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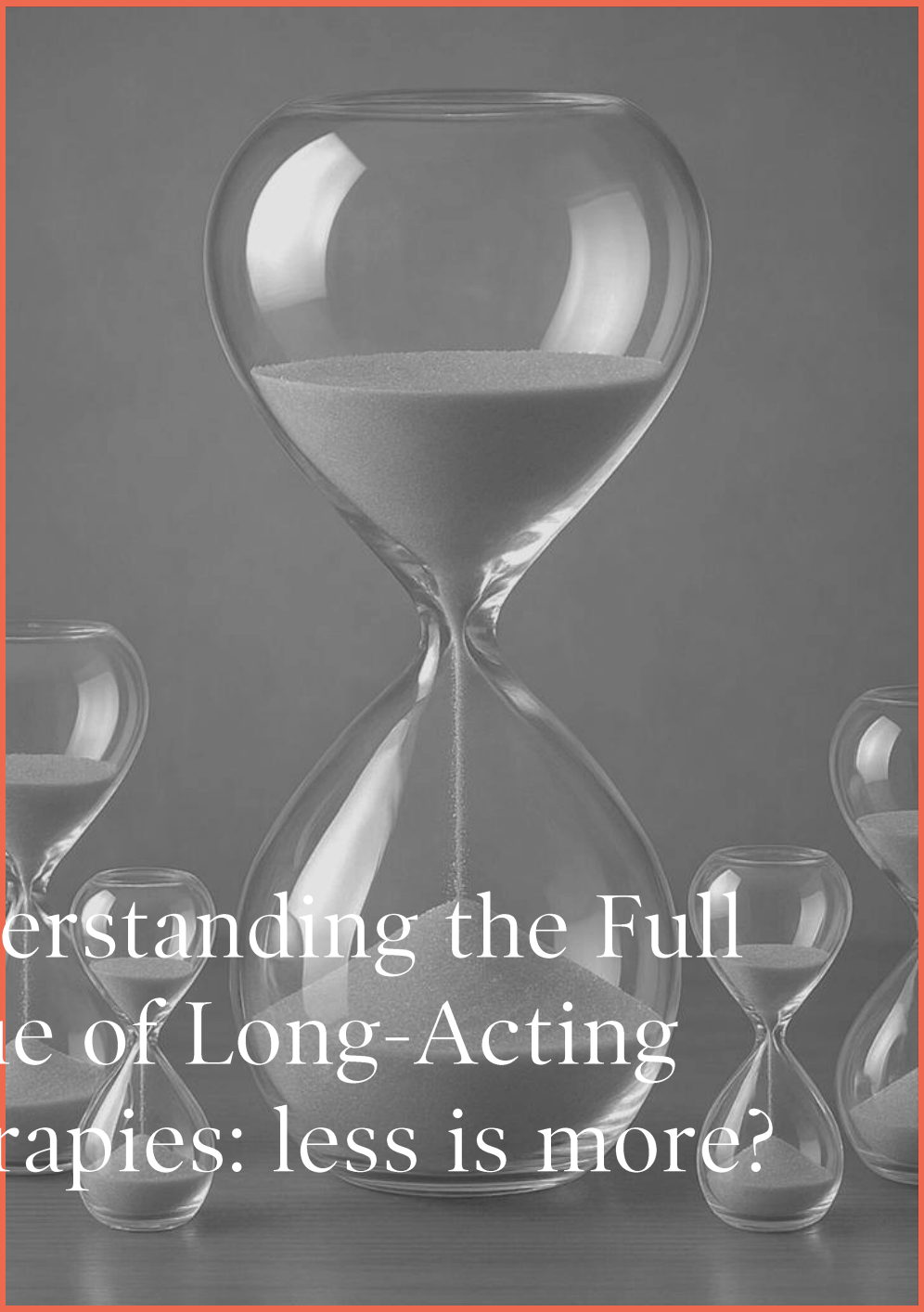

Understanding the Full Value of Long-Acting Therapies: less is more?

CONTRACT RESEARCH REPORT
MAY 2025

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Henry Fong
Matthias P. Hofer
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ohe.org

The report was commissioned and funded by GSK.

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Please cite this report as:
El Banhawi H., Fong H., Hofer MP., Steuten L., 2025. Understanding the Full Value of Long-Acting Therapies: less is more? OHE Contract Research Report, London: Office of Health Economics. Available at: https://www.ohe.org/publications/full-value-of-long-acting-therapies/

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Funding and Acknowledgements

This consulting report was commissioned and funded by GSK.

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List of acronyms

AMR	Antimicrobial resistance
ART	Antiretroviral therapy
C2H	Center for Outcomes Research and Economic Evaluation for Health
CADTH	Canadian Agency for Drugs and Technologies in Health
G-BA	German Federal Joint Committee
HAS	Haute Autorité de Santé
HCP	Healthcare professional
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICER	Institute for Clinical and Economic Review
IQWiG	Institute for Quality and Efficiency in Health Care
ISPOR	The Professional Society for Health Economics and Outcomes Research
LA	Long-acting
MS	Multiple sclerosis
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMPA	National Medical Products Administration
NRDL	National Reimbursement Drug List
PBAC	Pharmaceutical Benefits Advisory Committee
PLHIV	People Living With HIV
PMDA	Pharmaceuticals and Medical Devices Agency
PROM	Patient-reported outcome measure
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised-controlled trial
SMC	Scottish Medicines Consortium
SoC	Standard-of-care

Executive Summary

KEY TAKEAWAYS

Compared to shorter acting therapies, long-acting (LA) therapies might be overlooked and hold potential for patients, healthcare systems and society:

- **Enhanced Patient Outcomes**: LA therapies have potential to improve treatment adherence and clinical outcomes by reducing dosing frequency, thereby lowering treatment burden and minimising symptom relapses for chronic conditions. They also may improve patients' quality of life, enabling greater patient choice and satisfaction, and addressing stigma.
- **Healthcare System Efficiency**: LA therapies have the potential to alleviate healthcare system pressures by reducing the frequency of patient visits, freeing up resources, and lowering overall healthcare expenditures through improved disease management. However, some LA therapies in certain healthcare settings and disease areas may need more frequent visits to allow for HCP administration.
- **Broader Societal Impact**: LA therapies can help to increase productivity by minimising disruptions for patients and caregivers. Some LA therapies can also be a part of strategies to enhance patient choice, equity, help mitigate antimicrobial resistance through sustained drug concentrations and may have a lower environmental footprint compared to shorter- acting alternatives.

Realising the potential value of LA therapies is currently hindered by a narrow view of value in health technology assessment (HTA) and variability across HTA agencies. HTA value frameworks risk under-recognising the broader value of LA therapies. The potential for benefits in key areas such as patient choice, productivity gains, and environmental impact are often overlooked. Countries with more flexible HTA frameworks, like Canada and the UK, are better positioned to capture these broader value elements than others like Germany and France.

Stakeholder collaboration can help to achieve the necessary policy changes. To account for broader potential of LA therapies, HTA frameworks need to adapt by incorporating broader value elements and leveraging real-world evidence. This will incentivise innovation, ensure equitable patient access, and support sustainable investments in transformative treatments for chronic disease management.

Long-acting (LA) therapies represent a significant innovation in pharmaceutical development by offering a sustained drug effect with reduced administration frequency.

These therapies are particularly effective for chronic conditions, which require long-term treatment. In this report, we primarily focus on injectable therapies that have durations of action and administration frequencies of up to six months, acknowledging for some therapies it can be even more.

This report aims to identify the potential value of LA therapies for patients, physicians, healthcare systems, society, and the economy. Furthermore, it investigates whether the potential value of LA therapies is considered in health technology assessment (HTA) and payer decision-making. We

conducted a targeted literature review and analysed four LA therapy product case studies in HTA decision making.

THE FULL VALUE OF LA THERAPIES

This report shows that LA therapies have the potential to offer a variety of benefits for patients, health systems, and society more broadly.

