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Challenges and Solutions for Budget Impact Analysis of Gene Therapies

CONTRACT RESEARCH REPORT
MARCH 2025

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Table of Contents

Executive Summary

Gene therapies represent a paradigm shift in medicine, offering the potential for significant improvements in both quality and longevity of life (Besley et al., 2022), by addressing the root genetic causes of diseases (FDA, 2020). Due to this potential for substantial health gains, gene therapies often come with substantial upfront prices. In addition, their one-time administration means the cost of the treatment is incurred at one point in time (assuming the cost is due at the point of care), rather than spread over the patient's lifetime as it would be with chronic treatment. As a result, gene therapies are often assumed to raise affordability challenges.

Budget impact analysis (BIA) plays a role in informing healthcare decision-making. BIA are typically conducted using short time horizons (2-5 years), and from the perspective of the budget holder (e.g. the health system). Gene therapies, with their significant upfront costs, are therefore likely to be viewed unfavourably via current approaches to BIA, as longer-term cost savings and wider spillover effects fall outside of the scope of these analyses. To date, the impact of BIA on reimbursement of and access to gene therapies has not been considered in detail.

This report reviews the current approaches to and use of BIA in the context of gene therapies across a selection of European countries: Belgium, England, Denmark, France, Germany, Ireland, Italy, Poland, Scotland and Spain. Via a series of literature reviews and discussions with an expert panel, we find four main ways in which the results of BIA are used:

1) to inform commercial negotiations, either routinely or when the conditions of a budget impact test are met

2) to inform reimbursement decisions

3) to inform a decision as to whether a full HTA is required (HTA routing)

4) for budget planning.

Whilst there is little international harmonisation in the timing of BIA or its use within the decision-making process, we find greater international harmonisation in the approach to undertaking BIA. Many countries utilise similar time horizons, approaches to selecting comparators, and requirements for sensitivity analysis, amongst other aspects.

We also explore the impacts of the different uses of BIA in decision making and identify elements of good practice amongst our countries of interest. We argue that too much focus on short term BIA risks impacting incentives for future innovation, and that this must be balanced against short term affordability concerns.

Finally, we set out a series of recommendations across the use of BIA, BIA methodology, and tools to be used alongside BIA. The full set of recommendations is presented below. It's important to recognise that BIA methods and processes vary significantly across European countries, so recommendations should be tailored to each country's health system and reimbursement processes.

Recommendations on the use of BIA in decision making

- Health Technology Assessment bodies and other relevant institutions should be explicit and transparent about the purpose of BIA, including whether and how it will be used in reimbursement decision making.
- Further research into the implications of the use of BIA in decision-making, including its impact on static and dynamic efficiency, would be helpful. This will facilitate decision makers' ability to make informed trade-offs between short term affordability and longer-term incentives for innovation.

Recommendations on budget impact analysis methodology in the context of gene therapies

- BIA guidance should allow for flexibility where appropriate and justifiable, for example, willingness to accept;
  - longer time horizons (e.g., to capture potential future costs and cost savings)
  - broader perspectives (e.g., to capture the budget impact on other government departments such as social care, social security and education).
- Uncertainties inherent in BIA of gene therapies should be explored through sensitivity analyses that vary patient eligibility criteria and target population size.

Recommendations on additional tools to be used alongside HTA

- Existing horizon scanning activities could be strengthened to aid budget planning in the context of high upfront cost therapies such as gene therapies. International collaborations could be leveraged further to maximise the usefulness of available information and minimise the duplication of efforts.
- Innovative payment models should be considered as tool to facilitate access to gene therapies. In doing so, the risk associated with uncertainty is shared between the payer and manufacturer, while also spreading the initial cost across a longer period.
- Where innovative payment models are likely to be employed, these models must be factored into budget impact analyses to help inform decision-making, commercial negotiations and implementation. If BIA is conducted prior to proposed innovative payment models, flexibility in processes should allow for the BIA to be updated to reflect the proposal.

1. Background

Gene therapies represent a new era of medicine, offering the potential for transformational health gains in terms of both quality and length of life (Besley et al., 2022). In contrast to traditional small molecule medicines, gene therapies have the potential to correct underlying genetic mutations rather than simply manage symptoms (FDA, 2020). Moreover, successful gene therapy may require only a single dose to confer lifelong improvement, replacing a lifetime of ongoing treatment. This may dramatically reduce the treatment burden and costs associated with chronic care management (Besley et al., 2022; Firth et al., 2021). The substantial health gains may also have positive spillover effects for caregivers, families and wider society.

The development of these new treatments presents a new combination of challenges. For example, given the potential long-term nature of the health gains associated with gene therapies, there is often substantial uncertainty in outcomes, which complicates the use of conventional value assessment approaches. In addition, the one-time administration means the cost of the treatment is incurred at one point in time (assuming the cost is incurred at the point of care), rather than spread over the patient's lifetime as it would be with chronic management. Gene therapies to date have also been concentrated among rare diseases, where trial populations are smaller, bringing another set of challenges. Whilst many of these challenges are not unique to gene therapies, they face a higher concentration of these issues due to the one-time administration, long-term benefits, populations they target (often rare and/or severe diseases), and uncertainties that arise as a result (Marsden and Towse, 2017).

Budget impact analysis (BIA) plays a critical role in informing healthcare decision-making by projecting the financial consequences of a new healthcare intervention within a specific healthcare setting or system context given inevitable resource constraints (Mauskopf et al., 2007b). As such, it is commonly required by payers as part of health technology assessment (HTA) or reimbursement submissions (Sullivan et al., 2014). The results of BIA are commonly used by local or national-level decision makers for planning purposes (YHEC, 2016), and/or as an input to reimbursement decisions for new health technologies (Patented Medicine Prices Review Board Canada, 2021; Cohen, Stolk and Niezen, 2008).

BIA are typically conducted using short time horizons (2-5 years), and from the perspective of the budget holder (e.g. the health system). Gene therapies, with their significant upfront costs, are therefore likely to be viewed unfavourably via current approaches to BIA, as longer-term cost savings and wider spillover effects fall outside of the scope of these analyses. This impact on access to gene therapies will depend on how the BIA is used by decision makers in each context. Indeed, guidelines on the recommended methodology to conduct BIA and the application of the results vary considerably across countries (see Chapter 2).

To date, the impact of BIA on the reimbursement of and access to gene therapies has not been considered in detail. With increasing numbers of gene therapies coming to market and the potential for them to treat broader populations than they have in the past (Segal, 2024), it is critical that the challenges with BIA are addressed now. The objectives of this report are therefore to:

- explore the application of BIA in the context of gene therapies in a selection of European countries
- identify areas of best practice and areas for improvement
- propose actionable policy recommendations in relation to BIA to facilitate appropriate access to these therapies.

1.1. Methods

To achieve these objectives, we combined desk research with a three-phase interaction with an international panel of experts.

Desk research

We undertook a series of targeted literature reviews:

- The first review focused on current approaches to BIA according to BIA guidelines in the countries under consideration (Belgium, England, Denmark, France, Germany, Ireland, Italy, Poland, Scotland and Spain). Key aspects of the methodology were extracted to enable a cross-country comparison.
- The second review focused on summarising the challenges faced by gene therapies in the context of budget impact. Both peer-reviewed and grey literature were considered.
- The third review sought to understand the role of horizon scanning as a tool for budget planning in the context of gene therapies.

We also undertook an analysis of best practices and risks within the current use of BIA and horizon scanning based on our existing expertise in this field, the review of challenges faced by gene therapies in the context of BIA, and a review of the ISPOR Budget Impact Analysis Principles of Good Practice (Sullivan et al., 2014).

