Applied Health Economics and Health Policy (2024) 22:771–781
https://doi.org/10.1007/s40258-024-00904-1

PRACTICAL APPLICATION

Utilising Health Technology Assessment to Develop Managed Access Protocols to Facilitate Drug Reimbursement in Ireland

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Accepted: 14 July 2024 / Published online: 12 August 2024

Abstract

The Health Service Executive, responsible for operating the Irish health service, has introduced health technology management (HTM) initiatives to manage expenditure on medicines. One such approach is managed access protocols (MAPs) to support access to high-cost medicines, while providing oversight, governance and budgetary certainty to the payer. Herein we describe the development and operation of MAPs, using case studies of liraglutide (Saxenda®), dupilumab (Dupixent®) and calcitonin gene-related peptide monoclonal antibodies. A MAP imposes the eligibility criteria attached to reimbursement support of a medicine. Criteria applied include controls on prescribing authority, clinical diagnostic and severity criteria, previous lines of treatment, concomitant treatments, outcome data collection, and validations within the reimbursement claims system. The choice of criteria are specific to each medicine, dictated by the areas of uncertainty highlighted in the health technology assessment report, such as the place in treatment, population, duration of treatment, etc., the commercial arrangements reached with the marketing authorisation holder, and specific recommendations made by the decision maker. By December 2023, there were 28 medicines reimbursed subject to a MAP in Ireland. Across the three case studies outlined, over 3000 patients were accessing novel treatments for chronic illnesses in September 2023. Managed access protocols can provide some cost certainty for the payer by aligning utilisation and expenditure with committed funds, while enabling access where unmet need is highest. Managed access protocols are now established in the drug reimbursement process in Ireland, meeting the needs of both payers, patients and industry, and are likely to remain a feature of the reimbursement landscape.

1 Introduction

The Health Service Executive (HSE) in Ireland manages medicine expenditure within the publicly funded health system. Ireland has a well-established process for the reimbursement of medicines, with a robust system of pharmacoeconomic evaluation, and largely centralised decision-making and reimbursement arrangements [1]. The National Centre for Pharmacoeconomics (NCPE) are commissioned by the Corporate Pharmaceutical Unit (CPU) of the HSE to conduct pharmacoeconomic evaluations of pricing and

Key Points for Decision Makers

Managed Access Protocols (MAPs) impose the eligibility criteria attached to reimbursement support of a medicine, and are part of a number of health technology management initiatives applied by the Irish health service to manage expenditure on medicines.

The MAP criteria are specific for each medicine (and indication), developed based on areas of uncertainty highlighted in the health technology assessment for the medicine, contractual arrangements as negotiated with the marketing authorisation holder, and any other specific directions from the decision maker.

Managed Access Protocols can enable access to high-cost drugs for patient cohorts with greatest unmet need, while providing oversight, governance and budgetary certainty to the payer.

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reimbursement applications for new medicines, and additional indications for reimbursed medicines (with the exception of generics and biosimilars). Their recommendation is considered by the HSE Drugs Group, the committee responsible for drug reimbursement recommendations for the HSE, alongside the outcome of commercial negotiations and additional criteria as specified in the Health Act 2013 [2]. The HSE Drugs Group then make formal reimbursement recommendations to the HSE Executive Management Team, the final reimbursement decision maker.

Despite this effective interrogation of pre-reimbursement pricing, the HSE faces challenges with managing the increasing expenditure on medicines. In 2022, the HSE Primary Care Reimbursement Service (PCRS) reported expenditure of over €2.7 billion on medicines; this excludes fees and costs for most medicines administered in the hospital setting [3]. This cost is rising year-on-year [3–5]. Of particular concern are high-cost medicines reimbursed under the High Tech Arrangement [5]. This arrangement typically covers novel high-cost medicines for specialist prescribing, such as biologics for inflammatory conditions and oral oncology medicines. Under this scheme, expenditure has increased from just over €400 million in 2013, to almost €1.1 billion in 2022, while the number of patients receiving medicines under the scheme has increased at a slower rate, from 63,701 to 113,016 [3, 5].