Patient-level effects:

- Effectiveness: LA formulations have the potential to reduce treatment burden and reduce symptom relapses compared to daily oral therapies, for example for conditions like schizophrenia or osteoporosis. When integrated into clinical practice, LA therapies can also improve patient adherence by reducing dosing frequency and lead to better clinical outcomes. However, reduced dosing frequency might not lead to improved adherence in all cases and the prolonged treatment effect of LA therapies may extend or lead to different side effects compared to short-acting therapies.

- Quality of life (QoL): LA therapies potentially improve the QoL of patients, including health and functional status, as well as enhance the quality of patient's social and occupational lives. For some conditions l, this value element may also capture the impact on stigma experienced by patients affected by the condition, reducing stigma-associated treatment burden and the risk of disclosure, and daily medication reminders.

- Patient-centeredness and choice: Less frequent dosing from LA therapies may align with patient preferences and lifestyle, enhancing patient satisfaction or sense of control over their condition. Nevertheless, in the cases where LA therapies also increase frequency of routine interactions with healthcare professionals as part of treatment administration, may improve the health and well-being of patients, by identifying any additional health needs and enabling intervention in a timely manner.

Healthcare system impact:

- Cost savings: LA therapies may contribute to overall cost savings through improved adherence and reduced disease incidence, which in turn lowers long-term healthcare expenditures.

- Health system capacity: With improved disease management and reducing dosing frequency, LA therapies can help alleviate pressure on healthcare system resources. The extent to which this benefit is realised may vary by therapeutic area, depending on existing treatment schedules and service delivery models.

Societal and economic impact:

- Increased productivity: Patients and caregivers can benefit from fewer treatment-related disruptions to productivity, but this may also depend on the frequency, type of administration and location of the administration site.

- Equity improvements: LA therapies can help addressing medical needs for patient populations facing treatment challenges (e.g. non-adherence or discontinuation).

- Prevention of antimicrobial resistance: LA antimicrobial therapies may preclude the emergence of antimicrobial resistance by maintaining more effective plasma drug concentrations over extended periods, reducing dosing requirements and lowering the risk of missed doses.

- Environmental impact: some LA therapies may be the "greener" choice compared to current treatment options when considering a reduction on waste or production.

HTA CONSIDERATIONS

Results from product case studies demonstrate that in certain therapy areas, despite the potential wide-ranging impact, the broader value of LA therapies is currently under-recognised in HTA and reimbursement decisions. Analysis across ten global HTA bodies reveals significant variability in the extent to which and how elements of broader value relevant to LA therapies are considered. While clinical effectiveness, patient quality of life, and healthcare cost reductions are commonly assessed, elements like productivity, patient choice, equity, and environmental effects are often overlooked. Notably, countries that use broader, more flexible value frameworks as part of their HTA and those that are open to considering real-world evidence, like Canada and the UK, incorporate these broader elements more frequently than markets focused strictly on additional clinical benefit, such as Germany and France.

CONCLUSION

Compared to shorter acting therapies, LA therapies hold great potential to transform chronic disease management, delivering value across multiple dimensions. Realising LA therapies' full potential requires adapting HTA frameworks to reflect their comprehensive benefits, enabling equitable access for patients and incentivising further innovation. This strategic approach will ensure optimal healthcare outcomes in the short term and allow for sustainable ongoing investment in these treatments in the future.

RECOMMENDATIONS

Stakeholders should collaborate and involve patients and their healthcare professionals to ensure that the development and implementation of LA therapies align with patient needs, health system improvements, and societal or economic goals.

- **The research community** should prioritise generating real-world evidence on LA therapies' impacts and advance methodologies that quantify societal and environmental benefits.
- **Innovators** should incorporate robust evidence generation of broader value elements into clinical development strategies.
- **Policy makers and payer decision-makers** should expand value frameworks used in HTA to integrate broader value dimensions, fostering a comprehensive evaluation of the full value of LA (and other) therapies. Furthermore, this will help to foster a patient-centric approach where the choice and preferences of patients, caregivers, and healthcare professionals are acknowledged.

1. Introduction

What do we mean by LA therapies in this report?

Injectable therapies that have durations of action and administration frequencies of up to six months, acknowledging for some therapies it can be even more.

Long-acting (LA) therapies span a variety of therapeutic areas, including schizophrenia, hormone replacement treatments, HIV, and tuberculosis (Holm et al., 2023). They can be created by a multitude of different chemical and/or physical processes to create sustained-release depots, which include techniques to improve the duration and release of oral therapies (Jha, 2012). Furthermore, they can be designed to optimise and prolong drug effect and provide steady drug exposure, like in the case of injectable LA therapies which allow for continuous drug effects over weeks or months (Flexner et al., 2022; Jha, 2012; Holm et al., 2023).

Importantly, LA therapies are designed to provide a favourable benefit-risk profile that may contribute to improving adherence, which may ultimately contribute to better clinical results (Flexner et al., 2022). For example, in asthma, recent real-world studies show a median adherence to LA therapies of 87%, as measured by the proportion of days covered (Ledford et al., 2023). LA therapies can offer benefits in many disease areas, with the most distinguishable benefits expected in chronic conditions or diseases, where medication is often prescribed for prolonged periods or for life, and adherence rates of daily oral therapies can be lower than 80% and even lower in case of multiple daily administrations (Holm et al., 2023; Priest et al., 2021).

LA injectables were first authorised by the FDA in the 1950s and saw an increase in interest and approvals from the year 2000 onwards. For example, there is a healthy pipeline of LA options for prevention and treatment of HIV (Cook, 2021). Despite the increased interest in LA therapies in the pharmaceutical industry, drug discovery and formulation can be more complex and (financially) risky compared to standard developments, and access pathways are still being explored (Flexner et al., 2022). In addition, the value they bring may extend beyond the clinical endpoints that are typically considered in health technology assessment (HTA) decision making.

Beyond individual patient benefits, LA therapies can offer broader value to the healthcare system and society when compared to the current standard of care. Value frameworks like the ISPOR Value Flower help conceptualise the broad range of benefits that can be generated by healthcare interventions. Beyond clinical benefit and healthcare costs, this framework includes productivity, adherence, disease severity, hope, equity, and scientific spillovers (Lakdawalla et al., 2018).

Applying a framework like this to better understand the full value of LA therapies is important for all stakeholders involved in measuring, assessing, and appraising these products and appropriately informs pricing, reimbursement, and coverage decisions, while providing the right signals for innovation.

This report therefore aims to 1) Identify and characterise the potential value of LA therapies for patients, physicians and healthcare systems, society, and the economy; and 2) Investigate how and to what extent the potential broader value of LA therapies is considered in HTA and payer decision-making.

2. Methods

2.1 Literature review for value framework and therapeutic focus areas

A rapid, targeted literature review was conducted using Google Scholar to identify broader value elements of relevance to LA therapies from scientific and grey literature. English language journal articles and grey literature published between 2014 and 2024 that evidence an impact (positive or negative) of LA-acting therapies on elements of broader value were identified and assessed for quality and relevance. The results were then extracted using a standardised extraction form and synthesised into a disease-agnostic broader value framework. We also applied the snowballing technique to find further papers on specific value elements. More information can be found in the Appendix.

This literature review also supported the characterisation of the five therapeutic focus areas to which we applied the broader value framework. These conditions were all chronic with LA therapies being available and/or in development (Box 1).

2.2 Review of HTA reports for product case studies

We conducted four product case studies to evidence the HTA appraisals of four already fully developed LA therapies in chronic conditions. A review of HTA reports was conducted across ten key geographical regions including Australia (PBAC), Canada (CADTH), China (NMPA), Denmark (Medicinrådets), England (NICE), France (HAS), Germany (G-BA/IQWiG), Japan (C2H), Scotland (SMC), and the US (ICER). The review included reports published up to December 2024. Unlike the other HTA bodies, ICER's status in the US is different from that of the other bodies as it operates without a formal government mandate, and its recommendations are not binding for decision makers. We also note that the CADTH is now called the CDA-AMC, and that name, CADTH, was used at the time HTA for the product case studies and hence will be used when reporting from the product case studies. HTA outcomes and the types of evidence submitted for supporting different value elements were extracted from the reports.

