A current state analysis of patient expectations, experiences, and outcomes for gene therapies. Implications for health technology assessment and pharmacovigilance.

Background.

Health Technology Assessment is the process of evaluating the risks and benefits of a health technology, including medicines, vaccines and devices, to inform access and funding decisions early in a product's lifecycle: authorisation to reimbursement (1). Pharmacovigilance (PV) is the science of evaluating the safety and efficacy of a medicine, in various populations, once is has been marketed and relies heavily on real world evidence (RWE) (2). As end-users of health technology, patient's expectations, experiences and outcomes are critical but often poorly integrated into HTA processes (3). This is especially true for innovative therapies such as gene technologies (4). Gene therapies potentially provide life-changing health outcomes for patients and consequently long-term benefits to society and health care systems (4). Internationally, gaps in HTA and PV frameworks do not address the uniqueness of gene therapies which translates into delayed patient access, inequitable funding models and short-sighted safety monitoring programs (4).

Objective.

To develop a framework to address gaps in patient-reported expectations, experiences, and outcomes with gene therapy to inform future HTA and PV approaches.

Rationale.

Gene therapies provide life-changing health outcomes for patients and consequently long-term benefits to society and health care systems (4). Given their uniqueness, contemporary evidence on what patient-centred data should be captured to inform both HTA and long-term safety and efficacy outcomes for gene therapies are lacking (PV). Pharmacoepidemiologists are well placed to capture RWE to inform this research. This evidence is critical to the evolution and strengthening of traditional HTA and PMS approaches to improve safe and equitable patient access (3).

Issues to be addressed.

Traditional approaches to HTA and PMS do not address the uniqueness of gene therapies thereby limiting regulator's and payer's understanding of the true real-world benefit of these therapies and potentially impeding patient access to these life-changing therapies. This manuscript will present a framework for addressing gaps in evidence sourced from both the academic literature and stakeholder input.

Content

1. **Introduction and background**
    a. Overview of traditional approaches to capturing patient expectations, experiences and outcomes including current place in HTA and PMS including the use of RWE.
    b. Uniqueness of gene therapies and challenges with current approaches.
2. **Methods**
    a. Scoping review – current international approaches to using real-world patient data.
    b. Stakeholder engagement – views of critical gaps and when/ how they can be addressed.
3. **Findings**
    a. Synthesis of key gaps in knowledge/evidence

b. Themes to build framework.

4. **Future perspectives**
    a. Summary of findings
    b. Recommendations for future research

Composition of manuscript research and writing team

Name and Qualifications	Affiliation	Country	Expertise
Jodie Hillen PhD (Group Lead)	University of South Australia and University of Queensland	Australia	Pharmacoepidemiology, literature reviews, patient engagement and HTA.
Lourens Bloem PharmD, PhD	Utrecht University	Netherlands	Pharmacoepidemiology, HTA and CGTs.
Kui Huang PhD	Pfizer. Inc	US	Observational studies including LTFU studies in Gene Therapy and HTA.
Jamie Geier, PhD	Novartis	US	Observational studies and HTA.
Karla Therese Sy, PhD	Pfizer Inc.	US	Observational studies including LTFU studies in Gene Therapy, Pharmacoepidemiology
Katie Miller, PhD	Genentech/Roche	US	Pharmacovigilance, epidemiologist and RWD expert
Genomics and Precision medicines CGT representatives.	TBC		
Patient representative	TBC		

Budget

1. The manuscript writing team would like to request funding for open access publication. Cost estimated at $USD 2000.
2. The manuscript team would like to request funding for stakeholder honorariums ($USD 50 to 100 per interview = 1000)
3. The manuscript team would like to request funding for a research assistant to assist with data analytics and synthesis ($USD 3500).

Target Journals

1. Journal of Precision Medicine 2. Value in Health 3. Health Expectations 4. HTA 5. BMJ Open 6. International Journal for Quality in Health Care.

Proposed timeline

Date	Duration	Activity
Jan 2024		Finalise manuscript methodology and outline. Assign team tasks.

Feb -Mar 2024		Scoping review of literature. • Refine search terms and inclusion/exclusion criteria. • Conduct database searches. • Screen identified literature and finalise search result flowchart. • Synthesise findings for the manuscript.
Jan 2024		Identify suitable stakeholders to interview (n=10).
Feb 2024		Finalise interview guide.
March 2024		Submit interview guide for Human Research Ethics Committee approval.
April 2024		Conduct interviews.
April 2024		Synthesise interview findings into relevant themes.
May 2024		Internal approval processes for writing team????
June 2024		Integrate interview and literature review findings and finalise manuscript for submission to ISPE Public Policy Committee.