Expert panel

We recruited a panel of international experts covering the following countries: Belgium, Denmark, Germany, Ireland, Poland and Spain. The coverage of countries from the literature review and interactions with the expert panel is summarised in the Appendix.

Our experts had a variety of backgrounds including academia, consulting and pharmacy, all with expertise in BIA of gene therapies. We interacted with experts through three main phases of engagement, undertaken between October and November 2024.

1. Pre-meeting survey – the pre-meeting survey was used to validate the preliminary findings of the literature review and to gather expert's perspectives on the key challenges and potential solutions. This enabled us to tailor the roundtable discussion based on the topics considered most critical by the experts.

2. Virtual Roundtable – during a three-hour virtual roundtable, we discussed the challenges of BIA of gene therapies, playing back the results of the pre-meeting survey to highlight key areas of convergence and divergence of opinion. The panel identified and discussed potential solutions to the challenges and considered the feasibility of implementation within national HTA and health system processes.

3. Post-meeting survey – the post-meeting survey served as a sounding board for the proposed policy recommendations derived from the roundtable. This gave an opportunity for the participants to edit the recommendations and gave insight into the level of consensus achieved.

1.2. This report

The remainder of the report is structured as follows: Section 2 presents an overview of BIA methodology and application in the selected countries of interest including any gene therapy-specific considerations. Section 3 describes the application and methodological aspects of BIA as well as other policy tools such as horizon scanning and innovative payment models in the context of gene therapies, and provides examples of best practice. Finally, Section 4 presents actionable policy recommendations to improve the use of BIA with the intention to facilitate patient access to gene therapies.

2. Current approaches to and use of BIA across Europe

The chapter summarises the core components of BIA and variations in their application across a selection of European countries: Belgium, Denmark, England, France, Germany, Ireland, Italy, Poland, Scotland, and Spain.

2.1. Cross-country summary

Figure 1 provides a simplified illustration of where BIA fits within reimbursement decision-making.

The diagram highlights that BIA is typically conducted around the same time as value assessment (or HTA), although it can be conducted before or after depending on national guidelines. It shows four main ways in which the results of BIA are used:

1) to inform commercial negotiations, either routinely or when the conditions of a budget impact test are met

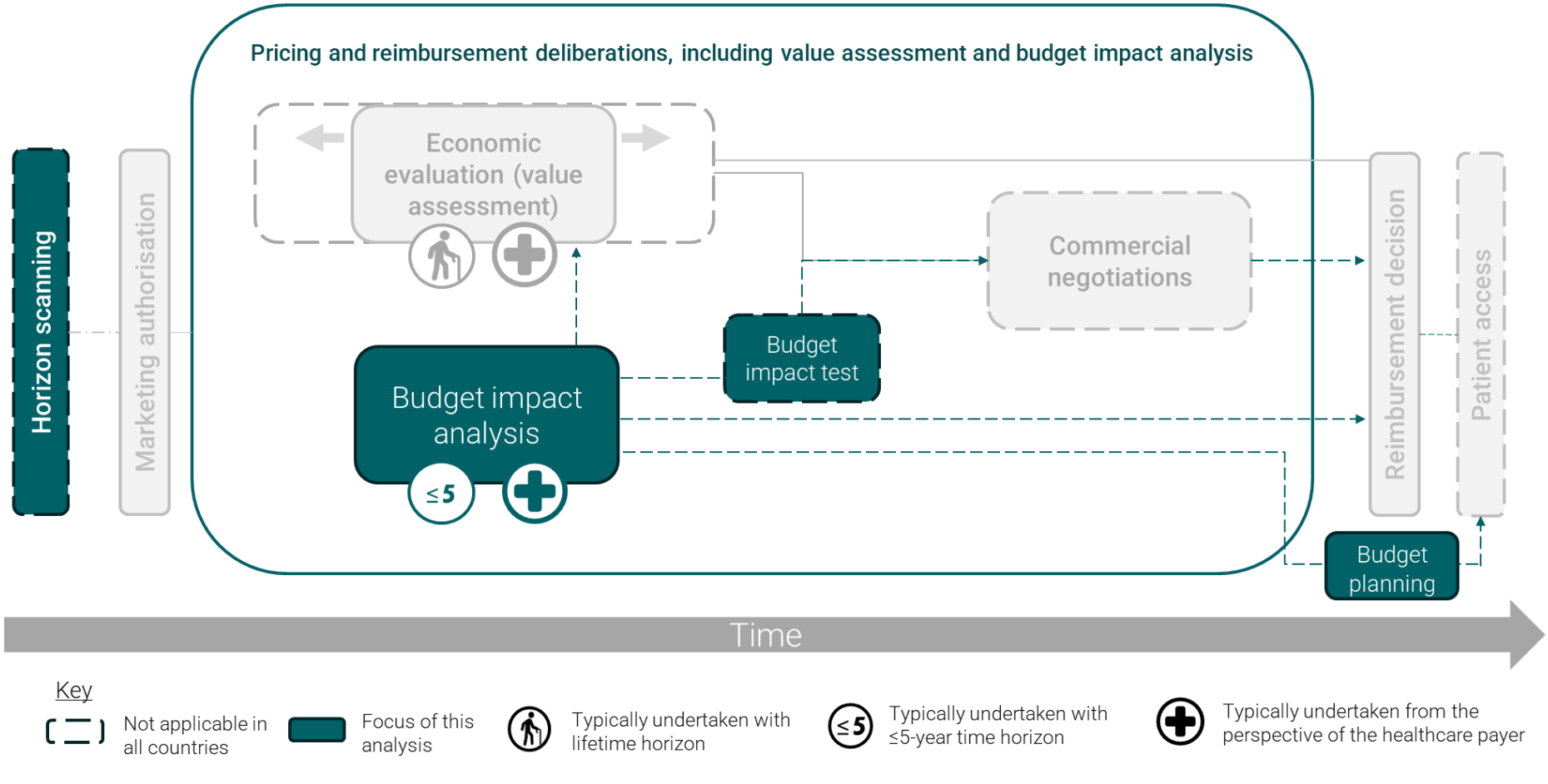
2) to inform reimbursement decisions

3) to inform a decision as to whether a full HTA is required (HTA routing)

4) for budget planning.

These uses are not mutually exclusive. For example, results could be used to inform the reimbursement decision and for budget planning and where they are used for commercial negotiations, this is also likely to impact the reimbursement decision.

FIGURE 1: SIMPLIFIED MAP OF BIA WITHIN REIMBURSEMENT DECISION MAKING



We find that while all our countries of interest use BIA in some way, there is little international harmonisation in its timing or use within the decision-making process. Table 1 provides a summary of how BIA is used in each country.

TABLE 1: USE OF BIA IN DECISION MAKING BY COUNTRY

		Use of BIA in decision making		
Country	**For commercial negotiations**	**To inform reimbursement decision**	**HTA routing**	**For budget planning**
Belgium[a]	✓	✓		✓
Denmark[b]	✓	✓		✓
England[c]	✓(if budget impact threshold met)			✓
France[d]	✓			
Germany[e]	✓(if initial price negotiations fail)			✓
Ireland[f]	✓	✓	✓	
Italy[g]	✓	✓		✓
Poland[h]	✓	✓		
Scotland[i]	✓			✓
Spain[j]	✓	✓		

Sources: [a](Neyt et al., 2015), [b](DMC, 2022), [c](NICE, 2023a), [d](HAS, 2016), [e](IQWiG, 2023), [f](HIQA, 2018), [g](AIFA, 2024), [h](Jahnz-Różyk et al., 2017), [i](Brown, n.d.), [j](Oliva-Moreno et al., 2020), plus roundtable input.