As no HTA report in English was identified for China (NMPA) and Japan (C2H), where HTA processes have only recently been implemented, positive reimbursement of each product was determined based on whether the product is included on the National Reimbursement Drug List (NRDL) and the Pharmaceuticals and Medical Devices Agency (PMDA)-approved drug list, respectively (Huang et al., 2022; Kamae et al., 2020).

We then structured the results by four market archetypes of the countries in scope: The first archetype, "added therapeutic benefits", emphasises the demonstration of unmet clinical needs and focuses on additional clinical benefit compared to the standard of care (SoC) (OXYGY, 2018), such as Germany and France. The second archetype, "cost-effectiveness", integrates both clinical and economic outcomes, with decisions strongly influenced by cost considerations (OXYGY, 2018). Australia, Canada, Denmark, England, and Scotland fall into this archetype. The third archetype, "decentralisation and budget optimisation", balances clinical benefits with budgetary constraints and accounts for multiple levels of decision-making across central, regional, and local funding levels,

such as seen in China and Japan (OXYGY, 2018). Finally, the "multiple payers and prices" market archetype, exemplified by the US, is characterised by both private and public sector payers determining individual pricing with limited government price control.

BOX 1: THERAPEUTIC FOCUS AREAS IN THIS REPORT

1. Human immunodeficiency virus (HIV) targets the body's immune system, making it more susceptible to other illnesses (WHO, 2024). HIV can be treated with antiretroviral therapy (ART), which has transformed HIV infection into a long-term, chronic medical condition (Masters et al., 2019). ART regimens require lifelong administration, and most antiretrovirals are taken as daily pills to suppress HIV infection (Masters et al., 2019). There is a strong pipeline of LA options for the treatment (and prevention) of HIV.

2. Osteoporosis is a bone disease associated with decreased bone mineral density and bone mass, or structural changes in bones. This can make bones fragile and increase the risk of fractures (broken bones) (NIAMS, 2017). Osteoporosis is more common in elderly populations, and women are more at risk of developing osteoporosis than men (NHS, 2017). A number of medicines are commonly used to treat osteoporosis, typically used daily or weekly (NHS, 2018).

3.Hyperlipidaemia (or high cholesterol) is an excess of lipids in the bloodstream. The main causes of hyperlipidaemia include lifestyle-related factors, genetics, certain medications and other medical conditions (Cleveland Clinic, 2022). Untreated, fat can accumulate inside the blood vessels increasing the risk of heart attack and stroke (Cleveland Clinic, 2022). Statins are the most commonly prescribed medications for hyperlipidaemia (NHS, 2019). These are usually lifetime medications and are taken daily.

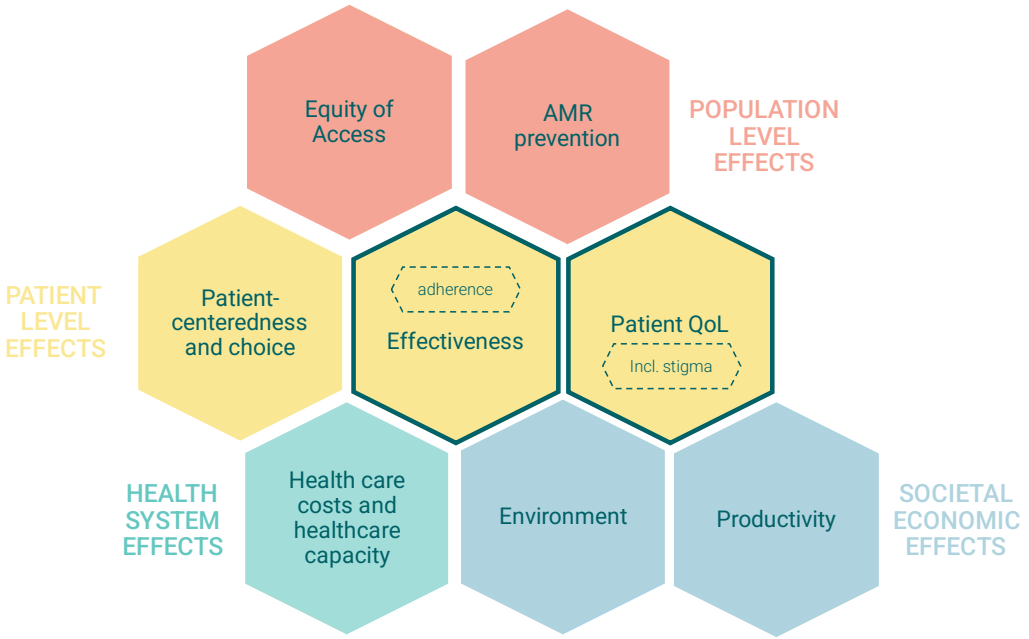
4. Multiple sclerosis (MS) is an autoimmune condition in which the immune system attacks the body's myelin cells. Myelin sheath damage disturbs signals sent by nerves to perform functions including sight, sensation and movement (Cleveland Clinic, 2024). The exact causes are unclear and there is currently no cure. Disease-modifying therapies can slow down disease progression, while daily corticosteroids can manage inflammatory symptoms usually for shorter periods (NHS, 2024).

5. Schizophrenia is a long-term mental health condition responsible for a range of different psychological symptoms. While the exact cause of schizophrenia is unknown, it is believed to be caused by a combination of genetic and environmental factors (NHS, 2021). Schizophrenia is usually treated using a combination of behavioural therapy and daily antipsychotics (NHS, 2021).

3. Identifying the full value of LA therapies

The targeted literature review identified eight elements of value which can potentially apply to a wide range of LA therapies. As shown in Figure 1 below, this includes the value elements that are most commonly and consistently considered, such as effectiveness, healthcare costs, and patient quality of life (QoL). In addition, it includes potential 'broader' value elements for which we found evidence of impact specific to LA therapies that are currently under-recognised in the academic literature and decision-making frameworks used by health systems worldwide (Breslau et al., 2023; Avsar, Yang and Lorgelly, 2023).

The value elements were categorised into the following four domains: patient-level effects, population-level effects, health system effects, and societal economic effects. In the following sections, we provide definitions that were synthesised from the existing literature and describe each of the value elements as related to LA therapies based on the findings from the targeted literature review. To demonstrate the application of the value framework, we provide illustrative examples of each of these value elements for specific focus disease areas, based on published evidence for each.



QoL: Quality of Life; AMR: Antimicrobial resistance. AMR prevention relevant to chronic infectious diseases. Elements with solid outline (effectiveness and patient quality of life) are elements of value that are commonly considered in HTA. The other elements are broader elements of value that are less commonly considered.

FIGURE 1: VALUE FRAMEWORK FOR LA THERAPIES

Patient level effects

EFFECTIVENESS (INCLUDING ADHERENCE)

This value element captures the extent to which an intervention achieves the intended therapeutic effects in a typical clinical setting and the extent to which the benefits of a technology exceed any potential harm (adverse events) (HIQA, 2018). Certain attributes of an intervention can improve patient adherence to treatment and subsequently progress towards achieving the intended therapeutic effects (Lakdawalla et al., 2018). Especially in chronic conditions, where adherence rates of daily oral therapies can be lower than 80%, or and even lower in case of multiple daily administrations (Holm et al., 2023; Priest et al., 2021).

Here we focus on the incremental improvement of effectiveness relative to the standard of care (SoC). LA therapies may be associated with enhanced therapeutic efficacy compared to standard of care by improving drug action, absorption, or bioavailability and may offer a better side effect profile related to less frequent dosing.

For example, LA therapies in areas such as osteoporosis and MS, provide extended drug action over months via a mechanism of action distinct from their respective SoC treatments, which require daily to weekly administration. These therapies have demonstrated enhanced effectiveness compared to the SoC (McCool et al., 2019; Silva-Fernández et al., 2013).

