteristics (age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation)
- Other characteristics (socio-economic status, literacy, prevalence of a condition amongst particular groups, commonality of condition compared with other conditions, region – across countries and within country).

For some protected characteristics we found no studies (for example gender reassignment, marriage and civil partnership, and sexual orientation). The issues around advanced therapies which were raised for certain groups generally referred to both accessing clinical trials and treatment in the clinic. The characteristics which were associated with unequal access were: race (non-white minority groups), age (younger and older groups), socio-economic status (lower SES), literacy (lower health literacy and digital poverty), a high prevalence of a condition when it occurs in certain groups (homeless, drug users, ethnic minorities), general prevalence of condition (ultra-rare), and geographical region (disparities across countries and those living further away from treatment facilities). Other issues which may be associated with health inequalities were around costs (of research and development, and treatment), lack of diversity in the development of patient reported outcome measures, the comprehensiveness of data collected and the impact of historical data collected on non-diverse groups.

The search strategy that formed the basis for the literature review, and the full literature review, are available in the supplement, appended to this report.

ROUNDTABLE DISCUSSION

A half day facilitated discussion, via zoom, was held in March 2023, with 11 participants, and observers from Cell and Gene Therapy Catapult and Genetic Alliance UK. The facilitator was an independent consultant with experience in rare conditions, advanced therapies and regulatory issues. Information about the participants' characteristics, and biographical summaries, are given in annexes 2 and 3. Quotes included in this report are not attributed to individuals and this was communicated to participants ahead of the event to encourage free discussion.

Prior to the roundtable participants were provided with links to key resources that provide a grounding in ATMPs (the EuroGCT introductory text 'What is gene and cell therapy?'[6]) and in health inequalities (the Kings Fund explainer 'What are health inequalities?'[7]). A summary of the literature review findings and the slide deck developed for the discussion were also circulated, along with biographical information about the participants and a consent form.

The literature review findings were presented at the start of the event, ahead of the facilitated discussion. The agenda was organised around three elements in the development and application of ATMPs:

- research, development and regulatory
- clinical application
- acceptability / inherent nature of ATMPs.

Potential access risks were identified and discussed, and several key themes arose, many of which cut across the different elements of the agenda. Calls for action for identified stakeholders were proposed during the roundtable, and subsequently developed by Genetic Alliance UK. Issues related to global inequalities and the cost of development and treatment (to developers and the NHS) were deemed out of scope for the discussion.

PRIORITY THEMES AND CALLS FOR ACTION

'Recognising where do these potential inequalities or biases come in along the entire pipeline… whether that's an access issue, whether that's an efficacy issue, tackling all of it requires different efforts, both from a data and multi-disciplinary, multi-sector perspective.'

Five themes were drawn from the discussions, each spanning one or more of the elements that drove the meeting agenda (research, development and regulatory; clinical application; acceptability / inherent nature of ATMPs). The themes are described below, and followed by a list of calls to action for specific stakeholders.

[6] eurogct.org/what-gene-and-cell-therapy
[7] kingsfund.org.uk/publications/what-are-health-inequalities

1. Who is taking part?

Concerns were raised that without comprehensive collection and sharing of data about who is participating in ATMP trials and treatment it will not be possible to ascertain specific, existing bias over and above that which is already reported for clinical trials and new treatments generally. Clearly a range of personal data is collected as part of trial protocols, but there is a question as to whether additional information, designed to identify under-served groups/characteristics, could be captured. Contributors acknowledged the risk of identification of individuals when personal data is collected alongside rare condition research, and the need for stringent data handling precautions to mitigate this. Better data collection on those involved in trials could be extended to assessing the diversity of professionals delivering clinical trials, as there is evidence of an association between their diversity and participant diversity.

'If you don't involve different ethnicities you end up having medicines created that work better for some than for others'

'We've never had insight into the conversations which people have, particularly if people were to say "were the people in the trial like me?", there's really no answer [to] that.'

Depending on the criteria for joining trials and for receiving treatment, there will be individuals who are excluded based on the severity or progression of their condition. The high cost of ATMPs may mean that this becomes a particularly significant issue compared with less expensive treatments, and will be seen as an injustice.

Good data on protected and other characteristics is also necessary to ensure that higher prevalences of conditions in specific groups can be understood, and can then be acted on in a targeted way to ensure treatments are delivered effectively and appropriately. For example, improving the granularity in self-reported ethnicity surveys can highlight specific groups with high rates of genetic conditions.

The use of artificial intelligence, and health data and algorithms, in treatment development was raised and it was suggested that this is an area that should be scrutinised as a potential route for the introduction of bias in terms of who treatments are effective for.

There was a feeling that awareness of the importance of diversity in those contributing to public and patient involvement (PPI) in clinical trials and service development generally is relatively well advanced, but that the evidence base is lacking and could be improved.

2. Support during trials and treatment

Although treatment with ATMPs is a 'one-off', it can require lengthy stays at clinics far from home and a significant time commitment for work-up and follow-up appointments, leading to a direct financial burden and an impact on an individual's ability to work. The consequences for families with less financial resilience will be most acute.

It was suggested that the risks of inequalities are likely to be greater when these treatments are licensed and adopted for use in the NHS than during trials: trials are resourced to deliver well-coordinated treatment and to reimburse fully for out-of-pocket expenses incurred by participants (although not for lost income). In the 'real world' of the clinic, resources are more limited and coordination between local and specialist services are likely to be less efficient: there is a need to collect data on individuals' experiences of receiving treatment with ATMPs within the NHS, to identify early the impact on the lives of those receiving treatment and any associated potential inequalities.

Support needs more broadly, such as emotional and logistical support, and support with communicating about treatment decisions within families and communities, need to be better understood and addressed to facilitate access to advanced therapies. The group was aware of ongoing work to understand support needs for trial participants with a neurodegenerative condition.

Concerns were flagged around trial recruitment being potentially biased toward those who would need less support to participate and would therefore be more likely to consent, and a temptation for clinicians recruiting to trials to favour their own patients for whom support might be more easily or willingly put in place.

Living with a condition for years before an ATMP becomes available can mean there is irreversible damage to health that an ATMP cannot undo. A concern was raised about potential impacts on benefit claims, such as personal independence payments, if an individual is seen to have received a 'curative' treatment and is therefore no longer eligible for state support.

3. Health service readiness

The risk of geographic and socioeconomic inequity in access to ATMPs within the UK were repeatedly raised during the roundtable. Health service readiness will have a huge impact on how these factors influence access. As advanced therapies leave the development pipeline, health services need to be ready to deliver equitable access in the face of restricted budgets for support for patients and their families, different approaches among the four home nations, and despite varying levels of coordination and communication between local and specialist clinics.

'During a trial is when they have the most access to absolutely everything so for me the inequalities are not clear during a trial because everything is paid for … you get people back to their local environment and they may be from a borough where they don't have a good community team, they don't have easy access and suddenly that disappears and that is where the inequality lies. My fear … [is] that those inequalities will become very clear – that access will be determined by your postcode.'

4. Communication and information

A clear theme running through the discussion was good communication and information as key tools to support equity of access. The novelty of the technology behind ATMPs and of the patient experience in receiving them, raises communication challenges.

Potential patients, their families and healthcare professionals require trusted sources of information. The signposting to reliable information provided by the EuroGCT website was quoted, and attendees noted that work is needed to ensure healthcare professionals are aware of opportunities to join trials and of how to signpost their patients to good sources of information. Where specific groups have a high prevalence of a condition that is amenable to treatment, bespoke culturally-sensitive information may be required. The backdrop to concerns about trusted information is the pervasiveness of social media, which at once means that access to information is relatively straight forward, but it comes with a huge amount of 'accessible misinformation'.