Short biographies of writing team and statements of conflict of interest

1. **Jodie Hillen (PhD, MClinEpi, BPharm).**
   Jodie has over 20-years' experience in clinical pharmacy, quality use of medicines and pharmacoepidemiology. Her most recent research has focused on the safety and efficacy of biologic medicines to treat autoimmune disorders and a white paper with recommendations to the Australian regulatory bodies for improving access to CGTs. Jodie has no conflicts of interest to declare.
2. **Lourens T. Bloem (PharmD, PhD)**
   Lourens is assistant professor Clinical Therapeutics at the Centre for Clinical Therapeutics of the Division of Pharmacoepidemiology and Clinical Pharmacology, within the Utrecht Institute for Pharmaceutical Sciences (UIPS) of Utrecht University, the Netherlands. Here, he is involved in several large national research consortia that aim to make cell and gene therapies better available to patients.
   Lourens obtained his PhD in Drug Regulatory Science in 2021. In addition, until December 2022, he was Programme Manager Drug Regulatory Science for the Utrecht Science Park, drawing on his specific research experience in Drug Regulatory Science as well as previous 4-year work experience as a pharmacovigilance assessor at the MEB. Here, he was involved in the assessment of safety data and Risk Management Plans (RMPs) for medicines authorised on the national and European level (particularly in the field of psychiatry, neurology and the musculo-skeletal system). Conflict of interest statement: none.
3. **Kui Huang (PhD, MPH, BSc)**
   Kui has more than 17 years of experience leveraging epidemiology and real-world data (RWD) research strategy to support business and regulatory activities throughout the lifecycle of products in oncology, vaccine, rare disease, and internal medicine therapeutic areas. She has successfully designed and led implementation of more than 45 observational studies in US, Europe and Asia including the first post-approval commitment study using Chinese RWD, which paved the way for the future use of RWD/real world evidence to support regulatory decision making in China. Kui has deep knowledge of various electronic health care databases in North America, Europe and Asia. She is the lead author for the chapter "Benefit-Risk Assessment in Risk Management" in Pharmacoepidemiology 5th Edition in Chinese. Prior to entering the pharmaceutical industry, she worked as a

biostatistician at academia and as an epidemiology fellow at CDC in the US. She holds a PhD in Epidemiology with concentration on genetic epidemiology from UNC-Chapel Hill. Conflict of interest statement: Kui is an employee of Pfizer and holds Pfizer stocks.

4. **Jamie Geier (PhD)**
   Jamie is the Global Head of Quantitative Safety and Epidemiology (QSE) at Novartis. In this role, she is responsible for the QSE safety strategies to support clinical development and health authority interactions. She is also the Scientific and Strategic Lead for the Novartis PRegnancy outcomes Intensive Monitoring (PRIM) Initiative as well as a PRIM Steering Committee member. Before joining Novartis in 2020, Jamie was Group Head and Senior Director, Epidemiology Strategist for Inflammation & Immunology at Pfizer, Inc. In this role she led a team of epidemiologists to deliver regulatory safety strategies with a focus on risk characterization. She has 16 years of pharmaceutical industry experience as an Epidemiology Lead and Strategist for a wide range of drug therapies within Neuroscience, Gene Therapy, Rheumatology, Medical Dermatology & Gastroenterology. Jamie has extensive regulatory and strategic experience, including epidemiological study design strategies and the use of non-interventional data sources for regulatory decision-making. Jamie received her PhD in Epidemiology from Columbia University. Conflict of interest statement: Jamie is an employee of Novartis and holds Novartis and Pfizer stocks.
5. **Karla Therese Sy (PhD)**
   Karla a third-year doctoral candidate in Epidemiology at Boston University School of Public Health. Her research experience combines epidemiologic methods with novel approaches to analysing infectious disease data, with a focus on epidemic modelling, geospatial modelling, and machine learning in tuberculosis and COVID-19. She earned her B.A. in Molecular Biology and Biochemistry at Wesleyan University, and her M.S. in Epidemiology at Columbia University. Conflicts of interest: TBC.
6. **Mary. K. Miller (PhD)**
   With over 20 years industry experience, Mary K (Katie) Miller is an effective international collaborator and a Stanford-trained epidemiologist with expertise in design, analysis and interpretation of real-world primary data collection and secondary data use studies across numerous disease areas with particular interest in real-world data (RWD) when applied to pharmacovigilance, access and regulatory topics. Conflicts of interest: TBC.

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