Furthermore, therapeutic delivery through some LA technologies which release drug doses in smaller volumes is associated with enhanced therapeutic efficacy, higher absorption of drug substances, and greater drug bioavailability (Dash and Kundu, 2023; Gorantla et al., 2020). For some indications, maintaining therapeutic medication levels in the bloodstream for longer periods of time can be beneficial for long-term prognosis, and provide extended relief of symptoms by impeding the return of symptoms between doses (Shi et al., 2021; Kalaydina et al., 2018; Kumari et al., 2023). By controlling drug delivery and maintaining steady drug plasma concentrations, some LA formulations avoid fluctuations and high peaks in drug concentration levels, limiting the frequency and intensity of adverse effects (Kumari et al., 2023; Gorantla et al., 2020; Álamo et al., 2021; Laracuente, Yu and McHugh, 2020; Jindal et al., 2023; Chaudhary, Patel and Mehta, 2019). Limiting adverse side effects can, in turn, increase patient tolerance of therapy and lessen the risk of discontinuation or poor adherence due to negative side effects (Kumari et al., 2023; Park et al., 2017; Laracuente, Yu and McHugh, 2020).

Despite these benefits associated with improved adherence, adherence to LA therapy can be a multi-faceted issue that is driven by behavioural, psychological, and socioeconomic factors (Kardas, Lewek and Matyjaszczyk, 2013). As a result, LA therapies and reduced dosing frequency might not lead to improved adherence in all cases (Freemantle et al., 2012; Greene et al., 2018). The clinical outcomes and safety profiles of LA therapies are indication-specific. Accordingly, generalisations cannot be made about the potential additional therapeutic merits of LA therapies. Despite their potential to improve efficacy and safety, longer-lasting effects of LA formulations can potentially result in extended adverse reactions, highlighting the importance of thorough initial patient examination and ongoing monitoring for some LA therapies (Ullah Nayan et al., 2023; Kanazawa et al., 2021; Modi et al., 2024).

BOX 2: ILLUSTRATIVE EXAMPLES OF EFFECTIVENESS (AND ADHERENCE) VALUE

Schizophrenia 	Results of a systematic review and meta-analysis of mirror-image studies suggest that LA injectables are superior to oral antipsychotics for preventing psychiatric hospitalisation (Kishimoto et al., 2013). LA injectables are also effective for early-phase schizophrenia treatment: results of a randomised controlled trial (RCT) found that the use of LA injectables was associated with a significant delay in time to first psychiatric hospitalisation (Kane et al., 2020). Additionally, an expert panel on the management of schizophrenia and LA injectables in the US noted that there is a treatment gap between in-hospital treatment for acute episodes of schizophrenia and subsequent outpatient care after discharge, and that LA injectables can help bridge the gap and ensure patients are discharged with effective antipsychotic coverage (Correll et al., 2016).
Osteoporosis 	A systematic review of cost-effectiveness analyses demonstrated that higher adherence associated with LA osteoporosis treatment was, in turn, associated with higher clinical effectiveness (Li et al., 2021). This finding was echoed in a cost-effectiveness analysis of a LA osteoporosis therapy. The therapy was associated with higher persistence and adherence, which were the main drivers of the higher clinical effectiveness observed (Mori, Crandall and Ganz, 2017).
HIV 	Adherence is particularly important for the effectiveness of HIV treatment and prevention in patient with suboptimal adherence; a systematic review found that higher adherence is associated with higher rates of viral suppression (Thakur et al., 2019). Qualitative evidence from healthcare workers in Alford et al. (Alford et al., 2025) suggests that LA therapies could be beneficial for people with HIV with adherence issues and those with a high pill burden. Additionally, a stakeholder panel discussion suggested that LA ARTs have the potential to play a key part in HIV treatment in populations or in contexts where poor adherence may hinder effective treatment or prevention (Nachman et al., 2019). By achieving viral suppression in a greater number of individuals, LA therapies could reduce HIV transmission rates, leading to additional public health benefits (Cobb et al., 2020; NIH 2024).

PATIENT QOL (INCLUDING STIGMA)

This value element captures the QoL of patients, including health and functional status, usually measured by patient-reported outcome measures (PROMs) (HIQA, 2018). Depending on which instrument is used this may also capture the impact of stigma in terms of the nature of the disease and its impact on patients' QoL, e.g. anxiety from the disease leading to social stigma (Visintin, Tinelli and Kanavos, 2019; Hendriks and Pearson, 2021).

Health-related QoL studies suggest that LA therapies may be associated with better QoL outcomes given that they require less frequent administration and in some cases generate fewer side effects (Modi et al., 2024; Gorantla et al., 2020). Research also finds improvements in the quality of patients' social and occupational lives following the introduction of LA antipsychotics and LA antiretrovirals (Jindal et al., 2023). In contrast, patient injection-related anxiety or pain or discomfort at the injection site may represent potential challenges when moving from oral pills to LA injectables administered by a health practitioner (Chaudhary, Patel and Mehta, 2019).

Furthermore, stigma associated with disease and (short-acting) disease management can adversely affect patient QoL and LA therapies have been shown to have the potential to alleviate external and internal stigmas (e.g. due to clinical visits or regularly self-administered medications or devices) (Ullah Nayan et al., 2023; Cuestas et al., 2021).

BOX 3: ILLUSTRATIVE EXAMPLES OF QOL (AND STIGMA) VALUE

Schizophrenia 	A cost-effectiveness study performed in Sweden found that treatment with LA injectables produces an improvement in quality-adjusted life-years (QALYs) compared to daily oral treatment, while resulting in fewer relapses and reduced relapse duration (Hensen et al., 2010). The benefits of LA therapy on QoL appear to increase with increasing the time interval between injections: an assessment of the impact of 2-week, 4-week, and 3-month treatment intervals for LA injectables found improved QoL scores with longer intervals (Osborne et al., 2012). A review of studies on LA delivery systems for the treatment of chronic conditions concludes that the emergence of LA injectable antipsychotics has been associated with improvements in the quality of social and occupational life of schizophrenic patients (Jindal et al., 2023).
Osteoporosis 	A prospective cohort study (Hayashi et al., 2019) found that LA injectable treatment was associated with statistically significant improvements in health-related QoL and significant reductions in pain scores.
HIV 	A review of pharmacological advancements in LA-ART found that societal pressure due to reinforced HIV-related stigma can adversely affect patients living with HIV's (PLHIV's) mental health (Ullah Nayan et al., 2023). Daily oral medication may act as a reminder of a PLHIV's stigmatised infection (de los Rios et al., 2021), which, according to patient and healthcare worker perspectives, could be reduced with the use of LA ARTs (Alford et al., 2025). In addition, for those who fear the presence of pill bottles may reveal their HIV status, there is the potential that LA ART could reduce stigma (CAI Global, 2023).

PATIENT CENTEREDNESS AND CHOICE

This value element refers to the extent to which patients and their families have therapeutic options available to receive care that best matches their preferences. It involves collaboration between providers, patients and their support network (e.g. family members, caregivers) (Correll et al., 2016). In the case of LA therapies, this could involve agreeing on the goals of therapy, discussing the suitability of LA treatment and the patient's preferred mode of administration, and offering LA options if deemed appropriate (Correll et al., 2016).

Patients with chronic diseases often express higher satisfaction with LA therapies. Reducing the need for frequent healthcare visits places the patient at the centre of care and is an economically sustainable method of providing care for chronic illness, particularly in resource-constrained environments (Modi et al., 2024; Verma et al., 2019).

Despite the potential to improve choice and convenience, the introduction of LA therapies may also contribute to the burden of therapy. For example, in the case of moving from oral pills to subcutaneous administration, multiple injections per dosing may be necessary for injectable LA therapies such as antiretroviral and antituberculosis agents, which can be associated with pain or discomfort and can be inconvenient for patients (Jindal et al., 2023).