There is, however, greater international harmonisation in the approach to undertaking BIA. Table 2 provides an overview of the current approaches to budget impact assessment in the countries of interest. The table is based on national guidelines, validated, and supplemented with additional information provided via the expert panel. It highlights that all our countries of interest take a healthcare system or payer perspective in the base case analysis (although they use different terms to describe this) and utilise relatively short time horizons (up to five years). The comparator is also the same across all countries (except potentially Scotland where this is not stated), although different terms are used to describe this. Sensitivity analyses around key parameters are required in most cases, and local data is typically preferred where available.

TABLE 2: SUMMARY OF APPROACHES TO BIA

Country	Decision maker	Perspective	Time Horizon	Data Source/s	Comparator	Sensitivity Analysis
Belgium[a]	**KCE**	Public Payer perspective[1]	3 years minimum	Belgium real-world sources where possible, or extrapolations from reasonable alternatives	Current standard practice	Probabilistic sensitivity analyses and scenario analyses
Denmark[b]	**DMC**	Healthcare perspective	5 years	Danish sources	Existing standard treatment	Required when assessing BIA for sub-groups or when key assumptions significantly influence estimates or are uncertain.
England[c]	**NICE**	Commissioner or provider perspective (whichever is more appropriate)	5 years	Best available datasets used and supplemented with expert opinion	The 'world without' the technology	Required (the most sensitive variables are reported)
France[d]	**HAS**	French statutory social insurance scheme[2]	3-5 years	French data, where possible	Current standard practice (in the "world with" and the "world without the intervention"	Deterministic sensitivity analysis for parameters that drive the BIA results and scenario analysis
Germany[e]	**IQWiG**	Statutory health insurance system	3 years	Up to date, relevant and justified. German data where possible.	The "world with" and the "world without" the intervention	Scenario analysis (parameters include target population and treatment mix changes)
Ireland[f]	**NCPE/ HIQA**	Health and social care system[3]	5 years minimum[4]	Irish data where possible, consistent with the corresponding economic evaluation, if conducted	Routine care	Sensitivity analyses (for costs, cost offsets and patient populations) and Scenario analyses (Current versus new technology)

Country	Decision maker	Perspective	Time Horizon	Data Source/s	Comparator	Sensitivity Analysis
Italy[g]	**AIFA**	NHS Perspective	2 years minimum	Italian sources, where possible	Existing standard clinical practice without the product	Required (Scenario and sub-group analysis)
Poland[h]	**AOTMiT**[5]	Public Payer perspective[6]	2 years	Polish data where possible	Current standard practice	Required (focus on variables with the highest uncertainty e.g. population size, costs)
Scotland[i]	**SMC**	Health service perspective	5 years	Scottish sources, where possible	No information found	No information found
Spain[j]	**CIPM/MoH**	NHS Perspective	3 years[7]	Spanish sources at state, regional or autonomous community levels	Current best practice or alternative technology with similar indication	Scenario analyses (focus on acquisition cost and target population)

Notes: [1]If significant, indirect costs are included; [2]Patient or hospital-centred perspectives may be adopted in secondary analyses if relevant; [3]Broader or narrower perspectives in addition to the reference case may be considered if sufficiently justified; [4]Guidance notes that 5 years may not be sufficient to capture peak/'steady-state' usage due to slow diffusion of new technology; [5]Ministry of Health is the final decision-maker regarding reimbursement, AOTMiT makes a recommendation to the MoH based on the BIA and HTA [6]If justified social perspective (service provider or public finances), [7]5 years or more can be used if justified.

Sources: [a](Neyt et al., 2015), [b](DMC, 2022), [c](NICE, 2023a), [d](HAS, 2016), [e](IQWiG, 2023), [f](HIQA, 2018) [g](AIFA, 2024), [h](AOTMiT, 2016) [i](SMC, 2022), [j](Ortega et al., 2016)

Additional detail for each country is provided in sections 2.2-2.112.11, with a focus on whether BIA is required, who is required to conduct it, and how the results of BIA are used by decision-makers.

Where relevant, specific considerations for gene therapies and/or other high-cost therapies are highlighted in these boxes.

2.2. Belgium

In Belgium, the Health Care Knowledge Centre (KCE) guidelines mandate BIA for all reimbursement claims. The manufacturer is responsible for completing the initial BIA (Neyt et al., 2015). This is then reviewed and validated by the Drug Reimbursement Committee (CTG-CRM) based on preparatory assessments conducted by National Institute for Health and Disability Insurance (INAMI-RIZIV) (Neyt et al., 2015; Cleemput et al., 2012).

The decision on a medicine's reimbursement lies with the Minister of Social Affairs and Public Health, who is guided by recommendations from the Commission for the Reimbursement of Medicinal Products (CRM). The CRM's recommendation is typically based on an assessment of therapeutic value, the market price of the drug, clinical benefit, the BIA and the Cost-effectiveness(Neyt et al., 2015).

The results of the BIA are therefore used for reimbursement decision-making, commercial negotiations and for budget planning.

The Policies for Rare Diseases and Orphan Drugs (Denis et al., 2009) indicate that orphan drugs must demonstrate therapeutic added value, but do not currently require a pharmacoeconomic evaluation. However, a BIA is still required for these drugs (Picavet, Cassiman and Simoens, 2014).

If the CRM issues a negative recommendation, a "convention" or managed entry agreement may be considered (Gerkens et al., 2017). To be eligible for this convention, a drug must either fall under the class 1 category (i.e. products for which the manufacturer claims a therapeutic added value), be an orphan drug, or have a new indication that addresses an unmet medical need (Gerkens et al., 2017).

2.3. Denmark

A BIA is mandated by the Danish Medicines Council (DMC) for every new medicine submission. The BIA is initially completed by the submitting manufacturer and subsequently validated (and sometimes edited) by the DMC secretariat.

The Danish system focuses on clinical value, budgetary implications and cost per patient when making reimbursement decisions about new medicines. These decisions are primarily driven by per-patient costs, and only when certain factors such as a large patient population raises potential budget issues does BIA become a driving factor. The DMC conducts HTA assessments, focusing first on evaluating the clinical effectiveness of new treatments, and then completing economic analyses. These include cost-effectiveness analyses and BIA, the results of which are used in reimbursement decision making (Danish Medicines Council, 2021).

The results of the BIA also help decision makers understand how regional hospital budgets will be affected if the new drug is adopted (budget planning) and are crucial for commercial negotiations of pricing and procurement contracts, as well as informing reimbursement decisions.

When a negative reimbursement recommendation is made due to price, the DMC takes an active role in encouraging manufacturers to adjust their pricing and engage in further negotiations with AMGROS. Manufacturers are requested to lower the price or (less commonly) to enter a managed access agreement (Odelle Technology, 2024). This may be particularly relevant to gene therapies which often have high prices.

Denmark does not have any special reimbursement pathways for orphan drugs (Charles River Associates, 2021). These medicines go through the same assessment and reimbursement processes as any other drug, undergoing assessment by the DMC and standard price negotiations with Amgros before hospitals can use them. At the procurement stage, Amgros purchases orphan drugs through the same EU-wide tender process used for all other medicines.

2.4. England

Budget impact assessments (referred to as resource impact) are mandated by the National Institute for Health and Care Excellence (NICE) for all technologies under assessment. The budget impact assessment is conducted either by the manufacturer or the resource impact team, concurrently with the HTA review.

NICE is responsible for recommending reimbursement decisions. The decisions are to a large extent guided by an expert committee's assessment of clinical and cost-effectiveness of the technology, as well as disease severity (NICE, 2023a). Results of BIA are not used as part of the decision to recommend or not but for commercial negotiations and for budget planning.