'A lot of people don't know where to look [for information] and need a certain level of technical literacy even to engage with it'

'It's the specialists who know about the trials which are going on … if GPs don't know there is a new treatment or they don't know there is a trial they can't recommend these things to their patients.'

In the face of such novel treatments, and with information (both good and bad) being so readily available on the internet, low literacy and lack of English were raised as potential risks for unequal access (to both trials and clinical services). This can be compounded where family members who may not be neutral act as translators and family dynamics can lead to a bias in the transmission of information.

5. Trust in the medical profession and new treatments

Examples of 'experimentation' and lack of consent for medical procedures on people from some minority ethnic backgrounds were raised as a cause of deep distrust of the medical profession. It was questioned whether healthcare professionals are sufficiently aware of this backdrop which should influence how trials and treatments are offered and explained if certain groups are not to self-exclude from receiving ATMPs.

It was suggested that looking to the high uptake of other types of treatments and health technologies among groups such as Amish and Askenazi Jewish people, and to how communication works within communities (such as around the covid vaccine uptake), might suggest fruitful approaches to building trust.

The invasive nature of some ATMP treatments, such as delivery directly into the brain, may also be inherently less acceptable in some cultures. Similarly, it would be beneficial to better understand the decision-making process when people are faced with an irreversible, one-off treatment, which might make them ineligible for future similar treatments should the first not be durable, versus their existing long-term management which they may be comfortable and confident with. There may be personal, demographic characteristics (such as educational attainment) that influence that process and what kinds of information and support will be most suitable and acceptable.

'Amongst some ethnicities, some groups, is a concern of being 'guinea pigs' especially at the early stage and this emanates from a long history of that kind of behaviour in the 1930s.'

'Refugees and migrants as a particular population or group to consider in terms of their participation or hesitancy.'

'Very specific to the ATMP space is … the one-off nature of the treatments and if this is something that patients will opt for or not a lot of that depends on their particular circumstances.'

Theme	Stakeholder	Calls to action		
		Research, regulatory, HTA	Clinical	Acceptability
All themes	ATMP Engage	ATMP Engage should respond to this report with a set of proposals for: – Additional initiatives for ATMP Engage to take forward (acknowledging limited resources). – Messages to disseminate within the wider ATMP community, particularly with respect to specific activities as detailed below that this report demonstrates have direct impact on equitable access to ATMPs. – A regular horizon scanning process to map current, ATMP-specific diversity and access initiatives along the development and clinical pathway.		
Who is taking part?	Catapult, NIHR and other research funders, researchers	Explore potential for data collection harmonisation to identify under-served groups. Raise awareness of ATMP trials to improve range of referring HCPs. (This may have a broader value outside ATMPs).		
	Research funders	Address gaps in evidence base, e.g. specific characteristics and activities such as HTA.		

Continued on next page

Theme	Stakeholder	Calls to action		
		Research, regulatory, HTA	Clinical	Acceptability
Health service readiness	NHS Specialised Commissioners		Collect referral data ('accessibility audit'). Work systematically with patient advocacy organisations when commissioning services.	
Communication and information	ATMP Engage EuroGCT	Work with professional organisations and Health Education England to raise awareness of ATMPs among HCPs, to improve communication and signposting to trusted information.		
Trust in the medical profession and new treatments	Health Education England			Develop awareness raising for HCPs of historical basis of mistrust and its impacts, in partnership with community groups and academics.

ANNEX 1 SUMMARY OF EVIDENCE GAPS

The following tables indicate the scope of the published studies and reports that were found in the literature review carried out in February 2023 for this work. The tables cover evidence relating to ATMPs specifically, drug development more generally, and either legally protected characteristics (table 1), other vulnerabilities (table 2), or other specific issues associated with inequalities (table 3). Empty cells indicate where no studies were found.

Table 1 Legally protected characteristics and ATMPs or general drug development

		Any phase	Research Pathway				Treatment Pathway		Acceptability
			Research and development		Regulatory Processes		Clinical stage		
Inequality	Groups that experience inequalities		Basic research / preclinical development	Clinical Trials including Early clinical trials	Local practices - regulation / licencing	Health Technology Assessment (HTA)	Accessibility	Effectiveness	
Protected characteristics									
Age	Younger Older								older – treatment adherence
Disability	Intellectual disability/ limited language ability								
Gender reassignment									
Marriage and civil partnership									
Pregnancy and maternity	Pregnant and / or lactating women								
Race	Non-white minority groups								
Religion or belief	General conflict between religious and scientific beliefs								
Sex	Women–especially phase I trials								
Sexual orientation									

Key:

Rare/inherited | Cancer | Non-cancer / non-rare | Generic

Solid colour relates to ATMP studies; faded colour to general drug development studies.

Table 2 Characteristics not legally protected and ATMPs or general drug development

Inequality	Groups that experience inequalities	Any phase	Research Pathway				Treatment pathway		Acceptability
			Research and development		Regulatory Processes		Clinical stage		
			Basic research / preclinical development	Clinical Trials including Early clinical trials	Local practices - regulation / licencing	Health Technology Assessment (HTA)	Accessibility	Effectiveness	
Other characteristics									
Socio-economic status (SES)	Lower SES								
Knowledge acquisition / reading age / digital access	Lower health literacy / digital poverty								
Particular groups having higher prevalence or more severity of certain conditions	Ethnic minorities / homelessness / drug users								
How common is the condition	Ultra-rare conditions								
Global geographical	Under developed								
Regional geographical (across close country borders)	Varies (i.e. across EU countries)								
Local geographical (within country including rural / urban and travel times to treatment centres)	Those living further away from treatment facilities								

Key:

Rare/inherited | Cancer | Non-cancer / non-rare | Generic

Solid colour relates to ATMP studies; faded colour to general drug development studies.

Table 3 Other specific issues and ATMPs or general drug development

	Comment	Any phase	Research Pathway				Treatment Pathway		Acceptability
			Research and development		Regulatory Processes		Clinical stage		
			Basic research / preclinical development	Clinical Trials including Early clinical trials	Local practices - regulation / licencing	Health Technology Assessment (HTA)	Accessibility	Effectiveness	
Issue									
Cost	High cost of development and treatment								
Patient reported outcome measures / patient engagement	Measures may not be developed in diverse groups								
Transparency / type of data collected	Historically Euro-centric, data collection inconsistent								
Definition of health inequalities / equity	Non consensus on definitions								
Other impacts of health inequalities	Differences in diagnosis and accessing other services								
Recruitment to clinical trials – general limitations, exclusions and barriers	Global disparities / inconsistent exclusions / patients want accessibility, support & plain language								

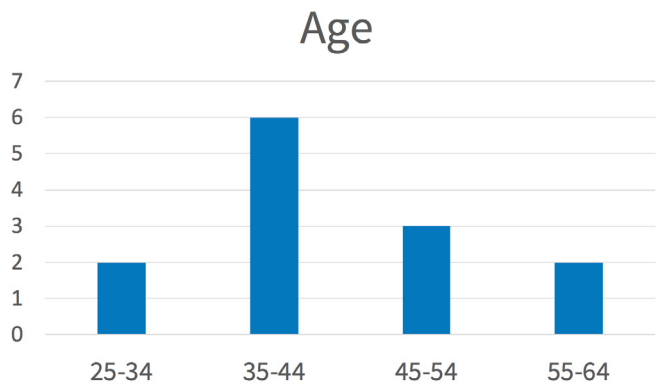
Key:

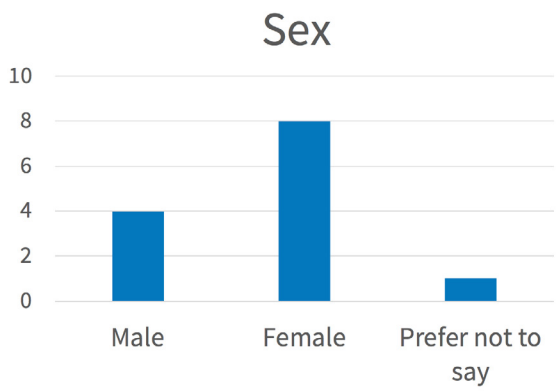
Rare/inherited | Cancer | Non-cancer / non-rare | Generic

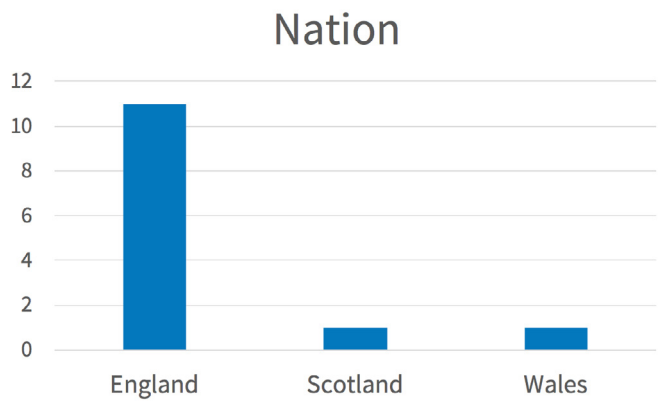
Solid colour relates to ATMP studies; faded colour to general drug development studies.

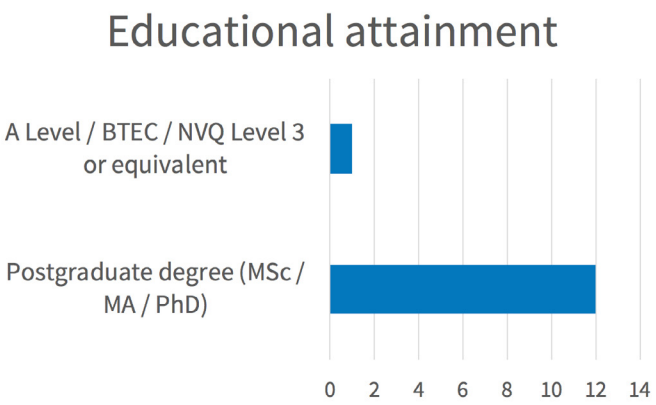
ANNEX 2 DEMOGRAPHICS OF ROUNDTABLE CONTRIBUTORS

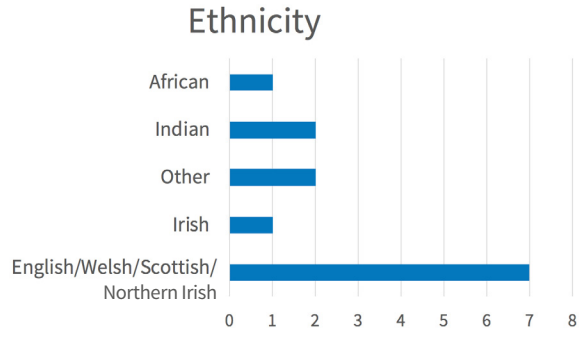
The following charts include those who contributed separately to the main event, and exclude the facilitator, organisers and observers.











ANNEX 3 BIOGRAPHIES OF ROUNDTABLE CONTRIBUTORS, ORGANISERS AND OBSERVERS

Biographies are listed in alphabetical order.

Claire Booth

Professor of Gene Therapy and Paediatric Immunology
Great Ormond Street Hospital/UCL Institute of Child Health

Prof Claire Booth, MBBS PhD is a Gene Therapist and Paediatric Immunologist at UCL Great Ormond Street Hospital Institute of Child Health in London and leads the clinical stem cell gene therapy programme. She graduated from Guy's, King's and St. Thomas' School of Medicine in 2001 and then trained in Paediatrics, subspecialising in Paediatric Immunology and Immunodeficiency. She undertook a Wellcome Trust funded PhD at UCL developing haematopoietic stem cell gene therapy, with continued NIHR and Wellcome Trust post-doctoral support to establish her own research group. She was appointed as a Consultant in Paediatric Immunology at Great Ormond Street Hospital in 2014.

Claire now works as a clinical academic leading an expanding number of gene therapy clinical trials at Great Ormond Street Hospital which treats patients with immune deficiencies, haematological and metabolic disorders. Her lab group is focused on developing novel therapies for immune system disorders using both gene therapy/gene editing and targeted small molecules. She has extensive experience of translating, leading, and delivering first in human clinical trials and the commercialisation pathway. As an attending physician she oversees the clinical management of patients with immune deficiencies, including hematopoietic stem cell transplantation and maintains a strong interest in HLH disorders.

Claire is an internationally recognised expert in gene therapy and immunology, an elected board member of the European Society of Gene and Cell Therapy, Chair of the International Committee of the American Society of Gene and Cell Therapy and previously served two terms on the board of the British Society. She serves on the editorial board of several journals and grant review committees and holds an honorary position at Boston Children's Hospital/Dana Farber Cancer Institute and Harvard Medical School.

She is also the co-founder of the AGORA initiative (Access to Gene therapies fOr Rare disease) which has founding members across 6 European countries and brings together clinicians and scientist with direct experience of developing and delivering ex vivo gene therapies for rare diseases, aiming to facilitate access to effective gene therapies for treatment of patients with ultra-rare diseases.

Heather Brown

Professor of Health Inequalities
Lancaster University

Heather Brown is a Professor of Health Inequalities at Lancaster University. Her main research interests are the economics causes and consequences of health inequalities and policy evaluation. She is particularly interested in inequalities across and between generations and how policies can reduce these inequalities by removing structural barriers.

Heather uses large datasets including linked data to evaluate policy as well as identify current trends and areas for future policy and interventions. She is also interested in engaging with a wide range of stakeholders to make complex quantitative data analysis accessible and user friendly.

Ben Doak

National Senior Programme of Care Manager (innovative treatments)
NHS England

Ben's primary role is to fulfil NHS England's commissioning responsibility to ensure that, where applicable, specialised services are in place to deliver innovative treatments (such as ATMPs) recommended by NICE in the NHS in England.

Ben has worked in innovation through various roles in his career, including working with surgical innovations in NICE's interventional procedures programme, overseeing the placement of innovations in treatment pathways through NICE clinical guidelines and streamlining commercial activity for new technologies in NHS England's Commercial Medicines Directorate.

Ben is an active member of ATMP Engage.

Cheney Drew

Research Fellow and Senior Clinical Trials Manager
Cardiff University

Cheney is a research fellow and senior trials manager for the Mind, Brain Neuroscience study portfolio at the Centre for Trials Research in Cardiff University. She has a background in pharmacological research, with particular reference to neurodegenerative diseases, having completed her PhD in Huntington's disease.

Since transitioning to clinical research, Cheney has been involved in the development and delivery of trials aimed at evaluating interventions (non-pharmacological and novel advanced therapies) in people with Huntington's disease and other neurological disorders including Tuberous Sclerosis and epilepsy.

She is a member of the European Huntington's Disease Network advanced therapies working group, aimed at devising the most efficient and robust methods for evaluating novel, non-traditional, treatments for this rare disorder.

Given the complex and experimental nature of advanced therapies, she is particularly interested in how participants are approached, informed and how they provide consent to involvement in these trials. This includes listening to the participant voice as a central tenet of trial design.

Kye Gbangbola

Managing Director, and expert in the inherited genetic condition of Sickle Cell Disorder
Recent past Chairman of the Kings Fund Award winning patient organisation Sickle Cell Society in the UK

Kye Gbangbola MBA FCIOB FIEMA CIHCM CEnv Dip DEA GDA PGDCM PGCDM EurBE GACSO LCSAP

Kye is the former Chairman of the Kings Fund/ GSK award winning Sickle Cell Society a national patient organisation in the UK. He uses his health literacy to drive, and advocate for patient centred care within a complex medical system.