BOX 4: ILLUSTRATIVE EXAMPLES OF PATIENT CENTEREDNESS AND CHOICE VALUE

Osteoporosis 	A systematic review of studies evaluating the values and preferences of women with osteoporosis highlights that for decision-making, women consider the effectiveness and side effects equally, followed by the convenience of taking the drugs and its effects on daily routines. Lower dosing frequencies were preferred, with the injectable route preferred over the oral route if administered less frequently (Barrionuevo et al., 2019).
HIV 	LA ART may better cater to patient preferences. Survey data found that people living with HIV often prefer LA ARTs (or ultra-LA ARTs) over daily pills (Meyers et al., 2014; Cobb et al., 2020). People living with HIV describe the potential convenience and simplicity of LA therapies reducing adherence concerns and enabling normalisation of life with HIV, akin to receiving routine vaccinations (Alford et al., 2025).

Population Level Effects

ANTIMICROBIAL RESISTANCE PREVENTION

Antimicrobial Resistance (AMR) occurs when bacteria, viruses, fungi and parasites no longer respond to antimicrobial medicines, infections become difficult or impossible to treat, and the risk of disease spread, severe illness, disability and death increases (WHO 2025). This value element captures the impact of a healthcare intervention on the rate of development and transmission of resistant microbial infections (Brassel et al., 2021). The management of chronic infectious diseases often requires high dosing frequencies and prolonged treatment, which fuels nonadherence to therapy and generates a higher risk of missed doses, both significant causes of emergence of drug-resistant strains (Jindal et al., 2023; Cobb et al., 2020). By maintaining effective plasma drug concentrations over extended periods and reducing dosing requirements (and thereby the risk of missed doses) LA therapies may preclude the emergence of antimicrobial resistance (Ullah Nayan et al., 2023; Jindal et al., 2023). Ultimately, this also means that LA therapies potentially enhance other elements of clinical and public health value related to antimicrobial resistance, especially via reduced transmission of infectious disease amongst the population (Colson et al., 2021)

BOX 5: ILLUSTRATIVE EXAMPLE OF ANTIMICROBIAL RESISTANCE PREVENTION VALUE

HIV 	A review of advances and challenges in the development of various LA drug delivery strategies for HIV suggests that low adherence to daily oral ART regimens precludes the attainment of viral suppression and avoidance of drug resistance, ultimately limiting treatment effectiveness and its potential to reduce viral transmission and spread in the population (Cobb et al., 2020).

EQUITY OF ACCESS

This value element captures the extent to which healthcare interventions affect health disparities e.g. inequalities across racial, gender, socioeconomic, and regional categories (Jakab et al., 2021). Health equity can be achieved by eliminating all barriers to accessing innovative treatments and addressing social determinants of health, like poverty and discrimination (Hader et al., 2024).

Having the option of both SoC or LA therapies offers value to patients and patient sub-populations in line with their preferences and characteristics. By lowering the frequency of administration, LA therapies may address unmet patient needs by improving the accessibility of medications to different population demographics or in different contexts. For example, less frequent dosing can be particularly useful for the treatment of elderly, paediatric, or other patients and socioeconomic groups who may have difficulty taking medication or appropriately adhering to treatment regimens on their own (Chaudhary, Patel and Mehta, 2019; Park et al., 2017). Further, poorer patients are often disadvantaged and at a higher risk for treatment discontinuation in contexts where direct medical and non-medical cost burdens fall on the patient (Jindal et al., 2023). Women can also be disadvantaged in contexts where they have limited mobility (Cobb et al., 2020). It is therefore important to consider the affordability and potential out-of-pocket costs of the LA therapy and its administration, and also weigh in any potential equity considerations (Kumari et al., 2023), especially in health systems where out-of-pocket payments can be substantial. Furthermore, equitable access requires ensuring accessibility of administering health clinics (particularly in the case of physician-administered therapies), given that geographic and transportation-related barriers can be associated with poor treatment outcomes in certain subgroups (Havlir and Gandhi, 2015).

BOX 6: ILLUSTRATIVE EXAMPLES OF EQUITY VALUE

Schizophrenia 	A Lancet correspondence argued that expanding access to LA injections could overcome medicine supply barriers in low- and middle-income countries associated with non-adherence to treatment (Ostuzzi and Barbui, 2021). These barriers include challenges in offering and maintaining regular clinical follow-up, which can increase the risk of missing daily medication and poorly functioning supply chains which can affect the regular availability of medicines, especially in remote areas (Ostuzzi and Barbui, 2021).
HIV 	A six-month prospective uncontrolled trial of a LA therapy in combination with a patient-centred behavioural approach can improve outcomes for homeless patients with high-risk serious mental illness (Sajatovic et al., 2013). Dedicated equity-focused strategies which are tailored to the specific context and population may be needed to help deliver LA treatment options to people whose treatment needs are not being met by available therapies (Hojilla et al., 2022). Empowering patient choice can improve equitable access to HIV care. A structure choice amongst therapies has demonstrated to improved coverage versus only one option.

Health System Effects

HEALTHCARE COSTS AND HEALTH SYSTEM CAPACITY

This value element captures the impact of healthcare interventions on reducing healthcare costs along the patient pathway (e.g. due to a reduction in the number of medical consultations, treatment, screening, and hospitalisations (Brassel et al., 2021)), and to alleviate strain on healthcare system

capacity (Breslau et al., 2023) (e.g. due to the COVID-19 pandemic or other country-specific circumstances (Brassel et al., 2022; Asukai et al., 2021)).

Enhanced symptom control and better clinical outcomes can result in reduced need for healthcare resources like medical consultations and hospital admissions (Shi et al., 2021; Modi et al., 2024). This decreases healthcare costs and reduces the use of medical resources down the clinical pathway, which can generate ripple effects in the health system, reducing strain on health professionals and resources, liberating these for alternative use (Kumari et al., 2023; González, Moscoso and Lago, 2018). This is especially beneficial in the context of constrained health system capacity, for example, in the situation created by the COVID-19 pandemic (Breslau et al., 2023; Brassel et al., 2022). Despite the potential to improve health system capacity and reduce costs, there may be the need for additional healthcare resources when switching from more frequent oral therapies to LA injectables, including the need for a trained practitioner and related infrastructure (Chaudhary, Patel and Mehta, 2019).

BOX 7: ILLUSTRATIVE EXAMPLES OF HEALTHCARE COSTS AND HEALTH SYSTEM CAPACITY VALUE

Schizophrenia 	Results of a systematic review and meta-analysis of real-world evidence found that compared with patients treated with oral antipsychotics, patients initiated on LA injectables had fewer hospitalisations and ER admissions (Lin et al., 2021). These findings are echoed by a systematic review of observational studies on the burden of schizophrenia in privately insured US patients, which found that after initiating LA injectables, average all-cause hospitalisations, hospitalisation durations and average all-cause and schizophrenia-relates hospitalisation costs reduced significantly (Zhang et al., 2018). Accordingly, an expert panel on LA injections for schizophrenia suggested that payers should be encouraged to look beyond short-term funding decisions and consider the long-term health system benefits: higher initial costs for anti-psychotic LA injectables may be offset by lower subsequent costs for medical care down the patient pathway, largely attributable reduced hospitalisation rates and shortened inpatient stays associated with LA injectables (Correll et al., 2016). This finding is supported by a systematic review of economic evaluations by Achilla and McCrone (2013).
Osteoporosis 	A cost-consequence analysis in South Korea found that the reduced risk of fractures was associated with the continuous use of an LA therapy for osteoporosis, which subsequently avoided medical treatment costs, leading to significant lifetime healthcare cost savings per patient (Cha et al., 2024).

Societal and Economic Effects

ENVIRONMENT

This value element concerns the environmental footprint of health care, i.e. it evaluates the contribution of healthcare interventions in producing toxic waste pollution (Sanders et al., 2016). Less frequent administrations associated with LA therapies (particularly injectable formulations) can reduce the carbon footprint associated with waste along the clinical pathway, for example by reducing the exploitation of sanitary resources and tackling both procurement and travel-associated emissions (Álamo et al., 2021; Power, Brady and Connell, 2021). It should however be considered that changes to the administration of LA therapies may also lead to additional wastage associated with, for example, disposable syringes compared to pills (Kanazawa et al., 2021; Zakumumpa et al., 2024).