According to NICE, the resource impact of a technology is considered 'significant' if, at a national level, in any of the first 5 years, there is a cost or saving of £5 million (NICE, 2023a). If significant, the resource impact estimate is shared with various stakeholders including Department of Health and Social Care (DHSC), NHS England and Improvement, the manufacturer, companies for comparator technologies and commissioners (NICE, 2023). The DHSC uses resource impact estimates in budget planning to anticipate and address the financial implications of adopting new health technologies across the NHS. In addition, NICE uses a budget impact test. If the cost of a technology recommended by NICE will exceed a set threshold (currently £40 million in any of the first 3 years[1]), NHS England and NHS Improvement will commence negotiations with manufacturer, with the aim of agreeing special commercial arrangements to better manage the introduction of the technology (NICE, 2023a).

New gene therapies with high upfront costs may exceed this budget threshold, (£40 million in any of the first 3 years) triggering a dialogue between the manufacturer and NHS England to facilitate special arrangements (NICE, 2018).

[1] *Following recent consultations between NHS England, NICE, and other stakeholders, a decision has been made to raise this threshold from £20 million to £40 million as of January 2025 (NHS England, 2025).*

2.5. Germany

In Germany, BIAs are not a routine component of the HTA process. If no agreement of the pricing negotiation is reached an arbitration board is held. BIAs are possible in the arbitration board or if arbitration board fails (Die forschenden Pharma-Unternehmen, 2023). If no agreement can be reached between the submitting company and the statutory health insurance (SHI) providers, a BIA is optional and is submitted by the manufacturer to IQWiG under the commission of the Federal Joint Committee (G-BA) (Die forschenden Pharma-Unternehmen, 2023).

Germany's HTA process focuses on clinical benefit as a base for pricing. National guidelines emphasise that any BIA is supplementary to the initial dossier which focuses on evaluating the clinical evidence and added clinical benefit of the new product compared to existing treatments (Die forschenden Pharma-Unternehmen, 2023). Beyond price-quantity agreement and total expenditure, volume must be considered in reimbursement amount negotiations.

If gene therapies can demonstrate significant clinical benefit, high associated cost may not be a barrier to a positive reimbursement decision.

2.6. France

In France, BIA is required for therapies estimated to have a turnover in excess of €50 million in the second year of commercialisation, and for 'innovative' medicines which provide a significant improvement in clinical benefit (Raimond et al., 2021; Ghabri et al., 2018). These innovations are defined by ASMR grades of 1 – 3 which correspond to moderate, important or major clinical improvement over existing therapies (Ghabri et al., 2018). Manufacturers must submit a BIA (along with a cost-effectiveness analysis) to the French National Authority for Health (HAS) and the medicine pricing committee (CEPS).

National guidelines for BIA were produced in 2016 (HAS, 2016). The objectives of these guidelines were to set robust methodologies and support decision-makers in assessing the financial impact of public health interventions, signalling an intent to make BIA a more integral and influential component of the HTA process (Ghabri et al., 2018). However, the extent to which this has been achieved is unclear because there is ambiguity around how BIA should influence price decisions.

The outcome of the BIA is used by the CEPS during pricing negotiations (HAS, 2021), potentially leading to discounts and price-volume agreements.

Gene therapies are typically classified as innovative medicines due to their potential to provide major clinical improvements, and as a result are likely to be rated with a high ASMR grade, and thus require BIA under the current guidelines.

2.7. Ireland

BIA is used in Ireland by the National Centre of Pharmacoeconomics (NCPE) as part of a preliminary review to determine if a new therapy shows a high-cost relative to comparable treatments or poses a significant net impact on the drug budget (National Centre for Pharmacoeconomics, 2022). If so, a full cost-effectiveness analysis is required. While there is no specific threshold to define a 'significant' net impact in Ireland (Tilson et al., 2010), a health technology may not undergo a full HTA if its estimated annual budget impact falls between €0.75 and €1 million (McCullagh and Barry, 2016).

Recommendations on reimbursement are made by the NCPE to the Health Service Executive (HSE). NCPE recommendations specifically consider efficacy, added therapeutic value, and budget impact (National Centre for Pharmacoeconomics, 2022). The HSE then leads price negotiations with the manufacturer. The BIA results are used in these commercial negotiations.

Due to high costs, gene therapies are likely to trigger the need for a full evaluation in some circumstances, therefore requiring full cost-effectiveness analysis and BIA.

Gene therapies are likely to be reimbursed through the High-Tech Drug program, designed for high-cost treatments addressing serious, complex or chronic conditions. Access is facilitated through confidential agreements following the 2021 framework established between the HSE and the Irish Pharmaceutical Healthcare Association (IPHA) (Merlin et al., 2024).

2.8. Italy

In Italy, the Agenzia Italiana del Farmaco (AIFA) explicitly requires pharmaceutical companies to submit a BIA as part of the Price and Reimbursement Dossier for new medicinal products, orphan drugs, and new therapeutic indications for patented products (AIFA, 2024).

AIFA (2024) states that the BIA is an essential part of the reimbursement process and is used in reimbursement decision-making as well as in budget planning. In addition, BIA is also used in commercial negotiations (Villa et al., 2019). AIFA is responsible for assessing and making reimbursement decisions concerning drugs across Italy (Carletto et al., 2020). AIFA's reimbursement decisions are then implemented by each of Italy's 21 regions, with some regional discretion in how these decisions are applied. While each region engages in some form of HTA activity, the exact role of these activities in reimbursement remains unclear (Merlin et al., 2024).

Innovative therapies, which AIFA assesses based on unmet medical need, added clinical benefit and quality of evidence, are of strategic importance, as they must be included in all regional formularies *once they receive positive reimbursement guidance from AIFA* (Jørgensen and Kefalas, 2015) and are eligible for funding through an innovative drug fund for up to 36 months before reassessment (Fortinguerra et al., 2020). Gene therapies are likely to fall into this category.

2.9. Poland

In Poland, the Agency for Health Technology Assessment and Tariff System (AOTMiT) mandates BIA for all HTA submissions. BIA is submitted by the manufacturer (AOTMiT, 2024).

The BIA is an integral part of the health technology assessment (HTA) process for new pharmaceuticals, and its results substantially contribute to the reimbursement decision (AOTMiT, 2016). If the BIA indicates extra spending by the public payer, the manufacturer must present an additional rationalisation analysis to identify the reallocation of the current budget to accommodate additional anticipated costs (AOTMiT, 2016). The BIA is thus used to inform reimbursement decisions and as a key component of commercial negotiations.

Health technologies classified as highly innovative are eligible for reimbursement through alternative funding programs, such as the Medical Fund. The pathway covers orphan and oncology medicines, with assessment limited to simplified BIA only. For the Medical Fund, AOTMiT submits an annual list of highly innovative therapies eligible for consideration to the Minister for Health (Kamusheva et al., 2021). The Minister then selects therapies for further price negotiations with manufacturers before issuing a final decision.

2.10. Scotland

BIAs are mandated by the Scottish Medicines Consortium (SMC) for all medicines. The manufacturer must submit them alongside the economic submission (SMC, 2022).

Budget impact information is not taken into account in the SMC decision to recommend reimbursement of the medicine or not (Brown, n.d.). Instead, it is used by local Health Boards for budget planning and to support the implementation of the decision (SMC, 2024).

SMC requires BIA to be conducted at the list price and at a discounted price if a patient access scheme (PAS) is proposed. A PAS improves the cost-effectiveness of a medicine that might otherwise be considered cost-ineffective by the SMC (SMC, 2019).