His Lancet Medical Journal 5 Star Reviewed 'The Sickle Cell Guide' is an ultimate guide to sickle cell, from its history, genetic cures, Coronavirus, health Commissioning, living with the condition, inequality, and much much more. A book for people who thought they knew a lot, and for people who know little.

Kye collaborates with a wide range of stakeholders including patients, the Department of Health and Social Care, Parliamentarians, NHS Boards, European Medical Association, National Institute for Health and Care Excellence, Medicines and Healthcare Products Regulatory Agency, and other licensing organisations. Kye is central member of the Sickle Cell and Thalassaemia All Party Parliamentary Group. In addition, he works with pharmaceutical companies, ambulance services, cell and gene research etc.

Kye wrote the Foreword to the SC Society publication 'Clinical Standards of Care for Adults with SCD' and gave the parliamentary address at its launch. He gave a call to action, for medical professionals, patients, and their families, to use the Standard as essential intelligence for better health care.

Amy Hunter (observer)
Director of Research
Genetic Alliance UK

Amy runs the research team at Genetic Alliance UK to support our policy and engagement work through developing a good evidence base about the experiences of those affected by genetic, rare and undiagnosed conditions. She also works directly with the member charities that make up the Genetic Alliance UK community, and with researchers at universities across the UK. As well as designing and managing research, Amy is experienced in establishing 'patient involvement' partnerships in academic research projects.

Jennifer Jones (Presenting, note-taking and analysis)
Research Associate
Genetic Alliance UK

Jennifer has a PhD in medical sociology, and has conducted research with people into lived experiences of rare conditions and cancer.

Manju Kurian
Professor of Neurogenetics
UCL

Dr Kurian is an academic paediatric neurologist who has worked at Great Ormond Street Hospital since March 2011. She is also affiliated to the Neurosciences Unit at the Institute of Child Health, UCL.

'I am constantly inspired by the patients and their families at the hospital. By combining my clinical practice with academic research, my aim is to improve clinical diagnosis in my area of expertise as well as to explore novel therapeutic options on a research basis. The long term goal is to improve the experience and outlook for patients with neurological disorders.'

Jennifer Lorigan
Information Officer
EuroGCT - University of Edinburgh

Jennifer Lorigan is the Information Officer - Gene and Cell Therapy for EuroGCT at the University of Edinburgh's Centre for Regenerative Medicine. She is responsible for developing content aimed at people affected by genetic or progressive conditions, as well as other interested non-specialist audiences. She works with researchers and patient advocates to create resources about gene and cell therapies, genetic disorders, and ongoing research, with an emphasis on information that is both useful and accessible to EuroGCT's audiences.

She is enthusiastic about contributing to a culture of improved health equity and literacy, and has previously worked with the NHS Research Ethics Service, Dublin Brain Bank, and Science Gallery Dublin.

Nick Meade
Director of Policy
Genetic Alliance UK

Genetic Alliance UK is the national charity supporting everyone living with genetic, rare and undiagnosed conditions. We have more than 200 support organisation members. There are more than 6,000 rare conditions, with around 70% having an identified genetic cause. Most rare conditions do not have a treatment that can adequately treat people affected. This enormous unmet health need leads us to a focus on innovative treatments that may deliver benefits to our community.

Alongside Finn Willingham of Catapult, Nick co-chairs ATMP Engage, the multistakeholder group focused on patient and public engagement around ATMPs which commissioned this work.

Anjali Mazumder

AI, Justice and Human Rights Theme Lead
The Alan Turing Institute

Anjali Mazumder is the AI and Justice and Human Rights Theme Lead and Research Chair for EDI (Equity, Diversity & Inclusion) at The Alan Turing Institute. She has over 15 years' experience tackling data problems of societal importance at the interface of research, policy and practice in the UK, the US, and Canada, fostering multi-disciplinary and cross-sector collaborations. She has overseen the delivery of national and multi-institutional programmes – health, education, justice. Her work is at the intersection of statistics (data, evidence, decision-making & expert systems) and the law with a focus on developing socio-technical, inclusive and system approaches to enable fairness, justice, robustness and privacy, interrogating issues of value of data and bias, assessing differential outcomes and opportunities and risks in combining data sources, and enabling infrastructure and oversight mechanisms for human-computer collaboration that respects human rights. She is a Trustee of the Royal Statistical Society, serving on the Statistics and Law, and Data Science and AI committees, serves on the Research Advisory Board for the Educational Testing Service, and contributes to a number of national and international working groups. She was appointed to Canada's National DNA Databank Advisory Committee (2012-2018). She holds a doctorate in Statistics from the University of Oxford and two masters' degrees in Measurement and Evaluation, and Statistics from the University of Toronto.

Stella O'Brien

Lived experience of genetic condition; carer experience for people who received gene/cell therapies.

Stella works with digital technology and researches the management and implementation of knowledge-based systems.

Stella has had caring responsibilities across her lifespan. She has friends and family who have benefited from ATMPs.

She volunteers for several charities and organisations in the arena of health and social care. She appraises research proposals for NIHR, CRUK, and other funders. She contributes a patient and public perspective to the development of living guidelines for NICE, and is a member of a NICE technology appraisal committee that has evaluated a number of cell and gene therapies, including CAR-T.

Kelsie Thomas (observer)

ATTC Business Programme Manager
Cell and Gene Therapy Catapult

Cell and Gene Therapy Catapult coordinated the Network of Advanced Therapy Treatment Centres (ATTC) to address the unique and complex challenges of bringing advanced therapy medicinal products (ATMPs) to patients.

Cell and Gene Therapy Catapult also coordinate the Advanced Therapy Medicinal Products Patient and Public Involvement and Engagement Working Group (ATMP Engage) bringing together UK-based stakeholders with an interest in ATMPs to discuss and collaborate on PPIE activity.

Portia Thorman

Advocacy Lead
SMA UK

Portia was a Primary school teacher for 12 years before she had her fourth child who was diagnosed with SMA type 1. Due to late diagnosis and treatment he lives with complex needs. She gave up her career to look after him. In 2022, Portia started a role as Advocacy Lead at SMA UK, advocating for the SMA community as a whole.

She sits on the SMA Europe treatment commitee and work closely with the leading UK SMA clinicians through the REACH clinical networks. She is on the UK Newborn Screening Steering Committee working to expidite newborn screening in the UK. Portia is also part of many SMA community social networks and strives to take their issues to the people that can make a difference.

Sheela Upadhyaya

Facilitator of the roundtable
Life Sciences Consultant - specialising in Rare Disease

Sheela Upadhyaya is a consultant to the life sciences industry and in 25 year her career has played several roles in the rare disease space. She led the NICE Highly Specialised Technology program,, at NICE, responsible for running the program to evaluate medicines and technologies for rare and ultra-rare conditions for commissioning in the NHS along with being their Rare Disease and COVID 19 strategic adviser.

She now consults with the life sciences industry and is currently chair for Together for Rare Diseases, an initiative to support collaboration with European Reference Networks and Industry to improve the landscape for research in rare diseases.

Sheela has extensive experience in understanding the issues that face the healthcare ecosystem when trying to secure access for medicines for orphan and ultra-orphan conditions. These include developing innovative access arrangements in liaison with industry, clinicians, patients and the NHS.

Sheela has co-authored several papers that discuss HTA methods for assessing the value of orphan medicines and presented at many conference issue panels on the subject.

Sheela also provides advice to the European Haemophilia Consortium Think Tank, is Chair for the ISPOR Rare Disease special interest group and Trustee of the My Name'5 Doddie Foundation.