In the context of the ever-increasing expenditure on medicines, the various challenges facing the healthcare payer have been well documented. There is an increasing level of uncertainty in health technology assessment (HTA) appraisals, due to accelerated approval pathways for new medicines, increasing regulatory acceptability of novel trial design and real-world data, rapid advances in therapeutics and clinical practice, and the advent of genomic medicine and greater understanding of the molecular pathology of disease [6–10]. Keeping pace with the lifecycle of drug development, and ever-expanding indications for use is an administrative, as well as financial challenge, for payers. Affordability remains a challenge, even for drugs which have demonstrated cost effectiveness, when there is significant budget impact [11]. Higher and higher pricing points for new medicines entering the market with this uncertain supporting evidence means the opportunity cost of an incorrect reimbursement decision is higher than ever [12, 13].

In response to these challenges, the HSE has recently introduced additional controls in the post-reimbursement phase, collectively referred to as health technology management (HTM). Health technology management has been defined as measures to enhance the safe, effective, and cost-effective use of medicines, thereby controlling utilisation and expenditure [14]. A variety of HTM strategies have been developed and utilised in different ways; (i) to drive judicious and appropriate use of products with associated cost savings, e.g., blood glucose test strips [15, 16], lidocaine patches [17]; (ii) to increase utilisation of biosimilars [18]; and (iii) to support the reimbursement of medicines in accordance with specific criteria, using managed access protocols (MAPs) [19].

The focus of this paper is on the third use of HTM as outlined above; using a MAP approach to support the reimbursement of medicines in accordance with specific criteria. The first formal MAPs managed by the HSE-Medicines Management Programme (MMP) were introduced in July 2019, for evolocumab (Repatha®) and nusinersen (Spinraza®). A MAP imposes the eligibility criteria attached to reimbursement support for a medicine. The purpose of MAPs is to enable oversight, audit and governance of utilisation and expenditure on high-cost medicines. Managed access protocols give the decision maker greater certainty regarding utilisation and expenditure on a medicine, enabling access for patient cohorts where the unmet need is greatest, or by directing utilisation of drugs to patient cohorts where treatments are most cost effective. Managed access protocols can be used to ensure prescribing occurs in the licensed population only, thereby promoting evidence-based use. They can also be used to restrict prescribing to a subgroup of the licensed population, usually for budgetary or cost-effectiveness reasons, but also in instances where the license is for a broader population than that enrolled in the clinical trials. As described, in the Irish context, MAPs are used to support managed entry agreements (arrangements between marketing authorisation holders and payers that allow for coverage of new medicines while managing uncertainty around their financial impact or performance) for medicines [20]. Managed access protocols are rooted in the outcomes of the HTA; the clinical evidence, the relative efficacy assessment, and the cost-effectiveness assessment, specifically the areas of uncertainty driving the cost-effectiveness measure.

The objective of this paper is to review the process for the development and operation of MAPs by the MMP, specifically illustrating how HTA outputs are used to inform the MAP eligibility criteria. We use the MAPs for liraglutide (Saxenda®), dupilumab (Dupixent®), and calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) as case studies for this approach.

2 Methods for Development of Managed Access Protocols

A recommendation for reimbursement conditional on a MAP is made at the discretion of the HSE Drugs Group, upon review of all evidence presented to support reimbursement

of a medicine, and in line with the criteria as outlined in the Health Act 2013 [2]. Typically, managed access has been recommended in the following circumstances: (a) when the estimated budget impact of a treatment is very high, e.g., rivaroxaban for coronary or peripheral artery disease [21], (b) where there is concern regarding the potential for off-label use, e.g., tolvaptan for autosomal dominant polycystic kidney disease [22], or (c) where the uncertainty in the clinical or cost-effectiveness evidence has led to reimbursement approval only for a defined cohort of the full licensed population, e.g., CGRP mAbs for the treatment of refractory chronic migraine [23] and nusinersen for spinal muscular atrophy [24]. In most instances a MAP has been recommended by the HSE Drugs Group following completion of a full HTA for a medicine; a limited number of medicines have been added to existing MAPs following rapid review by the NCPE but without HTA, where there are no concerns regarding additional financial risk.