NHS Scotland's ultra-orphan pathway enables access to high-cost medicines for ultra-rare conditions affecting fewer than 1 in 50,000 people. This may be relevant for gene therapies that target these conditions. The SMC requires manufacturers to submit a PAS that aligns with NHS Scotland's terms to qualify (SMC, 2019).

Furthermore, the SMC classifies a drug as "high impact" if its projected annual budget impact exceeds £500,000 (Anderson et al., 2022). Following this classification, health boards are informed to account for the drug in their budget planning, and manufacturers may be asked to submit a PAS if the drug is anticipated to be cost-ineffective. Given their high cost, some gene therapies are likely to undergo assessment through this pathway.

2.11.Spain

Manufacturers are required to submit BIA as part of a reimbursement dossier containing technical information, proposed prices and cost-effectiveness analysis to the Ministry of Health's General Directorate for the Common Portfolio of Services of the National Health System and Pharmacy (DGCYF) (Justin Stindt Consultants, n.d.).

Budget impact is a key factor in the reimbursement recommendations, considered alongside clinical effectiveness, cost-effectiveness, and patient needs (Oliva-Moreno et al., 2020). BIA is also used in pricing negotiations with manufacturers (Oliva-Moreno et al., 2020)

The Spanish Agency for Medicines and Healthcare Products (AEMPS) is responsible for producing a Therapeutic Positioning Report (TPR), which provides information on added therapeutic value to provide information for pricing and reimbursement decisions (Badia et al., 2020). Recommendations around pricing and reimbursement for new medicines are then made centrally by the Interministerial Committee on Pricing of Medicines and Healthcare Products (CIPM) (Epstein and Espín, 2020). This

involves the CIPM, along with the Ministry of Health, negotiating a national maximum reimbursable price. The 17 autonomous regions have the authority to negotiate further discounts with the manufacturer. Regional hospitals also have some discretion in procurement decisions.

In Spain, the approval of orphan drugs for pricing and reimbursement heavily depends on receiving a positive TPR and the lack of therapeutic alternatives. Orphan drugs with positive TPR opinions are significantly more likely to achieve reimbursement approval, while those with negative opinions are typically rejected (Badia et al., 2019).

3. BIA and related policy tools in the context of gene therapies

In this chapter, we:

- Discuss the impacts of the different uses of BIA in decision making, as described in chapter 2.
- Explore critical components of BIA methodology (time horizon, perspective, exploration of different sources and types of uncertainty) that are likely to disproportionately impact gene therapies. These elements were identified from our analysis of the literature review and in discussion with the experts.
- Highlight areas of best practice. Here we draw heavily on the most recent ISPOR Principles of Good Practice for decision making (Sullivan et al., 2014), leveraging information from our literature reviews and expert panel to assess the relevance to gene therapies.
- Discuss the use of horizon scanning and innovative payment models as tools (outside of BIA) that decision makers could use to help manage budgets in the context of gene therapies.
- Outline recommendations for improvements to BIA and the way it is used. The recommendations were developed based on research in the context of gene therapies, but many of the underlying issues apply more widely and thus the recommendations are not exclusively relevant to BIA for gene therapies.

3.1. Application of BIA in decision-making

The original ISPOR Principles of Good Practice for Budget Impact Analysis state:

> "*The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource constraints…. It can be used for budget planning, forecasting and for computing the impact of health technology changes on premiums in health insurance schemes*" (Mauskopf et al., 2007a).

This indicates that BIA's intended use is budget planning and evaluating potential financial impacts. Despite this, we find substantial evidence (see chapter 2) that BIA is used for three additional purposes: to inform decision making, to determine HTA routing, and for commercial negotiations. Input from our panel of experts suggested that these uses are likely interconnected (i.e. the commercial negotiations effect the decision to reimburse), and BIA often plays a more significant role in decisions than is often detailed in the relevant guidance.

This routine use of BIA in decision making, outside of its recommended use, may be problematic. To ensure maximum benefit is achieved from available budgets, reimbursement decisions should be rooted in assessment of value. Various forms of clinical and economic evaluation are available that can be used to compare the value of interventions versus standard of care, and thus to inform an assessment of whether new technologies such as gene therapies offer good value for money. BIA is not a value assessment and cannot perform this role.

Yet, roundtable attendees stressed the key role that short term affordability (and therefore BIA) considerations play in many reimbursement decisions, as decision makers struggle to meet tight short-term budgets in resource constrained health systems. Indeed, questions have been raised in the literature, and were echoed by the experts during the roundtable, over how we can implement a pragmatic use of BIA, reconciling consideration of the long-term care value of new interventions and its potential short-term financial impact (Ghabri and Mauskopf, 2018).

This is an important trade off. Focusing on BIA in decisions of reimbursement risks compromising the signals sent to innovators regarding what is important to decision-makers. Healthcare systems and policymakers are presumed to have the aim of maximising population health subject to their budget constraints. As part of this, they are responsible for encouraging a sustainable stream of investment in pharmaceuticals. One way this is achieved is through value-based pricing, which can be effective in aligning price signals to investors and industry with patients' and citizens' priorities. Such use of value-based pricing requires an assessment of value, not just budget impact. By rewarding innovation that offers desired (health) gains sufficiently through value-based pricing, decision makers send signals that stimulate and channel further research and development efforts (Henderson et al., 2024; Bell et al., 2023; Bruen et al., 2016).

However, BIA in its current form does not recognise a large proportion of the benefits on offer from new therapies, and thus when used in reimbursement decision making it risks undermining value assessments and the principles underlying value-based pricing. Decision makers thus face a trade-off between maximising health subject to budget constraints in the short term via reliance on BIA in decision making, and maximising health (and well-being) achievable in the long run. This is particularly relevant in the context of gene therapies, as if a gene therapy produces high clinical value and health gains then a value-based high price may be justified; therefore, pharmaceutical companies should be rewarded for the innovation and risk-taking during the development phases in a manner that is comparable to what we do for other patent-protected innovations (Garrison Jr et al., 2023).

This is not to say that BIA is not useful, but that the appropriate use of BIA is as stated above in the good practice guidelines (Mauskopf et al., 2007a). Use of BIA in this way provides a good opportunity to assess the net costs of adopting a new therapy and to explore fully the potential budgetary offsets. This is superior to a price comparison between the new therapy and the old, but is not a substitute for a full assessment of the economic impact of adopting the new therapy.

BEST PRACTICE ANALYSIS: USE OF BIA IN DECISION MAKING

Decision-makers should be explicit about the application of BIA in their context and how it influences reimbursement decision-making and/or price negotiations. Of the guidelines we reviewed, those from **Denmark, England, Germany, Ireland, Poland** and **Scotland** were explicit about how BIA is used within and outside of decision making. The remaining countries were either ambiguous or experts suggested the use of BIA in reality was different to how it was presented in the guidelines.

Where decision makers do choose to utilise BIA in decision-making, they should be aware of the potential adverse impacts on the incentives for future innovation.

Ideally, BIA would be used primarily for budget planning, with affordability concerns mitigated via alternative tools such as innovative payment models and advanced horizon scanning (see section 3.3). An example of best practice is offered by **Scotland**, where BIA is not used to inform the reimbursement decision but instead is used by local Health Boards for budget planning (Brown, n.d.) (SMC, 2024). Equally in **Germany,** BIA does not form part of the reimbursement decision and is only required if initial pricing negotiations fail.

Policy recommendations on the use of BIA in decision making

- Health Technology Assessment bodies and other relevant institutions should be explicit and transparent about the purpose of BIA, including whether and how it will be used in reimbursement decision making.