Finally, manufacturing resources for LA therapies may be reduced, as fewer products are needed, although some LA therapies may require more resources for packaging, and delivery (Brown Ripin et al., 2022).

BOX 8: ILLUSTRATIVE EXAMPLES OF ENVIRONMENTAL VALUE

Schizophrenia 	Reduced dosing of flupentixol decanoate LA injections is estimated to reduce a patient's carbon footprint due to reduced medication, needles and syringes, travel, and energy use during the appointment (Maughan, Lillywhite and Cooke, 2016).

PRODUCTIVITY

This value element captures the impact of healthcare interventions on patients' and caregivers' productive time, including labour market earnings, unpaid productivity and uncompensated household production (Sanders et al., 2016). The reduced frequency of administration associated with LA therapies can translate to increases in patient productivity, given reduced interference with daily life and work, particularly in the case of therapies administered in a healthcare setting, as well as lower frequency of adverse events related to administration (e.g. pain and injection-site reactions). (Modi et al., 2024; Verma et al., 2019). Reduction in dose frequency and improvements in clinical outcomes may also reduce caregiver productivity losses in the case of informal care requirements (Mori, Crandall and Ganz, 2017; Kaplan, Casoy and Zummo, 2013). However, the possibility that changes to the route of administration when switching to LA therapies may also lead to potential productivity losses associated with clinic visits for administration (in the case of shifts from self-administered oral therapies to therapies administered in a healthcare setting) should be considered (Kanazawa et al., 2021; Zakumumpa et al., 2024).

BOX 9: ILLUSTRATIVE EXAMPLES OF PRODUCTIVITY VALUE

Schizophrenia 	An economic evaluation comparing short-acting oral antipsychotics to once-monthly LA injectables in patients with schizophrenia was associated with a reduction in patient productivity costs due to psychiatric illness (30.9% reduction) and in informal caregiver costs due to patient care (44.1% reduction) (Liu et al., 2022). Additionally, results of a pooled analysis of RCT data of patients switching from oral antipsychotics to monthly or 3-monthly LA injectables demonstrated reductions in overall informal caregiver burden and decrease in workdays missed, leisure hours impacted and number of hours spent caregiving among informal caregivers of patients who switched to LA injections (Gopal et al., 2017).
Osteoporosis 	The higher persistence and adherence associated with a LA therapy for osteoporosis was associated with lower hip fracture incidence, thus reduced caregiver-time costs post-hip fracture (Mori, Crandall and Ganz, 2017).

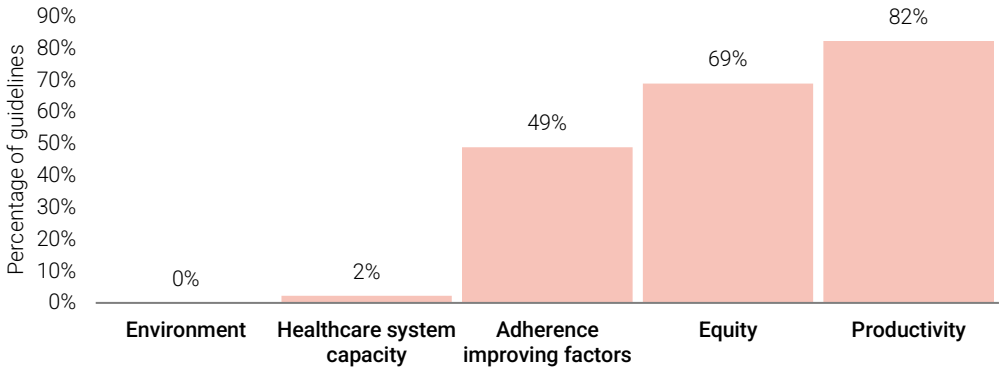
4. Consideration of LA therapy value in HTA

Healthcare decision-making approaches can vary significantly in governance, scope, assessment methods, and coverage decisions. These differences stem from the unique contexts of each healthcare system, reflecting each country's history, culture, values, preferences, and health system priorities (Avsar, Yang and Lorgelly, 2023). In this section, we first explore the level of consideration of broader value in HTA guidelines and then use case studies to understand how the value of LA therapies is considered in HTA practice across ten key markets.

Consideration of LA therapy value elements in HTA guidelines

The comprehensive value framework for LA therapies contains some elements that are commonly and consistently considered in existing HTA processes, i.e. clinical effectiveness, patient QoL, or healthcare system costs (Lakdawalla et al., 2018; Sanders et al., 2016).

When it comes to the other value elements for LA therapies, research has shown that these are less commonly considered in HTA decision-making (Sanders et al., 2016; Avsar, Yang and Lorgelly, 2023; Breslau et al., 2023). We used an existing and published analysis by Breslau et al (2023) to understand how broader value elements relevant to LA therapies resonate with HTA decision-makers and payers, i.e. if they are mentioned in their guidelines (Breslau et al., 2023). We found that payers and HTA decision-makers broadly acknowledge certain benefits for LA therapies related to productivity, equity, and adherence-improving factors (Source: Author analysis from Breslau et al. 2023, Figure 2) However, this analysis is limited by the fact that it does not cover all value elements from the LA therapy value framework. Further, Breslau et al (2023) and the literature more generally warns that there is a clear lack of guidance and large variability in terms of what is meant by a societal perspective, including analytic considerations (Avsar, Yang and Lorgelly, 2023; Breslau et al., 2023).



Source: Author analysis from Breslau et al. 2023

FIGURE 2: PERCENTAGE OF BROADER VALUE ELEMENTS RELEVANT TO LA THERAPIES THAT ARE RECOGNISED IN HTA GUIDELINES OF 45 COUNTRIES.

Consideration of LA therapy value elements in HTA practice

This section explores the incorporation of value elements for LA therapies in HTA decision-making using the four product case studies, across a range of therapies, patient populations, and clinical contexts, where LA innovations can provide substantial benefits (Table 1). Our analysis shows that for all case studies access was granted for LA therapies by most HTA systems across all market archetypes (Table 1). Seven of ten markets have reimbursed all five selected LA therapies. The LA therapy in hyperlipidaemia was not reimbursed in Canada. In Japan, the LA therapy MS was not approved and hence not on the Pharmaceuticals and Medical Devices Agency (PMDA)-approved drug list. In China, the LA antiretroviral, the LA therapy in hyperlipidaemia, and the LA therapy in MS have not yet been recommended due to ongoing revisions to the NRDL.

The case study analysis shows that reimbursement and access decisions were mostly driven by key value elements like clinical effectiveness, healthcare costs, and patient QoL in the three market archetypes that we found evidence for (Table 2). However, in one case for a LA antipsychotic, improved effectiveness versus the SoC was not required for a positive appraisal when acknowledging broader elements of value that were considered important. Generally, attributes that are unique to LA therapies such as extended therapeutic action and reduced administration frequency, are sometimes referenced under the innovation value element.

TABLE 1: CHARACTERISTICS OF PRODUCT CASE STUDIES

		Case study 1	Case study 2	Case study 3	Case study 4
Disease area		Osteoporosis	Hyperlipidaemia	Multiple Sclerosis (MS)	Schizophrenia
Product class		Monoclonal antibody	Small interfering RNA	Monoclonal antibody	Antipsychotic
Dosing		Every 6 months	Every 6 months	Every 6 months	Every 3 months
Route of Administration		Subcutaneous	Subcutaneous	Intravenous	Intramuscular
Country reimbursement status	**Australia**	✓	✓	✓	✓
	Canada	✓	×	✓	✓
	China	✓	×	×	✓
	Denmark	✓	✓	✓	*
	England	✓	✓	✓	✓

		Case study 1	Case study 2	Case study 3	Case study 4
	France	✓	✓	✓	✓
	Germany	✓	✓	✓	*
	Japan**	✓	✓	✕	✓
	Scotland	✓	✓	✓	✓
	USA	✓	✓***	✓***	✓

✓Positive reimbursement, ✕Negative reimbursement
**Reimbursement status in Denmark and Germany could not be confirmed. This may be due to the product's approval and marketing more than a decade ago, where its reimbursement was likely based on its comparative effectiveness and safety profile relative to the one-monthly formulation, as seen in Australia and Canada (CADTH, 2017; PBAC, 2016).*
***For Japan, positive reimbursement of each product was determined based on whether the product is approved and hence included the Pharmaceuticals and Medical Devices Agency (PMDA)-approved drug list.*
**** ICER economic assessment available. The other product case studies are authorised and available in the USA but without ICER assessment.*

Broader elements of value or societal perspective are more likely to be considered in cost-effectiveness and multiple payers and prices market archetypes which also allow for different types of evidence including trial data, patient preference studies or qualitative evidence (Table 2).