There are a variety of criteria that can be included in a MAP to manage access to a medicine. These different controls have been developed based on common areas of uncertainty in clinical and cost-effectiveness evidence, areas of uncertainty in clinical practice, and feasibility of implementation. The HSE operate a number of reimbursement schemes with different eligibility criteria to make medicines and medical devices available to citizens. It is possible on some reimbursement schemes to limit prescribing authority to specific prescribers who have agreed to abide by the terms and criteria of the MAP. Confirmation of clinical diagnosis (and evidence of exclusion of differential diagnoses where relevant) can be requested. Clinical severity criteria are used to target treatments to sections of the population where unmet need is greatest. Evidence of previous lines of treatment can ensure an adequate trial of lower cost agents prior to commencement of a new higher cost agent, or can be used to demonstrate adherence to an optimised medication regimen, which has generated a sub-optimal response. Outcome data collection to confirm ongoing reimbursement support may also feature. Finally, validations (such as controls on maximum reimbursement quantities, reimbursement intervals, and duration of reimbursement), can be applied within the reimbursement claims IT system. These validations prevent the use of unlicensed dosing regimens, and can be used to limit duration of treatment where appropriate.

The development of MAPs is a qualitative, iterative process. It involves an extensive review of the clinical literature supporting licensing and reimbursement of the medicine, inclusion and exclusion criteria from the relevant clinical trials, contraindications and cautions for use in the Summary of Product Characteristics (SmPC), national and international clinical guidelines in the therapeutic area, and reimbursement recommendations and criteria in other jurisdictions. There is an extensive review of the HTA report, whereby the parameters implemented in the cost-effectiveness model are translated into clinically and operationally feasible definitions of eligibility for treatment. A review of areas of uncertainty highlighted in the HTA is undertaken, and measures are implemented within the MAP to address this uncertainty, where feasible. The choice of criteria to include in any particular MAP is determined by a number of factors, such as any specific requests from the HSE Drugs Group, clinical aspects of the treatment and target population, the setting and route of administration, chosen reimbursement scheme, feasibility of implementation, and existing controls in the therapeutic area. If there are specific conditions included in commercial arrangements made with the marketing authorisation holder to enable reimbursement, such as individual patient reimbursement conditional on demonstrable clinical outcomes, this must also be considered in the development of the MAP.

For medicines for which a large number of reimbursement applications are expected, an online application system is the preferred approach, which requires a period of IT development, user testing and integration into existing software. Where an online application system is developed, applications are submitted and reviewed in an online portal. Approval occurs within the portal, which is linked directly to the reimbursement claims system; approval is visible to the prescriber, and to community pharmacists responsible for dispensing the medicines. Where fewer applications are expected, a paper-based application form may be used, and applications are managed via secure email. In this situation, individual reimbursement approval is assigned via an online system, and is visible to community pharmacists.

Below, we provide three case studies to illustrate how MAPs function in practice. These case studies were chosen to showcase the various scenarios where a MAP can be utilised, such as where reimbursement is limited to a subgroup of the licensed population, or where ongoing reimbursement is conditional on attaining clinical outcomes. These case studies highlight the flexibility of MAPs to extend to new medicines with the same indication, or new indications for the included medicine, and to encompass administration and funding across both the community and hospital settings, as well as illustrate the challenges in developing and implementing MAP criteria. All three of these MAPs are in full operation at a national level in Ireland, delivered via online infrastructure that is accessible from the community and hospital settings.

Two data sources were used for this study, in addition to the published MAPs on the MMP website. Expenditure data were extracted from the PCRS reimbursement claims database, an administrative database containing information on reimbursement claims for drugs reimbursed on any of the publicly funded drugs schemes. Data on reimbursement applications were extracted from the PCRS Special

Drug Request (SDR) online application system, the portal through which prescribers can submit reimbursement applications for medicines reimbursed under MAPs. Application and expenditure data were analysed using Microsoft Excel 2016™.