Sheela has a passion for partnership working and believes that collaboration across the sector is the key to delivering high quality outcomes for all.

Catherine van Niekerk

Lead Project Manager
Newcastle upon Tyne Hospitals NHS Foundation Trust

Working on the UKRI funded project Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC) to increase adoption of these complex products. The NA-ATTC is part of the Advanced Therapies Treatment Centre network, one of three centres in the UK and working with the Cell and Gene Therapy Catapult.

Finn Willingham (observer)

Head of ATTC Network Coordination; Co-chair of ATMP Engage
Cell and Gene Therapy Catapult

I have over 25 years' experience in the biotechnology and healthcare sectors. In my current role, I coordinate the Advanced Therapy Treatment Centre (ATTC) Network, a major Innovate UK-funded programme established to help accelerate adoption of Advanced Therapy Medicinal Products (ATMPs) by the UK's National Health Services - and as part of my remit, I co-chair ATMP Engage along with Nick Meade (Genetic Alliance UK).

Laurence Woollard

Director / Patient consultant / Lived experience of a genetic condition
On The Pulse Consultancy Ltd.

Strategy consultant in patient education and engagement for rare diseases. Person living with severe haemophilia A; a rare, chronic bleeding disorder. MSc candidate in Health Policy at Imperial College London (2022-2024).

ATMPs AND EQUITY OF ACCESS

Evidence review supplement

GENETIC ALLIANCE UK

ATMP engage Public & Patient Involvement Working Group

ATTC Advanced Therapy Treatment Centres

Coordinated by CATAPULT Cell and Gene Therapy

ABOUT GENETIC ALLIANCE UK

Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. We are an alliance of over 200 patient organisations.

Rare Disease UK is a multi – stakeholder campaign run by Genetic Alliance UK, working with the rare disease community and the UK's health departments to effectively implement the UK Strategy for Rare Diseases

SWAN UK (syndromes without a name) is a patient and family support service run by Genetic Alliance UK. SWAN UK offers support and information to families of children with undiagnosed genetic conditions.

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Registered company number: 05772999

SUPPLEMENT CONTENTS

SUMMARY

The literature review reports on existing evidence of health inequalities within the research and development pathway including regulatory and health technology assessment (HTA), clinical application, acceptability of the nature of ATMPs, and other issues across the whole of the treatment development pipeline. It highlights evidence gaps for particular characteristics. The literature review was based on identifying relevant research articles (via specialist sources such as the Web of Science, APA Psychinfo and Pubmed databases) as well as an internet-based search for 'grey' literature (reports and websites); this led us to nearly 70 relevant items which have been read and summarised. The search terms ranged from quite focused (e.g. 'advanced therapies' and 'health inequalities') to relatively broad (e.g. 'drug development' and 'health inequalities'). Most of the studies we found took place in the US or Europe and address one aspect of the treatment delivery pathway from research and development to clinical application; these tended to be quantitative studies identifying the groups who may experience inequality.

We found only a few studies which focussed on aspects of the research and development pathway outside of clinical trials, so we have limited evidence about health inequalities in the areas of basic research and preclinical development, local regulatory practices and HTAs. We found only few articles on health inequalities and the acceptability of the novel nature of advanced therapies; the studies we found in this area tended to be qualitative and aimed to understand attitudes towards advanced therapies. The discussions focussed on the conflict between religious and scientific beliefs held by some groups which are relevant for some particular advanced therapies.

We have categorised the health inequalities addressed in the articles we found into:

- Protected characteristics (age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation)

- Other characteristics (socio-economic status (SES), literacy, prevalence of a condition amongst particular groups, commonality of condition compared with other conditions, region – across countries and within country).

For some protected characteristics we found no studies (for example gender reassignment, marriage and civil partnership, and sexual orientation). The issues around advanced therapies which were raised for certain groups generally referred to both accessing clinical trials and treatment in the clinic. The characteristics which were linked with inequalities were; race (non-white minority groups), age (younger and older groups), socio-economic status (lower SES), literacy (lower health literacy and digital poverty), prevalence of a condition amongst certain groups (homeless, drug users, ethnic minorities), commonality of condition (ultra-rare), and geographical region (disparities across countries and those living further away from treatment facilities). Other issues which may be associated with health inequalities were around costs (research and development, and treatment), lack of diversity in the development of patient reported outcome measures, the comprehensiveness of data collected and the impact of historical data collected on non-diverse groups.

RESEARCH AND DEVELOPMENT (INCLUDING REGULATORY AND HTA)

Protected characteristics

Age

Several studies have noted how older people are under-represented in clinical trials for a variety of conditions (Banzi et al., 2016, Chow et al., 2022, Gouverneur et al., 2018). A US study looking at the recruitment to oncology trials by age found that *'40% of patients in practice-changing trials are older adults. Although they remain underrepresented in clinical trials compared with the general population, older adults in practice-changing trials seem to be better represented than in previously reported analyses of cooperative group trials.'* (Chow et al., 2022)

A review study looking at the inclusion of elderly / frail patients in RCTs for metastatic colorectal cancer found this group were underrepresented (Gouverneur et al., 2018). In addition, they found that the elderly patients who were included were not representative of the older population due to exclusion criteria based on frailty and therefore *'results concerning targeted therapies can be inferred only to relatively healthy elderly subjects.'*

Younger people have also been under-represented in clinical trials and there have been calls to include adolescents in trials with adult participants (Noel et al., 2021, Nachman et al., 2015). Gaspar and Fern (2016) recommend that *'abolishing the use of age as a barrier to drug and trial access'* is necessary in order to understand the biology of cancers in teenagers and young adults who are often underrepresented in trials. Trials tend to have inclusion / exclusion criteria which were found to not be consistent across CAR-T therapy trials (Jaggers et al., 2021). '*Institution-sponsored studies were more likely to have age restrictions (n = 29) than industry-sponsored (n = 20), (83% vs 45%, p < 0.01).'*

Disability

Those with intellectual disability or limited language ability are often excluded from relevant research and consultations about services directly affecting them but could be more included through the use of alternative methods (The Challenging Behaviour Foundation, 2021). Farmer and Thurm (2021) describe ways in which there could be opportunities for more inclusion of these groups to help improve autism spectrum disorders drug development.

Pregnancy

A paper by Roes et al. (2018) considers how pregnant women could be responsibly included within clinical trials. Pregnant women and children under 15 tend to be excluded from tuberculosis (TB) trials, one study considered whether reconsenting women who become pregnant during a trial could be a way of expanding the evidence base (Gupta et al., 2019). A study on the community perspectives of including pregnant women in TB trials led to the statement *'we believe TB researchers should begin from a position of presuming pregnant women eligible for research and then, based on the specific characteristics of particular clinical trials, carefully consider safety and whether the balance of risks and benefit warrants the exclusion of this population.'* (McKenna et al., 2017).

Race / religion or belief

In the US there is believed to be a gap in the access to precision medicine with minority populations being underrepresented in trials (Perera, 2019). For research findings to be generalisable to a broad group of people there is a need to recruit diverse patients into clinical trials. Although the findings of Thakkar et al. (2022) showed no differences between minority and non-minority groups, the authors still stated that it is important to include minority populations in clinical trials evaluating CAR-T cell therapy as it is known that there are differences in disease biology in different ethnic backgrounds and *'Minorities*

cannot rely on extrapolation from trials with only Caucasian patients'. A study by Ahmed et al. (2022) found that for CAR-T therapy clinical trial participation, African Americans and Hispanics were underrepresented. *'Among the patients with myeloma, all of whom received CAR T cell therapy on a clinical trial, only 1% were African American and 5.4% were Hispanic'*.