- Further research into the implications of the use of BIA in decision making, including its impact on dynamic efficiency, would be helpful. This will facilitate decision makers in making informed trade-offs between short term affordability and longer-term incentives for innovation.

3.2. Budget Impact Analysis Methodology

Views from the expert panel about the extent that current BIA methodology is appropriate for assessing gene therapies was mixed. Still, the majority of experts felt that BIA of gene therapies could be improved by adapting current methods to some or a great extent. Based on the literature review and roundtable insights, we consider the impact of the following methodological challenges in the context of gene therapies: perspective, time horizon, and exploration of uncertainty. Under each of these headers we also consider i) if best practice would depend on *how* the BIA is used, and ii) how the impact of this element of BIA would differ depending on the type of gene therapy (see Box 1).

BOX 1: HOW THE VALUE OF GENE THERAPIES MANIFESTS DEPENDING ON THE TYPE OF GENE THERAPY

As described in Firth et al. (2021), the economic value of a gene therapy on the health system will differ depending on whether the health gains (compared to the current standard of care) are primarily driven by an increase in length of life or an improvement in quality of life. In this box, we recap the three illustrative categories of gene therapies, distinct in their expected financial impact on the health system and wider society. The categories aim to demonstrate that not all gene therapies will have the same financial/budgetary impact on the health system. The three categories are intended to be illustrative, and we note that some therapies may sit between categories and/or exhibit the characteristics of multiple categories.

	Primary driver of health gain		Where do the cost offsets accrue?	
	Length of life	Quality of life	Inside the health system	Outside the health system
Category 1	✓			
Category 2		✓	✓	
Category 3		✓		✓

Category 1: Therapies with a large increase in length of life and limited expected cost offsets. Category 1 gene therapies are likely to target a condition with high early mortality and no alternative effective treatment options; they are least likely to demonstrate cost offsets because current standard of care incurs costs for a short period of time until the death of the patient.

Category 2: Therapies with large increases in quality of life and substantial cost offsets within the health system. Category 2 gene therapies are likely to target a condition which does not have high early mortality, which is currently treated with relatively inefficient care (high cost and/or poor outcomes). Successful administration of these therapies may create cost savings by eliminating the need the chronic care across a patients' lifetime.

Category 3: Therapies with large increases in quality of life and substantial cost offsets outside of the health system. Category 3 are likely to target conditions that limit quality of life but, due to the nature of the condition, do not require additional healthcare. Instead these diseases may have substantial burden falling outside the health system, e.g., social care, education or welfare systems.

3.2.1 Perspective

The health gains associated with gene therapies may lead to substantial cost savings both inside and outside of the health system. Inside the health system, this could be a result of the reduction or removal of ongoing healthcare needs, whereas outside, it could take the form of (e.g.) decreased social care or disability payments[2]. Capturing these budgetary impacts in other areas of governments spending will enable government level decision makers to see the budgetary benefits of health care interventions. This could, for example, help to justify a policy of increasing the healthcare budget as a means of getting people back to work and reducing welfare payments. The conventional health system payer perspective utilised for BIA means that these wider budgetary impacts are overlooked.

Category 3 gene therapies (as described in Box 1) may be particularly disadvantaged by the use of narrow perspectives. An example is voretigene neparvovec, a gene therapy to treat vision loss due to the dysfunctional RPE65 gene which is needed for the healthy function of cells in the retina. One study in Germany found that, of 351 blind people surveyed, 95% of received social allowances

[2] *Productivity gains and spillover effects on carers and family may also occur, although these are not direct budgetary impacts and thus would still not be captured in BIA.*

(Chuvarayan, Finger and Köberlein-Neu, 2020). Voretigene neparvovec is, therefore, likely to have substantial budgetary impacts outside of the health system which would not be captured under typical BIA.

Whilst broader perspectives can be presented as scenario analyses in many of the countries under consideration, it's difficult to ascertain the extent to which these scenarios are taken into account where BIA is used in decision-making or as part of price negotiations. Given the healthcare decision maker's budget is separate to that of other government departments, it's not clear how much weight any wider savings will be given. This will be even more of a concern in countries where there is a division of health insurance into statutory and private insurance, where there may be a lack of accountability from private healthcare providers for social costs incurred.

BEST PRACTICE ANALYSIS: PERSPECTIVE

ISPOR Good Practice guidelines (which assume BIA is largely used for budget planning) recommend that the perspective of the budget holder is applied, but that BIA should also highlight broader economic implications and impact on other budget holders.

The latter is particularly important where BIA is used to inform reimbursement decision making or price negotiations. By capturing cross-sector budgetary savings, decision makers can consider the full budgetary impact of introducing a new gene therapy.

Examples of good practice for choice of perspective include **Ireland** and **Belgium** where broader perspectives can be provided in BIA in addition to the reference case (healthcare payer perspective and health and social care system perspective respectively) if sufficiently justified.

3.2.2 Time horizon

Many guidelines for BIA recommend a time horizon of between two to five years in the base case. This is problematic for gene therapies as they have the potential for high upfront costs and longer-term benefits. Short term BIA may therefore capture the full costs of gene therapies, while reflecting little of the benefits.

Short time horizons may be particularly disadvantageous for category 2 and 3 gene therapies (Box 1) due to their long term expected cost savings. An example from category 2 is valoctocogene roxaparvovec, a gene therapy for treatment of haemophilia A. Haemophilia A is a genetic disorder characterised by the deficiency or dysfunction of coagulation protein factor VIII (NBDF, 2024). Individuals with severe haemophilia will experience recurrent, spontaneous bleeds (NBDF, 2024), and require frequent treatment with repeated intravenous infusions of clotting factor (Henderson et al., 2024). One modelling study estimated that treatment with valoctocogene roxaparvovec could lead to a mean per patient reduction of 1,808 factor infusions over the course of a lifetime compared to those who only received factor therapies (Cook et al., 2020). Additional savings arose due to reduced need for on-demand treatment of bleeds. The reduction in treatment costs translates into lifetime savings of USD $6.8 million per patients compared to standard FVIII prophylaxis (Cook et al., 2020). These substantial cost savings would not be captured by short term BIA.

BEST PRACTICE ANALYSIS: TIME HORIZON

ISPOR Good Practice guidelines recommend that BIA should be presented for time horizons of relevance to the budget holder in accordance with their budgeting processes. However, they highlight that longer time horizons may be needed in some cases to illustrate the cost savings that occur in future years. This aligns with the case of gene therapies, where there is an argument for including a longer perspective due to the long-term nature of the benefits, including potential cost savings.

An example of good practice for choice of time horizon is **Ireland** where the core analysis should estimate the annual impact over a minimum of 5 years, with a note that this may not be sufficient to capture peak/'steady-state' usage (HIQA, 2018). The guidance notes that the requirement for a longer-term analysis should be considered in each case and conducted as necessary.

Insights from the expert panel indicated that a potential barrier to adopting longer time horizons is that additional uncertainty may be introduced. This is particularly relevant for gene therapies where considerable uncertainty around long-term outcomes may be present (Besley et al., 2022). Historical cohort data and appropriate extrapolation techniques supplemented by expert elicitation where necessary can support decisions based on longer time horizons (ibid.).

Similarly to adopting a broader perspective, longer time horizons are less relevant if used for budget planning purposes only. For example, in Germany, where BIA does not play a role in the reimbursement decision making process, adopting longer time horizons may not be useful. The time horizon may only need to be that which is of direct interest to the budget holder for their planning purposes.

3.2.3 Uncertainty

Gene therapies are likely to be associated with uncertainty regarding long term outcomes (Coyle et al., 2020; Aballéa et al., 2020; Garrison et al., 2021). The short term follow-up of patients relative to the treatment effect means that there is uncertainty over the durability of effect and potential adverse effects (Besley et al., 2022; Coyle et al., 2020; Huygens et al., 2021).