3 Overview of MAPs Operated by the Medicines Management Programme

As of December 2023, four and a half years following the introduction of the first MAPs, there are now 28 medicines subject to MAPs overseen by the MMP [25]. In total, 9757 applications for individual reimbursement approval for drugs reimbursed subject to MAPs were received and reviewed by the MMP in 2023. These drugs are delivered across community and hospital settings, cover a broad range of therapeutic areas and include a number of gene therapy products and other medicines for rare diseases. Specifics of the controls applied in the three MAPs covered by our case studies are provided in Table 1.

3.1 Liraglutide (Saxenda®) for Weight Management

Liraglutide is marketed under the brand name Saxenda® for weight management [26], and is available in Ireland subject to a MAP since 1 January 2023 [27]. It underwent HTA by the NCPE, who estimated an incremental cost-effectiveness ratio (ICER) of €115,424 per quality adjusted life year (QALY) in the full licensed population, far in excess of the accepted cost-effectiveness thresholds for medicines in Ireland of €20,000 to €45,000 per QALY [28]. The marketing authorisation holder applied for reimbursement in a subpopulation of the licensed population, in adults with a body mass index (BMI) $\geq$ 35 kg/m^2 with prediabetes and high-risk of cardiovascular disease. In this cohort, the cost-effectiveness of liraglutide was estimated to lie between €25,668 and €63,199 per QALY, much closer to the cost-effectiveness threshold. The drugs budget impact for liraglutide (Saxenda®) was estimated between €8 and €10.2 million over 5 years. After price negotiations, the HSE Drugs Group recommended reimbursement subject to a MAP, to enable reimbursement in this defined subgroup of the licensed population, with a specific requirement for treatment discontinuation in non-responding patients [29].

The MMP developed a MAP to address some of the uncertainties highlighted in the HTA report [28] and the recommendations of the HSE Drugs Group [29]. The MAP is designed to allow individual reimbursement approval for persons who meet specific clinical diagnostic and severity criteria, with outcome data collection and treatment discontinuation for non-responders (Table 2).

The reimbursed population is aligned with that used for the cost-effectiveness analysis, that is, patients with a BMI $\geq$ 35 kg/m^2 with prediabetes and high-risk for cardiovascular disease. Establishing that a patient is part of this population leads to the requirement for demonstrated clinical diagnostic and severity criteria to be included in the MAP. The prescriber must provide the patient's weight and height at time of application, so that the MMP can validate the applicant meets the BMI criteria. Prescribers are required to submit copies of test results to validate both the prediabetes and cardiovascular disease criteria. Pharmacological management of hypercholesterolaemia and/or hypertension are also considered as part of the application.

The Drugs Group recommendation stipulated that non-responders should discontinue treatment; thus, a two-phase approval mechanism was implemented. In Phase I, reimbursement approval is for 26 weeks. Within 26 weeks of initial Phase I approval, or once the patient has received 12 weeks of treatment with liraglutide at a dose of 3 mg/

Table 1 Features of selected managed access protocol case studies, as of November 2023

Managed access protocol reimbursement criteria	Liraglutide (Saxenda®) for weight management	Dupilumab (Dupixent®)[b] for atopic dermatitis	Calcitonin gene-related peptides* for chronic migraine
Limited prescribing authority		●	●
Clinical diagnostic criteria	●	●	●
Clinical severity criteria	●	●	●
Previous lines of treatment		●	●
Concomitant interventions	●	●	
Outcome data collection as a condition of ongoing reimbursement support	●		
Validations within reimbursement claims system	●	●	●

[a]Erenumab, fremanezumab, galcanezumab, and eptinezumab

[b]Also applies to other medicines for atopic dermatitis available on the high tech arrangement, specifically tralokinumab, abrocitinib and upadacitinib

day, prescribers are required to submit an updated patient weight. The application system calculates the percentage change from the initial weight, and automatically approves reimbursement for an additional 18 months for patients who have attained ≥ 5 % weight loss. This brings in an outcomes data collection component to this MAP. Finally, treatment duration was limited to 24 months in the marketing authorisation holder's budget impact model; thus, the same condition was implemented in the MAP.