Several studies have called for there to be better representation of ethnicity in clinical trial participants (for all phases) for a wide range of conditions (Kim et al., 2022, Wojcik et al., 2019, Symes and Modell, 2020, Sedano et al., 2022, Dunlop et al., 2022, Walsh and Goh, 2019). To ascertain the race and ethnicity of people working in clinical trials a worldwide online survey was conducted (Getz et al., 2022). The study found that *'The representation of non-white site personnel is significantly higher in North America and Rest of World (ROW) compared to Europe.'* There was also found to be an association in that the more diversity there was of site personnel then the wider diversity there was in patients enrolled onto the clinical trial. The authors conclude that *'An opportunity exists to address under-representation in clinical trials through identifying, hiring and supporting investigative site personnel to best reflect the patient communities that they serve'*.

Sex

It has been recognised that there are improvements in the participation of women in clinical trials however there is still underrepresentation in women being enrolled in Phase I trials for a variety of reasons (Jain et al., 2020). The study found that *'women face discrimination during all stages of their participation in Phase I trials from their ability to qualify for studies, the treatment they receive in the clinic facilities, and a lack of social support.'*

Other characteristics

Socio-economic status

Several studies have included socio-economic status as a potential health inequality to participating in trials or accessing treatment (King et al., 2010, Ahmed et al., 2022). There are calls to changes to the current drug development model to incorporate individual health benefits alongside broader economic considerations, otherwise there is the risk that *'the current drug development model is likely to both propagate and widen disparities between rare disease families with more robust economic resources and those without.'* (Gaviglio et al., 2023).

Digital poverty

Patients need to understand the risks and benefits of treatments in order to make balanced decisions with their doctors, some may do this by accessing sites such as Reddit (Jenei et al., 2021). A qualitative study analysing Reddit posts identified four themes *'1) navigating uncertainty with community, 2) finding a cure, 3) managing treatment-related uncertainties, and 4) overcoming uncertainties related to access.'* The authors recommended that trial investigators should ensure that there is equitable access to studies for those in settings where access to the internet is less common.

Who gets the condition

It is possible that which groups experience certain conditions may impact what research is funded leading to variability in what conditions have potentially available treatments. It has been found that there are differences in funding between sickle cell disease (SCD) and cystic fibrosis (CF) within the US (Farooq et al., 2020). CF received far greater federal funding and foundation expenditures than SCD; there were also more research articles and US Food and Drug Administration drug approvals for CF. However, the numbers of clinical trials were similar but the authors called for *'Increased federal and foundation funding is needed for SCD and other diseases that disproportionately affect economically disadvantaged groups to address health care disparities.'*

Some conditions are more prevalent amongst certain populations for example amongst pregnant women it was found that there was a higher prevalence of HIV in some parts of the UK (London); in London the highest proportions testing positive were Black African women whilst in Scotland HIV was associated with drug injecting (Nicoll et al., 1998). Although for many conditions there are reports on the differences of disease rates amongst different ethnic / racial groups, there are fewer studies which have looked at disease severity differences in these populations (Cullen et al., 2022).

How 'common' is the condition

Research and development investment in rare diseases has been found to underserve rare diseases in children and those considered as 'ultra-rare' (Ali and Tubeuf, 2019). The number of people who may be affected by a condition is an important factor when considering therapies for development. It has been noted that *'inequities can be seen between rare disease and common disease communities; among various rare diseases; and even within a single rare disease.'* (Gaviglio et al., 2023). There are inequities in the awareness of different health conditions; relatively few genetic conditions are well known and have strong advocacy organisations so promoting research and development into appropriate therapeutics is challenged. The authors note that for especially ultrarare diseases, where in America this affects fewer than 100 individuals, it is not uncommon for novel therapies to be withdrawn due to cost and licensing procedures. This has led some to crowd fund in order to afford treatment and emphasises the critical role which patient advocacy groups and drug development organisations take *'in promoting drug development for these rare diseases and ultimately to consider equitable patient access.'*

Other issues

Reporting / recording participant data

A study looking at the reporting of the race and ethnicity of patients enrolled in clinical trials for ulcerative colitis found that there was poor reporting of race and that most trial participants were white (Sedano et al., 2022). A recent study in Canada looking into the potential barriers and enablers to patient and physician participation in early phase trials of cell therapy for stroke, only reports on the age and sex demographics of the patient respondents and the sex of the physician respondents (Lalu et al., 2020). Within the limitations the authors acknowledge that their sample may have been selected from a higher socio-economic group and they recommend that education level and socio-economic status should be collected in future studies so that the sample is more balanced and can be described. The authors also described how their sample was only amongst those who could speak English and that the perspectives of other non-English speaking participants would be valuable to assess equity of access. Another qualitative interview study which did not present information on the sample demographics, also commented on the study's limitations *'We also did not collect information on race and ethnicity. Future research should aim to understand how these factors may impact participant decision making and trial participation experiences.'* (Castillo et al., 2021).

RECRUITMENT TO CLINICAL TRIALS

General limitations, exclusions and barriers

Based on data from the ClinicalTrials.gov database, it has been shown that globally there are wide disparities in which countries are taking part in clinical trials for gene therapy (Cornetta et al., 2018). The authors reported that *'Of the 179 recruiting or not-yet-recruiting trials found using the search term "gene therapy," only 2 trials are open in Africa, 3 in South America, and 1 in South East Asia.'*

Patients and their advocates had three recommendations (accessibility, support and language) on how to improve the experience around the use of ATMPs (Public Policy Projects, 2022). Accessibility included knowing what trials were available and *'Barriers to entry in terms of travel or disruption to lives should be removed, and the eligibility criteria should be as broad as possible.'* Support centred around offering psychological support or play therapy where appropriate, for all those who participate in clinical trials. The importance of the use of language was also emphasised with the recommendation that greater use should be made *'of plain language summaries that are more visual, accessible and targeted at patients to explain complex scientific information.'* The NIHR has guidance on how inclusion for under-served groups in clinical research more generally could be improved (National Institute of Health and Care Research, 2022). A study in Switzerland about participating in a trial of a gene-modified cell therapy for people living with HIV found that *'The decision to participate would depend on their understanding of the trial, the availability of sufficient information, and the relationship with health care professionals.'* (Gilles et al., 2021). A Canadian study identified four themes related to barriers to participation in early phase clinical trials (Foster et al., 2022):

1. *'Theme 1 emphasizes that patients and physicians need accessible information to better understand the benefits and risks of the novel therapy and trial procedures and to address misconceptions.*
2. *Theme 2 underscores the need for clarity on whether the trial's primary purpose is safety or efficacy, as this may influence patient and physician decisions.*
3. *Theme 3 recognizes the resource and logistic realities for patients (e.g., convenient follow-up appointments) and physicians (e.g., personnel to assist in trial procedures, competing priorities).*
4. *Theme 4 describes the importance of social influences (e.g., physicians and family, peers/colleagues) that may affect decisions to participate and the importance of patient preferences (e.g., availability of physicians to discuss the trial, including caregivers in discussions).'*

The authors recommend that clinical trial protocols should address these issues in order to create more patient and physician-centred trials. One limitation which was highlighted was that those who took part in the interviews may have been more interested in research and of a higher socio-economic status; the recommendation was made that *'Collecting additional demographics would be valuable in future studies to assess diversity of participants.'*

Negative past events related to research projects *'understandably results in differential willingness by some populations to engage with the health care establishment—especially in treatment trials that are new or experimental.'* (Gaviglio et al., 2023). The authors recommend that understanding of potential reticence needs to be considered when discussing opportunities to get involved in research. Gaviglio et al. (2023) suggest that there could be investigator bias introduced when potential suitable participants are viewed unfavourably due to a history of missed appointments and low compliance to treatment regimes. Certain groups may experience this more than others *'due to economic, social or geographic elements outside of the family's control.'*

CLINICAL APPLICATION

Protected characteristics

Age

Adherence to oral therapies for metastatic renal cell carcinoma was found to be low amongst older patients (Hicks et al., 2022). The authors called for more research to understand the mechanisms and impact for this group. As well as increasing age, high comorbidity was also associated with decreased initiation of targeted therapies.