This additional uncertainty will impact all three categories of gene therapy as set out in Box 1. As an example from category 1, onasemnogene abeparvovec-xioi is a gene therapy used to treat spinal muscular atrophy (SMA). SMA is a genetic disease with onset of symptoms in childhood. It causes weakness of voluntary muscles, affecting patients' ability to roll, sit, stand, walk, and sometimes swallow or breathe (Muscular Dystrophy Association, 2024). At the time of NICE's assessment, trial data was available only up to 24 months and was limited to a single arm study of 15 children with SMA, with some follow up data available up to 4 years post treatment. Early interim results of ongoing phase III studies were also considered, the longest running of which (n=22) was able to provide some 6-month follow up data (NICE, 2023b). This highlights the extent of the immaturity of trial data available for gene therapies at the time of HTA and BIA.

Use of real world evidence (RWE) has been suggested as a means to tackle this uncertainty within HTA, e.g. by providing information on the natural course of the disease as a means to calculate relative efficacy (Besley et al., 2022), or via longer term trial follow up as in the case above. However, despite recent progress, RWE may not be being used to its full potential in this context (Besley et al., 2023; Hogervorst et al., 2022). This has direct knock-on implications for BIA where relative efficacy estimates are critical to the results.

Specifically impacting BIA, roundtable attendees noted that there is also often considerable uncertainty in estimating the size of the target population, which is a critical parameter determining

the results of BIA and may be particularly challenging for therapies for rare diseases, as is the case for many gene therapies. RWE may be helpful again here to form the basis of estimates of eligible populations.

Many of the national guidelines state that sensitivity analyses and/or scenario analyses are required to explore and characterise uncertainty. However, it is not clear how these additional results feed into the decision-making processes.

Of note, roundtable attendees suggested that due to the one-time administration of gene therapies, scenario analyses within BIA should account for the potential that initial eligible patient numbers may be high (representing the prevalent population), gradually transitioning to a steady rate of incident cases over time. The experts noted they have seen specific cases in which patient numbers in reality were significantly smaller than had been modelled in BIA.

BEST PRACTICE ANALYSIS: UNCERTAINTY

ISPOR Good Practice guidelines suggest parameters should be informed by the budget holder's own data where possible, e.g., for current intervention use and size and characteristics of the eligible population (Sullivan et al., 2014). They also suggest that a range of values to be used in uncertainty analyses should be obtained from the budget holders to best reflect their expectations.

Most of the BIA guidance reviewed included recommendations for sensitivity analysis and/or scenario analysis on the most important parameters or assumptions. Only Scotland does not provide any details on the requirements here. Explicit mentions of testing the impact of population size are included in **Spanish** and **Polish** methodology.

Roundtable attendees noted that reassessments of HTA or reimbursement decisions once more evidence had been generated would also be a feasible way of resolving uncertainty. The guise and extent of reassessments vary across jurisdictions and may involve a revision to the reimbursement decision and/or price renegotiations. Reassessments are fairly common for gene therapies in certain countries, e.g. France[3] and Germany (Famulska et al., 2023). However, the only evidence of BIA being used as part of reassessments that we identified was in China, where price renegotiations occurred they were primarily based on actual budget impact rather than predicted via BIA (Guo et al., 2023).

Other mechanisms similar to reassessments which allow decision makers to review their initial recommendation include conditional reimbursement or coverage with evidence mechanisms. These often fall under the umbrella of innovative payment models which are discussed in section 3.3.2.

Recommendations on budget impact analysis methodology in the context of gene therapies

- BIA guidance should allow for the flexibility where appropriate and justifiable, for example, willingness to accept the following;
    - Longer time horizons (e.g., to capture potential future costs and cost savings)
    - Broader perspectives (e.g., to capture the budget impact on other government departments such as social care, social security and education)

[3] *Although no health economic model (CEA or BIA) is submitted for reassessment.*

- Uncertainties inherent in BIA of gene therapies should be explored through sensitivity analyses that vary patient eligibility criteria and target population size at a minimum.

The impact of alternative payment models is considered in the next section.

3.3. Additional tools to be used alongside BIA

3.3.1 Horizon scanning

Horizon scanning or early alert systems involve systematically identifying upcoming health technologies that have the potential to affect health, health services and/or society. The purpose is to allow policy makers to be better prepared for the emergence of new medicines (Vogler, 2022b). In some cases this may mean using the data to facilitate budget planning, whilst in others, the data may be used to facilitate price negotiations by anticipating emerging competition for new therapies (Lepage-Nefkens et al., 2017). Insights from the roundtable indicated that the latter is the case for the Danish system, where horizon scanning is used to identify market entries of new drugs and anticipate potential competitors and opportunities for negotiation.

Horizon scanning occurs at both the national level and via international initiatives:

- In a 2019 survey of officials in European member countries of the Pharmaceutical Pricing and Reimbursement Information network, six countries reported systematic use of horizon scanning (Iceland, Italy, the Netherlands, Norway, Sweden and the UK) and four further countries reported ongoing horizon scanning activities (Austria, Denmark, France and Ireland)(Vogler, 2022b).

- The International Horizon Scanning Initiative is a collaboration of nine countries (Austria, Belgium, Denmark, Ireland, Netherlands, Norway, Portugal, Sweden and Switzerland) set up in 2019 which aims to mitigate the impact of disruptive innovation, support effective budgetary policy and support HTA and regulatory preparation (IHSI, 2024). It is comprised of two components, a Joint Horizon Scanning Database and High Impact Reports. The Joint Horizon Scanning Database represents IHSI's repository of upcoming pharmaceutical products whilst the High Impact Reports analyse and evaluate specific information sets from the database to highlight pharmaceuticals with a high potential to cause significant impact e.g. gene therapies.

The consensus from the roundtable was that inherent uncertainties associated with horizon scanning limit its usefulness, particularly regarding the unpredictable timing and impact of new products. Furthermore, horizon scanning does not provide information on the launch sequence, which is especially problematic for smaller European markets.

While there is international collaboration to enhance horizon scanning practices, its potential is not fully utilised as pointed out by Vogler (2022b) who notes a discrepancy between perceived importance and actual implementation. Countries can improve the quality and efficiency of their horizon scanning activities through work-sharing and capacity-building exercises e.g., sharing of information and best practices. Sharing information on emerging interventions can help countries avoid redundant processes.

Our panel of experts noted that the introduction of EU regulation 2021/2282 which establishes a framework for joint clinical assessment (JCA) may also have an impact on horizon scanning activities at the pan-EU level. The regulation outlines that a horizon scanning exercise should be provided to allow for the early identification of emerging health technologies that are likely to have a

major impact on patients, public health and healthcare systems. However, at the time of writing, no further official information could be identified.

BEST PRACTICE ANALYSIS: HORIZON SCANNING

In the context of budget planning, good practice for horizon scanning is likely to relate most to the identification and filtration phases of horizon scanning, i.e. the process of identifying medicines in the pipeline and filtering based on scope and potential impact. This will serve to highlight emerging technologies likely to be of high impact, thereby allowing budget planners foresight of these therapies and aid early service planning.

An example of good practice identified comes from **Scotland** via SMC's Advanced Therapy Medicinal Products (ATMP) report which summarises new ATMPs expected to launch within an extended timeline compared to their standard horizon scanning report (Forward Look) (SMC, 2023). These ATMPs are also included in the relevant Forward Look report allowing for more detailed service and financial planning (ibid.). England's NIHR Innovation Observatory undertook a Horizon Scan of ATMPs in 2021 up to ~2026 to gather intelligence and help plan for their introduction, however, this report is not routinely updated (NIHR Innovation Observatory, 2021).