A key challenge with the development of this MAP was the definition of prediabetes, in the absence of clearly defined parameters applied in the literature and clinical practice. Also, in the HTA there was an assumption that treatment initiation would be restricted to specialists in weight management clinics. In the development of the MAP, this was not considered administratively feasible, and so access to submit applications and initiate treatment was extended to general practitioners. This is expected to increase the number of applications received, the number of eligible patients identified, and the utilisation of liraglutide (Saxenda®) when compared with projections in the HTA.

By 30 November 2023 (after 11 months of reimbursement), 7602 Phase I applications had been submitted to the MMP (Fig. 1a). In this time period, 3966 (52.2 %) were approved, 3211 (42.2 %) were rejected and 425 (5.6 %) returned seeking additional information. In the same period, 854 Phase II applications were received, with 736 (86.2 %) of these approved. Between January and October 2023, total expenditure on liraglutide was €2.28 million (including fees and value added tax [VAT], excluding any confidential commercial arrangements) (Fig. 2), suggesting that the actual expenditure is likely to be significantly higher than projections in the HTA [28].

3.2 Dupilumab (Dupixent®) for the Treatment of Atopic Dermatitis

Dupilumab was first licensed for the treatment of moderate-to-severe atopic dermatitis (AD), in adult patients who are candidates for systemic therapy [30]. Dupilumab underwent HTA by the NCPE, and estimated ICERs of €93,693 to €136,062 per QALY for the licensed population were reported [31]. Included in the HTA was a subpopulation of patients with treatment refractory disease, i.e., where one previous line of immunosuppressant therapy had failed. In this cohort, the ICER was estimated at between €66,039 and €83,424 per QALY, closer to the cost-effectiveness threshold. The estimated patient numbers used in the NCPE budget impact assessments are not published; however, the gross drug budget impact was assessed at €51.9 million (including fees and VAT) over 5 years for the full population, and €38.3 million in the refractory population.

Following confidential price negotiations, the HSE Drugs Group recommended reimbursement in this refractory patient cohort, subject to a MAP [32]. Under the terms of the MAP developed by the MMP, approved consultant dermatologists can initiate treatment in adult patients who meet the severity criteria (Eczema Area and Severity Index [EASI] score ≥ 16), where one previous line of immunosuppressive treatment has produced a sub-optimal response, or where such treatment is contraindicated, or they have experienced intolerable side effects, and are using concomitant

Table 2 Eligibility criteria developed and implemented in the managed access protocol for liraglutide (Saxenda®) [27]

Control	HTA assumption	Approval criteria
Prescriber	Weight management specialists	General practitioners
Clinical diagnostic criteria	BMI ≥ 35 mg/m^2	BMI ≥ 35 mg/m^2
Clinical severity criteria	Pre-diabetes and high-risk for cardiovascular disease, based on population enrolled in a subgroup analysis of the SCALE 1839 trial	Pre-diabetes, defined as fasting plasma glucose level of 5.5–6.9 mmol/L, haemoglobin A1c (HbA1c) level of 42–47 mmol/mol, measured within 30 days of the date of the application AND High risk for cardiovascular disease, defined as having either fasting total cholesterol > 5 mmol/L, or mean systolic blood pressure > 140 mmHg confirmed on a 24-h blood pressure monitor
Concomitant interventions	Non-pharmacological interventions for weight management, i.e., reduced calorie diet and increased physical activity	Non-pharmacological interventions for weight management, i.e., reduced calorie diet and increased physical activity
Conditional reimbursement[a]	Non-responders discontinue treatment	Two-phase application system, with phase 1 providing reimbursement support for six months, and continued phase 2 reimbursement contingent on attaining pre-specified weight loss
Treatment duration	24 months in budget impact model	24 months

BMI body mass index, *HbA1c* haemoglobin A1c, *HTA* health technology assessment

[a]Included in line with the HSE Drugs Group recommendation and the summary of product characteristics