Qualitative evidence refers to treatment benefits that were considered as part of the deliberative process. In contrast, in markets predominantly basing decision-making on added therapeutic benefit, like France and Germany, elements beyond effectiveness are rarely addressed explicitly in HTA reports (Table 2). Nevertheless, the HAS framework for added clinical benefit in France can incorporate a limited spectrum of considerations, including disease severity, unmet medical needs, patient morbidity and mortality, QoL, and impacts on care pathways and healthcare delivery (HAS, 2022). Environmental benefits were not considered by any decision-maker in any of the product case studies.

While broader value elements may contribute to HTA recommendations, these decisions are influenced by multiple factors, including variations in the cost-effectiveness of existing alternative therapies, and differing healthcare priorities and unmet need between countries. Thus, the role of broader value elements beyond should be viewed as one additional component in a multifactorial decision-making process. The recognition of value elements AMR prevention and stigma (as part of patient QoL) could not be evaluated, because the selected product case studies did not involve therapies in infectious diseases or disease areas where stigma is a significant factor.

Here we present an overview of our findings. It should be noted that the decision-making for each product case study is context-specific, and the full information of product case study results can be found in the Appendix.

TABLE 2: RECOGNITION OF VALUE ELEMENTS AND EVIDENCE BASE ACROSS ALL FIVE CASE STUDIES

Country and market archetype	Australia Cost-effectiveness	England Cost-effectiveness	USA Multiple payers and prices	Scotland Cost-effectiveness	Canada Cost-effectiveness	Denmark Cost-effectiveness	France Therapeutic benefit	Germany Therapeutic benefit
Effectiveness	CT ITC	CT ITC CUA	CT ITC	CT ITC CUA	CT ITC	CT ITC	CT ITC	CT ITC
Health Care Costs and Capacity	CUA CCA	CUA	CUA CCA	CUA	CUA CCA	CUA CCA		
Patient QoL	CT	CT CUA	CT		PPS		CT	CT
Patient-Centeredness and Choice	QUAL PPS	QUAL		QUAL	QUAL			
Adherence *	QUAL	QUAL	QUAL	QUAL	QUAL			
Productivity	QUAL		CCA		QUAL	CCA		
Equity of Access	QUAL		QUAL					
Environment								

The table excludes stigma (as part of patient QoL) and AMR prevention as these elements of value are not directly applicable to the product case studies.
** Included in the framework under clinical effectiveness but sometimes addressed in a qualitative manner separate from other clinical effectiveness factors.*
Abbreviations: Cost comparison analysis (CCA), Clinical trial (CT), Cost-utility analysis (CUA), Indirect treatment comparisons (ITC), Patient preference study (PPS), Qualitative evidence (QUAL).

Recognition Key		
No recognition Element not mentioned in the reviewed HTA reports. This may also reflect that no data was presented to the HTA agency.	Minor consideration HTA reports discussed the value of the element and noted quantitative and qualitative evidence for specific element	Moderate consideration HTA reports discussed the value of the element supported by explicit evidence

EFFECTIVENESS (INCLUDING ADHERENCE)

Across all countries, effectiveness was the predominant value element considered in HTA. Improved incremental effectiveness was demonstrated for LA therapies in osteoporosis, hyperlipidaemia, and MS in certain regions, supported by trial data and indirect comparisons.

However, incremental effectiveness versus the SoC was not always required for a positive appraisal. For example, CADTH approved the three-monthly formulation of the antipsychotic based on its comparative effectiveness and safety relative to the one-monthly formulation (CADTH, 2017).

In the reviewed HTA reports, we could not find an acknowledgement of association between improving adherence and improved clinical outcomes. However, adherence was considered, for example NICE, CADTH and SMC acknowledged adherence benefits in LA or injectable products that reduce dosing frequency and adverse event rates, thereby supporting more consistent use. NICE cited the twice-yearly schedule of the LA therapy in osteoporosis as supporting adherence over daily oral therapies, and LA therapy in hyperlipidaemia for reducing administration frequency (NICE, 2010, NICE, 2021a). CADTH noted the LA antipsychotic could improve adherence in schizophrenia when dosed four times a year (CADTH, 2017, CADTH 2020). SMC mentioned that the LA therapy in osteoporosis offers adherence advantages over daily options (SMC, 2010, SMC, 2021).

PATIENT QOL (INCLUDING STIGMA)

Patient QoL is typically considered in cost-effectiveness-focused countries, such as Australia, Canada, and the UK, as well as in clinical effectiveness-focused countries, such as France and Germany, considered under the category of patient-relevant outcomes. The recognition of stigma (as part of patient QoL) could not be evaluated, because the selected product case studies did not involve therapies in disease areas where stigma is a significant factor.

PATIENT-CENTEREDNESS AND CHOICE

In the reviewed HTA reports, we could not find an acknowledgement of the association between patient-centeredness and choice with improved clinical outcomes. However, patient-centeredness and choice were considered. NICE, CADTH, ICER and SMC recognised patient-centeredness and choice by supporting treatments that align with patient preferences, lifestyle, and specific needs. NICE emphasised the value of the LA therapy for osteoporosis for those seeking regular monitoring (NICE, 2010). The LA therapy in MS was valued by NICE for its less disruptive 6-month dosing and LA therapy for hyperlipidaemia by ICER for its convenient twice-yearly schedule (NICE, 2018, NICE, 2021a).

AMR PREVENTION

The recognition of AMR prevention could not be evaluated, because the selected product case studies did not involve relevant therapies.

EQUITY OF ACCESS

Equity of access was considered by Australia's PBAC, although discussions were often linked to specific therapeutic areas rather than the therapy itself. PBAC noted a moderate clinical need for LA therapy in hyperlipidaemia in older patients and those in remote areas, reflecting considerations of accessibility within specific populations (PBAC, 2023).

HEALTH CARE COSTS AND HEALTHCARE SYSTEM CAPACITY

Healthcare costs and healthcare system capacity were also evaluated across all regions, though these considerations were not always explicitly detailed in HTA reports. Instead, such factors were often indirectly incorporated into cost-effectiveness analyses. Costs associated with administration, monitoring, and other healthcare resources, in addition to the acquisition cost of the therapy, were typically captured within economic models, such as cost-comparison or cost-utility analyses.

ENVIRONMENT

Consideration of environmental impacts in HTA is a relatively novel, emerging area of debate and methodological development. Consequently, this is not yet commonly or consistently considered in HTA across the regions studied. NICE, however, has begun to address environmental sustainability in its assessments, exemplified by their recent recommendations on low environmental impact inhaler devices for asthma (NICE, 2024). The NICE 2021-2026 strategy highlights ongoing efforts of incorporating environmental impact alongside health economic outcomes in HTA and recommendations (NICE, 2021b).

PRODUCTIVITY

CADTH, ICER and SMC considered productivity impacts, both for patients and carers, when assessing treatment options. CADTH highlighted the potential of the LA antipsychotic in reducing caregiver stress by lessening the need for daily supervision in schizophrenia (CADTH, 2017). ICER acknowledged that the lipid-lowering effects of the LA therapy in hyperlipidaemia could lead to fewer cardiovascular events, thus decreasing caregiving burden (ICER, 2021).

POTENTIAL DRAWBACKS

HTA reports also considered some potential drawbacks of LA therapies with regards to safety, in particular injection site-related adverse reactions. In addition, higher healthcare costs and resource use, affordability, and equity in health systems were noted in some of the HTA reports of LA therapies when relevant.