3.3.2 Innovative Payment Models

Gene therapies are often associated with high prices which largely reflect the high value they offer in terms of significant health gains, potential cost-savings and wider societal spillovers. This, however, can bring about affordability concerns for payers when confronted with high one-off payments (Horrow and Kesselheim, 2023). At the same time, payers may be further hesitant to reimburse gene therapies due to clinical uncertainty, further inhibiting patient access to these breakthroughs (ibid.).

In response to these challenges, various innovative payment models have been proposed to manage uncertainty and short-term budget impact. These have been discussed in theory (Horrow and Kesselheim, 2023; Michelsen et al., 2020; Phares et al., 2024) and applied to specific gene therapies in practice (DeMartino et al., 2024; Jørgensen, Servos and Kefalas, 2018).

Annuity payments (also referred to as amortisation) are often proposed in this context, whereby the cost of the intervention is split into instalments across a longer time period making it easier for a payer to absorb the budget impact each year (Zhang and Shugarman, 2024). Payers may also wish to link performance/outcomes to payments using outcomes-based annuity payments or pay for performance models (Coyle et al., 2020; Moradian et al., 2024; Firth et al., 2021; Schaffer et al., 2018). However, these types of payment models are hindered by difficulties with outcome selection, the need for additional data collection, lack of clear governance structures and resulting administrative burden (Michelsen et al., 2020).

An alternative approach is the use of dedicated funds for innovative or orphan treatments. These act as ring-fenced budgets to support the reimbursement of medicines that are innovative, address a high unmet need, offer life-saving or significant clinical benefits. Examples of these include NICE's Innovative Medicines Fund, Italy's Fondi Innovativi and Belgium's Special Solidarity Fund (Vogler, 2022a). However, these funds are usually subject to strict entry requirements and/or only provide temporary reimbursement subject to further data collection and reassessment (acting as a managed access/entry mechanism) (ibid.).

There is evidence of outcomes-based agreements and/or coverage with evidence development requirements in most of the countries under consideration including Belgium, Italy, Spain, France, Germany, Poland, UK (Dolon, 2024; Cole et al., 2019), although not all of these agreements were for gene therapies.

Innovative payment models transform the short term budget impact for payers, and thus where they are expected to be used, should be included in BIA to allow accurate assessment of the true budget impact. This could be presented as an additional analysis alongside the base case, where possible multiple types of payment models should be conducted as scenario analyses.

There may be process challenges in capturing these models in BIA, as highlighted by experts from Poland and Spain, particularly if BIA is submitted prior to the price negotiations being initiated. To overcome these challenges, payers and manufacturers should consider more dynamic and open communication during the development of BIA, iterating the BIA as negotiations progress.

BEST PRACTICE ANALYSIS: INNOVATIVE PAYMENT MODELS

Best practice for the design, implementation and evaluation of performance-based risk-sharing arrangements were outlined by an ISPOR task force in 2013 (Garrison et al., 2013); however, the use of these agreements and other innovative payment models have evolved significantly in the past decade. Furthermore, the feasibility of implementing such agreements varies considerably across countries due to resource and infrastructure constraints, as well as regulations.

A recent review of outcomes-based agreements in Europe described outcomes-based agreements with further data collection as a reimbursement solution for uncertainty and innovative health technologies (Avşar et al., 2024). However, the authors stress the practical challenges that remain, largely the burden of data collection and analysis. As such, in many circumstances, simpler solutions may be preferred by stakeholders (Avşar et al., 2024). Consequently, it is crucial that these types of agreements are designed carefully and collaboratively with all relevant stakeholders in order to minimise the burden of data collection (Avşar et al., 2024).

Where they are expected to be utilised, it is critical that innovative payment models are incorporated into BIA models as they will transform the budget impact. This approach is advocated, to some extent, by SMC in **Scotland**, where the BIA should be presented with and without the proposed Patient Access Scheme (PAS) where applicable (SMC, 2025). However, these patient access schemes are most commonly simple discounts rather than more complex innovative payment models.

Recommendations on additional tools to be used alongside HTA

- Existing horizon scanning activities could be strengthened to aid budget planning in the context of high upfront cost therapies such as gene therapies. International collaborations could be leveraged further to maximise the usefulness of available information and minimise the duplication of efforts.

- Innovative payment models should be considered as a tool to facilitate access to gene therapies. In doing so, the risk associated with uncertainty is shared between the payer and manufacturer, while also spreading the initial cost across a longer period.

- Where innovative payment models are likely to be employed, these models must be factored into budget impact analyses to help inform decision-making, commercial negotiations and implementation. If BIA is conducted prior to proposed innovative payment models, flexibility in processes should allow for BIA to be updated to reflect the proposal.

4. Conclusions

The emergence of gene therapies offers the potential for transformational health gains in terms of both quality and length of life. However, these innovative therapies also bring challenges associated with their one-time administration, long term benefits, often small population sizes, and related difficulties with assessing value and budget impact. While challenges around HTA and value assessment for gene therapies have been discussed at length, the impact of BIA, which also often plays a role in reimbursement decision making, has received much less attention.

BIA are typically conducted using short time horizons (2-5 years), and from the perspective of the budget holder (e.g. the health system). Gene therapies, with their significant upfront costs, are therefore likely to be viewed unfavourably via current approaches to BIA, as longer-term cost savings and wider spillover effects fall outside of the scope of these analyses. Innovative payment models that can be used to facilitate access to gene therapies are not routinely incorporated into BIA, meaning that the true budget impact is not accurately being assessed. These challenges may be exacerbated by increasing numbers of gene therapies coming to market, potentially serving larger populations than the first launches which were restricted to rare diseases. With increasing numbers comes an increasing budget impact, highlighting the urgent need for BIA reform.

Based on our reviews of the literature, supplemented by the insights and discussions of the expert panel, we present a set of policy recommendations, which highlight the changes to BIA methodologies as well as other budget planning activities that should be prioritised to enable the potential benefits of gene therapies to be realised. Whilst the recommendations were developed based on research in the context of gene therapies, many of the underlying issues apply more widely and the recommendations are not exclusively relevant to BIA for gene therapies. As part of our recommendations we highlight the need for further research into the implications of the use of BIA in decision-making on static and dynamic efficiency and incentives for future innovation.

It's important to note that the methods and processes for BIA that are implemented vary considerably across the European countries under consideration. As such, specific country considerations should be fully evaluated to adapt recommendations to reflect the health system and reimbursement processes.

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Appendix

TABLE 3: SUMMARY OF GEOGRAPHIC COVERAGE OF EACH COMPONENT OF THE METHODS

	Desk research	Pre-meeting survey	Roundtable	Post-meeting survey
Belgium	✓	✓	✓	✓
England	✓			
Denmark	✓	✓	✓	✓
France	✓			
Germany	✓	✓	✓	✓
Ireland	✓	✓		✓
Italy	✓			
Poland	✓	✓	✓	✓
Scotland	✓			
Spain	✓	✓	✓	✓

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- The costs of treating, or failing to treat, specific diseases and conditions
- Drivers of, and incentives for, the uptake of pharmaceuticals and prescription medicines
- Competition and incentives for improving the quality and efficiency of health care
- Incentives, disincentives, regulation and the costs of R&D for pharmaceuticals and innovation in medicine
- Capturing preferences using patient-reported outcomes measures (PROMs) and time trade-off (TTO) methodology
- Roles of the private and charity sectors in health care and research
- Health and health care statistics

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