Race / religion or belief

In the case of sickle cell disease in the US (the majority of people with sickle cell in the US are black), some have called for *'market incentives that encourages development of fairly-priced treatments for populations with historical health disparity to help patients who have been underserved by medicine in the past and should not be again.'* (Tessema et al., 2022).

Within the US, overactive bladder (OAB) has shown differences in symptom severity, prevalence and treatment received based on race, this is believed to stem from systemic racism (Roselli et al., 2022). The authors state that *'Patients from marginalized backgrounds are underrepresented in OAB literature.'* Another OAB study looking at the therapies received by the commercially insured found that *'racial and socioeconomic factors predict utilization of advanced OAB therapies, including race/ethnicity, age, gender, education level, and region.'* (Syan et al., 2020).

Access to CAR-T therapy for selected conditions in the US is impacted by race, socio-economic strata (SES), travel time to treatment centres and insurance coverage (Ahmed et al., 2022). *'Financial toxicity of travel and lodging likely creates a barrier to access to CAR T cell therapy for those from the lower SES.'* Another US study also found that for paediatric and young adult Latinx patients with B cell acute lymphoblastic leukaemia there were barriers to access CAR-T therapy due to distance and need for travel and this was believed to be due to structural racism (Hall et al., 2021). A study looking at the perceptions of US based haemotologists / onclogists found that the main barriers to adopting CAR-T therapies for diffuse large B-cell lymphoma were *'Cumbersome logistics, high cost and toxicity.'* (Gajra et al., 2020).

Other characteristics

Socio-economic status

Within countries such as USA there are access issues arising for those who are underinsured and can therefore not afford the costs of treatment (Cornetta et al., 2018). Gaviglio et al. (2023) suggest that although someone may have started treatment for a genetic condition in a financially stable position, the treatment may have led to a multitude of impacts which puts the individual / family into a position of inequality. *'Their social determinants of health—post-genetic diagnosis—may alter the future health, housing, educational, lifestyle, and mental health outcomes of the patient and their extended family. Indeed, inequities in access can lead to inequities downstream simply from having gone through the experience.'*

Knowledge acquisition / reading age

In order to decide whether to take part in a health treatment such as stem cell and umbilical cord blood therapy, people access information on the internet, some depend on this more than others (Al-Hasan et al., 2021). The study found that *'knowledge verification and trust in the internet influences knowledge conversion and the practice decision of patients for less practice-oriented knowledge, and this effect is higher for Kuwait than USA, and more so for stem cell than umbilical cord blood practice.'*

A US study assessing online information on ocular gene therapy found that it was *'generally of low quality, above the average reading level of the general population, and varies significantly between sources. The articles provide incomplete information that is not entirely accurate or easy to read, and as a result, the material would not support patients adequately in their medical decisions and questions about this new therapeutic option.'* (Davuluri et al., 2021)

Gaviglio et al. (2023) acknowledge that schemes such as newborn screening which aim to reduce health disparities by being provided universally may still favour *'those families with more economic resources and higher health literacy'* due to the need to access treatment at a pre-symptomatic stage in order to optimise outcomes.

Who gets the condition

Traumatic brain injury (TBI) has been shown to be particularly prevalent amongst those experiencing homelessness in the US but treatment for TBI remains a major clinical unmet need where there is the potential to develop novel therapies such as stem cell transplantation (Monsour and Borlongan, 2023). In order to reduce paediatric health disparities for acute lymphoblastic leukaemia (ALL) a targeted therapy has been identified (Payne and Dovat, 2016). The authors state that it has been shown that Hispanic children are 1.24 times more likely to develop ALL than non-Hispanic whites, by adolescence and early adulthood this rises to 2.09; this is due to a subtype of high-risk B cell precursor ALL occurring 5 times more often in Native American and Hispanic children.

How 'common' is the condition

Patient advocacy organisations are encouraged to represent the 'patient voice' and engage with policy makers to incorporate patient experience into the decisions made around accessing new therapies (Fox, 2018). Some people will try to access treatments by campaigning and fundraising outside of charity organisations (Kerr et al., 2021).

Where someone lives

Where someone lives can impact their access to treatment despite living in a country such as England which aims to have equitable access to advanced therapies (AT) (Kaul et al., 2021, NHS Confederation and Association of the British Pharmaceutical Industry, 2023). Kaul et al. (2021) stated that *'Although patients at identical stages of their disease course should have access to the same NICE-approved AT, we found this is not the case for large parts of England. Inequality of access was found between regions, mirroring the variability that occurs between countries throughout Europe.'* Aguilera-Cobos et al. (2022) also note that *'There are considerable variations between EU countries in how they regulate hospital exemption for ATMPs, and this can lead to inequitable access for patients.'*

A study in the US showed that those with diffuse large B cell lymphoma, a longer travel time to receive CAR-T cell therapy was associated with lower socioeconomic status and that site-of-care planning could help expand access and *'will help address regional, rural–urban, and sociodemographic equity in the geographic allocation of CAR T cell therapy.'* (Snyder et al., 2021). A systematic review into how where someone lives impacts on access to genetic / genomic services found that for rural populations there was *'a lack of clinician access to/relationships with genetic specialist staff, the need to provide more generalist services and a lack of genetic/ genomic knowledge and skill.'* (Best et al., 2022).

Other issues

Data

Historically polygenic risk scores (PRS) were developed based on people with European ancestry and therefore today the clinical implementation of PRS is more accurate for those individuals than for other ancestries thus exacerbating health disparities (Martin et al., 2019). The authors recommend that *'greater diversity must be prioritized in genetic studies, and summary statistics must be publicly disseminated to ensure that health disparities are not increased for those individuals already most underserved.'*

The data diversity issue has been described as problematic as it can lead to biases in machine learning and algorithms in medical AI (artificial intelligence) (Leslie et al., 2021, Chen et al., 2021). There is a data diversity resource library which can be used to find information from a variety of sources including scientific literature (peer reviewed journal articles) and grey literature (such as podcasts, news items, reports and events): DD Resource Library (notion.site).

ACCEPTABILITY / INHERENT NATURE OF ATMPS

Protected characteristics

To ascertain the acceptability of taking part in clinical trials for gene therapy for HIV, focus groups were run with ethnically diverse groups (from mostly African-American and low-income communities) (King et al., 2010). The focus groups included HIV positive persons (men, women and male to female transgender participants); religious and community leaders and healthcare professionals also took part.

'Three themes emerged from these groups: (1) the need for clarification of terminology and the ethics of understanding gene therapy–stem cell research, (2) strategies to avoid mistrust of medical procedures and provider mistrust, and (3) the conflict between science and religious beliefs as it pertains to gene therapy–stem cell research.'

A study into willingness to take part in early-stage prostate cancer trials found no differences between ethnic / racial groups (Kaplan et al., 2015).