5. Conclusion and recommendations

This report identifies potential elements of broader value of LA therapies and analyses the extent to which these elements are currently considered in HTA and payer decision-making. We developed and applied a generalisable value framework that brings together a comprehensive set of value elements relevant to LA therapies. While targeted in nature, our literature review demonstrates that LA therapies can have an important impact on a range of value elements that are relevant to patients, healthcare systems, and society.

Beyond clinical effectiveness, healthcare costs, and QoL, broader elements of value are less commonly considered in HTA decision-making (Avsar, Yang and Lorgelly, 2023; Breslau et al., 2023). This is in part due to choice, notably to adopt a healthcare system rather than a societal perspective during HTA, but also due to methodological challenges in collecting and analysing evidence (Beck et al., 2022; Bell, Neri and Steuten, 2021; Cafiero-Fonseca et al., 2017; Postma et al., 2022). Our research confirms that this also affects the value assessment of LA therapies, with potentially relevant broader value elements being overlooked.

The product case studies show that payer decisions are primarily driven by traditional cost-effectiveness parameters, which can capture certain value elements from the LA therapy framework, such as clinical effectiveness, QoL, and healthcare costs. While payers also recognise the broader values of LA therapies in a qualitative manner, their impact on decision-making remains relatively limited. Additionally, very few HTA agencies apply a societal perspective or consistently integrate broader value as part of more qualitative deliberations, further limiting the recognition of the full value of LA therapies.

In conclusion, while LA therapies can offer significant value beyond those broadly recognised today, their broader impacts may be underestimated by policy- and decision-makers. This could lead to suboptimal investment decisions posing risks to health systems and societies. This issue may become more critical as governments face challenges such as an ageing population, increasing pressures on health systems, and climate change. For example, a case study in Ireland highlights that HTA processes can move beyond health and multi-stakeholder collaboration can help to advance the agenda to capture the societal perspectives (Kinchin et al., 2023).Additionally, recognising and rewarding innovation is crucial for incentivising further scientific progress and future innovation (Henderson et al., 2024). Limited rewards and return on investment for LA therapy innovators may eventually lead to underinvestment in this promising area. Although manufacturers may still develop LA therapies because they believe they will be valued by patients and clinicians.

All stakeholders have a responsibility to ensure that a sufficiently comprehensive value assessment of LA therapies is achieved and adequately rewarded to the extent they demonstrate benefit to patients, healthcare systems and society, and enable ongoing innovation:

- **The research community** should further evidence the broader value of LA therapies, including developing methods to measure and capture this in a robust and timely way, e.g. using real-world evidence or other novel research designs. While some broader value elements (e.g., patient-centeredness and choice, healthcare costs and effectiveness) are already well-evidenced in the literature, others (e.g., environmental impact) are mostly absent.

- **Innovators** should consider the potential broader value of LA therapies during development and incorporate robust evidence generation strategies into clinical development plans early on to support their value proposition.

- **Policymakers and payer decision-makers** can foster a more supportive policy environment and expand value frameworks used in HTA to integrate broader value dimensions that allow a broader assessment and recognition of the impact of LA therapies. This will contribute to a pricing and reimbursement policy that adequately incentivises and rewards high-value LA therapies. Furthermore, this will help to prioritise a patient-centric approach where the choice and preferences of patients, caregivers, and healthcare professionals are acknowledged.

- All Stakeholders should facilitate **patient and caregiver involvement** throughout the development and assessment processes, to ensure that patient perspectives are appropriately considered as pivotal for LA therapies.

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7. References for product case studies

Product case study 1 (Osteoporosis)

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Appendix 1: HTA recognition data for product case studies

TABLE 3: RECOGNITION OF VALUE ELEMENTS FOR CASE STUDY 1 (OSTEOPOROSIS)

	PBAC	CADTH	HAS	IQ/fG	NICE	SMC
Market Archetypes	Cost-effectiveness	Cost-effectiveness	Clinical effectiveness	Clinical effectiveness	Cost-effectiveness	Cost-effectiveness
Value Element						
Effectiveness	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲ ●	⬟ ▲ ●
Adherence		◆	◆		◆	◆
Patient QoL	⬟			⬟	⬟	
Patient-Centeredness and Choice		◆			◆	◆
Equity of Access						
AMR Prevention						
Health Care Costs and Healthcare System Capacity	● ○	○	◆		●	●
Productivity						
Environment						

TABLE 4: RECOGNITION OF VALUE ELEMENTS FOR CASE STUDY 2 (HYPERLIPIDAEMIA)

	PBAC	CADTH	DMC	HAS	IQ/fG	NICE	SMC	ICER
Market Archetypes	Cost-effectiveness	Cost-effectiveness	Cost-effectiveness	Clinical effectiveness	Clinical effectiveness	Cost-effectiveness	Cost-effectiveness	Free pricing market
Value Element								
Effectiveness	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲ ●	⬟ ▲ ●	⬟ ▲
Adherence	◆			◆		◆	◆	◆
Patient QoL				◆				✕
Patient-Centeredness and Choice								
Equity of Access	◆							✕
AMR Prevention								
Health Care Costs and Healthcare System Capacity	● ○	●	● ○	◆		●	●	○ ●
Productivity			○					○ ◆
Environment								

TABLE 5: RECOGNITION OF VALUE ELEMENTS FOR CASE STUDY 3 (MULTIPLE SCLEROSIS)

	PBAC	CADTH	DMC	HAS	IQ/IG	NICE	SMC	ICER
Market Archetypes	Cost-effectiveness	Cost-effectiveness	Cost-effectiveness	Clinical effectiveness	Clinical effectiveness	Cost-effectiveness	Cost-effectiveness	Free pricing market
Value Element								
Effectiveness	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲	⬟ ▲ ●	⬟ ●	⬟ ▲
Adherence								◆
Patient QoL				⬟	⬟	●		⬟
Patient-Centeredness and Choice	■					◆		
Equity of Access								✕
AMR Prevention								
Health Care Costs and Healthcare System Capacity	○	●	○			●	●	○ ●
Productivity			○					○ ●
Environment								

TABLE 6: RECOGNITION OF VALUE ELEMENTS FOR CASE STUDY 4 (SCHIZOPRENIA)

	PBAC	CADTH	HAS
Market Archetypes	Cost-effectiveness	Cost-effectiveness	Clinical effectiveness
Value Element			
Effectiveness	⬟	⬟	⬟
Adherence	◆	◆	
Patient QoL		■	⬟
Patient-Centeredness and Choice	◆		
Equity of Access			
AMR Prevention			
Health Care Costs and Healthcare System Capacity	○		◆
Productivity	◆	◆	
Environment			

Appendix 2: Methodology for the literature review

We conducted a targeted review using Google Scholar Database, which is especially beneficial for identifying scientific as well as grey literature. The following search string was used: economic and societal benefits AND (medicine* OR pharmaceutical* OR drug* OR therapeutic* OR treatment*) AND ("long*acting" OR "sustained*release" OR "timed*release" OR "prolonged*action" OR "slow*release" OR "extended* release").

Results were filtered to capture the top 50 hits and literature between 2014 and 2024, and titles and abstracts of potentially relevant papers were screened regarding publication quality and relevance. The below inclusion and exclusion criteria were applied.

	Inclusion	Inclusion	Exclusion
Publication quality	Peer-reviewed papers with high in top field journals, journals with an impact factor of more than one, highly cited and field expert authors.	Peer-reviewed papers with an impact factor of less than one; less established journals, academic working papers and reports by reputable sources.	Mainly journalism without a scientific source, media, news, blogs, etc.
Publication relevance	Contains information on potential value elements of long-acting therapeutics (definition, identification, evidence, estimation).	May contain information on potential value elements.	No information on potential value elements.

Our initial literature search returned 15,200 papers. Out of the top 50 papers, we included 21 papers following full text review and conducted snowball searches and further limited targeted searches on the less investigated value elements. We subsequently applied a snowballing technique to do follow-up searches from identified literature or value elements.

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- 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

CONTRACT RESEARCH REPORT
MAY 2025

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