OTHER CONSIDERATIONS ACROSS THE WHOLE PIPELINE OF DRUG DEVELOPMENT AND DELIVERY

Cost of therapies

Having a positive marketing authorisation for a gene therapy does not equal patient access and of seven topic areas identified as being potential hurdles to patient access, affordability was a key one as was evidence generation (Carvalho et al., 2021). The Carvalho et al (2021) study was a systematic review covering all countries including the US and Europe, they found *'Seven major topics were identified as potential patient access hurdles, namely affordability, assessment of value, development of therapy, ethical/social factors, evidence generation, operational implementation and regulatory hurdles….The most frequently mentioned obstacle in the literature is related to the affordability aspect especially focusing on high cost of therapy (84%) and therapy payment/ reimbursement (51%). Importantly, the evidence generation focusing on limited trial outcomes (81%) seems as a strong obstacle in patient access to these therapies.'*

Even in countries such as Wales where the NHS operates there are discussions about the cost of ATMPs and the impact this has on the Health Technology Assessment and appraisal of ATMPs (Champion et al., 2021). *'This viewpoint reflects on the experience of introducing ATMPs into the National Health Service in Wales where £1 in every £200 spent on medicines (2019/2020) is expected to be on ATMPs for just 20 patients.'*

A recent narrative review paper critically reflected on the reimbursement and access of advanced therapies (Simoens et al., 2022). A paper which looked at how the net budget impact test which was introduced in England would affect patient access to certain cell and gene therapies found that *'Annuity-based payments in combination with an outcomes-based remuneration scheme reduce consequences of decision uncertainty and can increase patient access, without exceeding the net budget impact test.'* (Jørgensen and Kefalas, 2017). Within neither the Simoens et al paper nor the Jorgensen and Kefalas paper is there any mention of health inequalities related to payment but, depending on implementation, it might be that improved access to ATMPs through reimbursement schemes could potentially reduce inequalities.

Patient reported outcomes / patient engagement

To assess how different groups respond to different treatments it is valuable for quality-of-life measures and patient reported outcomes to be used both for trials and for treatments. A review study found that for patients with chronic myeloid leukaemia there was no specific validated patient reported outcome measure in existence at the time (Efficace et al., 2012).

The important role that patients play in influencing policy decisions and how early patient engagement is key when considering market access for ATMPs has been recognised (Goncalves, 2020). The author recommends a range of stakeholders should be involved *'to promote the ethical analysis in HTA, experts from different arenas such as HTA and bioethics, as well as health care professionals and patient representatives, should cooperate to further develop the methodology of reviews of normative ethical guidance to support evidence-based financing decisions.'* EuroGCT have a website which provides resources for all stakeholders in ATMP development to discuss and collaborate in Patient and Public Involvement and Engagement activities: eurogct.org/atmp-engage.

Definition / understanding of health inequality and equity

To understand how local healthcare systems conceptualise health inequalities, a document analysis was performed on accessible NHS healthcare planning documents (Olivera et al., 2021). The study found that health inequalities were conceptualised in a vague and varying manner. *'Only one document contained a chapter dedicated to health inequalities. After analysis, five themes were identified: (1) variation and (2) vagueness explained how health inequalities were conceptualised and (3) use of value judgements, (4) lack of prior conceptualisation and approach and (5) a lack of commitment to action in the documents to reduce health inequalities explained what led to the overall vagueness and variation.'*

The National Institute for Health and Care Research (NIHR) has defined under-served groups within four categories(National Institute of Health and Care Research, 2022):

1. By demographic factors (age, sex, ethnicity, education)
2. By social and economic factors
3. By health status (a long list including mental health, physical and learning disabilities, addiction, multiple health conditions, smokers, pregnant women)
4. By disease specific factors (this includes 'rare diseases and genetic disease sub-types' and 'people in cancer trials with brain metastases')

In the US a definition of health disparities was created by a sub-committee of the Secretary's advisory committee for Healthy People 2020 (Braveman et al., 2011). *'Based on that subcommittee's work, we propose that health disparities are systematic, plausibly avoidable health differences adversely affecting socially disadvantaged groups; they may reflect social disadvantage, but causality need not be established. This definition, grounded in ethical and human rights principles, focuses on the subset of health differences reflecting social injustice, distinguishing health disparities from other health differences also warranting concerted attention, and from health differences in general.'*

Using the World Health organisation's definition Gaviglio et al. (2023) describe the interplay between equity and health inequalities as *'The World Health Organization defines equity as the "absence of avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, geographically, or by other dimensions of inequality." In essence, health inequities are avoidable inequalities in health between groups of people. These inequities arise from inequalities within and between societies.'*

Other impacts of health inequalities

On the whole only those who are diagnosed would be eligible for taking part in clinical trials and treatment but there may be health inequalities in who gets a diagnosis. A Spanish study using data from the Spanish Rare Disease Patient Registry found that those who had to travel to see a specialist outside of their usual province, visiting more than 10 specialists and being diagnosed in a different region to the one where they first experienced symptoms all led to diagnostic delay (Benito-Lozano et al., 2022). As well as inequalities associated with receiving a diagnosis there are also inequalities evident in using services such as genetic counselling (Nikolaidis et al., 2019). The authors found that for young breast cancer survivors there was *'Racial inequalities of cost-related access to care and education create disparities in genetic services utilization.'*

CHARACTERISTICS NOT INCLUDED IN ANY STUDIES

Protected characteristics

No evidence was found related to how certain groups based on gender reassignment, marriage and civil partnership and sexual orientation engaged in either the research pathway, clinical pathway or acceptability of ATMPs. The study by King et al. (2010) described their focus groups sample as including male to female transgender participants but did not provide results which just related to this group. They did not have marital status information for all of the participants, they made no mention of the sexual orientation of the participants.

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SEARCH STRATEGY

Search strategy – published articles and grey literature

- Using agreed terms will search using databases such as Web of Science, Pubmed and Google scholar e.g. – {[(ATMP) OR (Advanced Therapy Medicinal Product*) OR (Cell and gene therapy)] AND [(inequality words) OR (inequality phrases)]}
- Limited to English language
- Human studies (i.e. not animals or cells)
- Worldwide
- Any time period
- If go 'beyond' ATMP, aim for review papers and broad papers addressing inequalities only
- References from selected papers will be screened to find any additional published sources and grey literature
- Sources identified from the ATMP directory will be screened for relevance
- Suggestions provided by expert advisors to the project will be followed
- Links to publicly available sources and open access articles will be included; those behind a pay-wall will be abstract only where that is available

Search terms

ATMPs

- ATMP
- 'Advanced Therapy Medicinal Product*'
- 'cell and gene therap*'
- 'cell therap*'
- 'gene therap*'
- 'tissue therap*'
- 'innovative therap*'
- 'targeted therap*'
- 'novel therap*'
- 'advanced therap*'

* wildcard would allow variations of word endings, for example therapy, therapies, therapeutic …

Inequalities

Words:

- Inequalit* [would include: inequality, inequalities]
- Inequit* [would include inequity, inequities]
- Equalit* [would include equality, equalities]
- Equit* [would include: equity, equitable]
- Divers* [would include: diverse, diversity, diversities]
- Inclusi* [would include: inclusion, inclusive, inclusivity]
- Exclu* [would include: exclude(d), exclusion, excluding, exclusive, exclusivity]
- Disciminat* [would include: discrimination, discriminatory, discriminate]
- Representati* [would include: representation, representative(ness)]
- Disadvantage* [would include: disadvantage, disadvantaged, disadvantageous]
- Barrier* [would include barrier and barriers]
- Obstacle* [would include obstacle and obstacles]
- Access* [would include access, accessible and accessing]
- Utili*ation [would include utilisation and utilization]
- Unjust* [would include unjust, unjustly and unjustifiable]
- Unfair* [would include unfair and unfairly]
- Underserved
- Minorit* [would include minority and minorities]

Phrases:

- 'seldom heard'
- 'hard to reach'
- 'under served'
- 'under represented'
- 'barriers to participation'
- 'health disparit*'
- 'social determinant* of health'
- 'social gradient of health'
- 'health determinant*'
- 'health outcome*'
- 'health status'
- 'health situation'
- 'health potential'
- 'vulnerable population*'