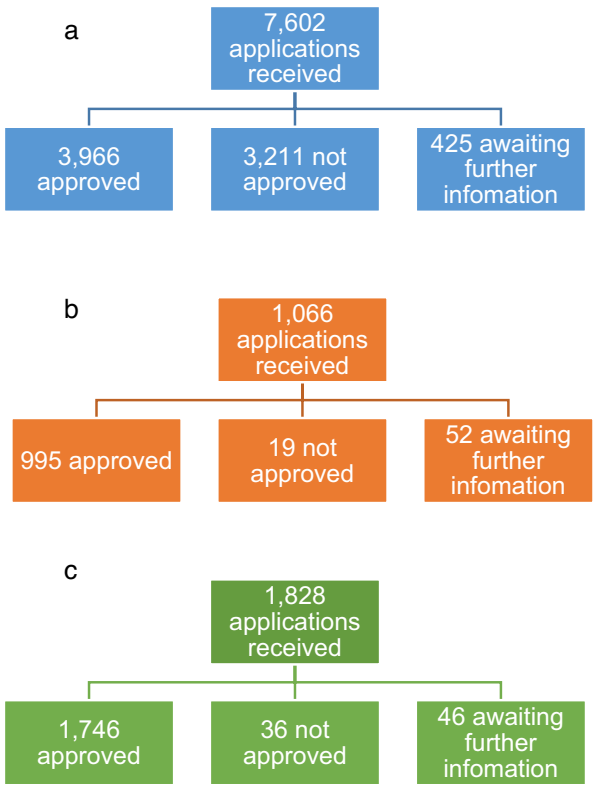

Fig. 1 Summary of outcomes of reimbursement applications received under each MAP, between the managed access protocol (MAP) launch date and 30 November 2023 (**a**) liraglutide for weight management (**b**) high tech treatments for atopic dermatitis (**c**) calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) for chronic migraine (correct as of 19 January 2024)

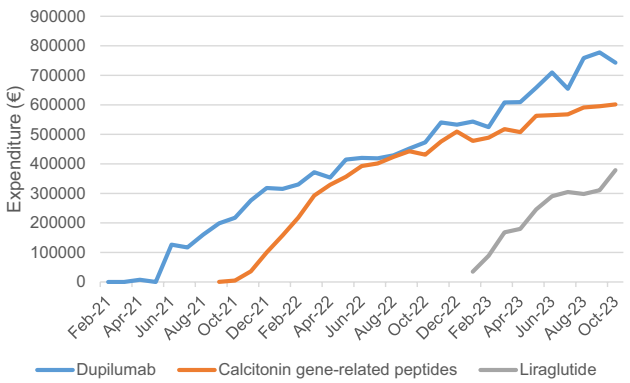

Fig. 2 Monthly expenditure on liraglutide, dupilumab and calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) under the various drug reimbursement arrangements. These figures are exclusive of confidential rebates for all products, and inclusive of VAT and fees for liraglutide, but exclusive of VAT and fees for dupilumab and CGRP mAbs

best supportive care [33]. Qualifying immunosuppressive agents are listed in the protocol (methotrexate, ciclosporin, mycophenolate and azathioprine, as outlined in international clinical guidelines). These criteria were developed based on the parameters that defined this subgroup in the HTA report, the clinical trials for the product, and clinical practice in Ireland [34, 35]. A challenge encountered in the development of this MAP was the specification of qualifying immunosuppressive agents for prior treatment, with differences noted in Irish clinical practice when compared with international practice.

Subsequently, the reimbursed population expanded to include firstly adolescents with moderate to severe AD [32, 33], then a separate MAP was introduced for children aged ≥ 6 years with severe AD (EASI ≥ 21) [36, 37]. This was possible to manage within the same online application system. Additionally, a number of new medicines for the treatment of AD were subsequently reimbursed, subject to the same reimbursement conditions: upadacitinib, tralokinumab and abrocitinib. Patients approved for reimbursement under the MAP automatically have reimbursement approval for any of the four medicines, which allows for greater treatment choice for both patients and eligible prescribers.

Reimbursement support for dupilumab for the indication of severe asthma was subsequently endorsed by the HSE Drugs Group, subject to a MAP that ensures use in patients with severe eosinophilic asthma [38, 39]. This MAP came into effect in November 2023, requiring a bespoke IT infrastructure build, with approved prescribers from a different speciality, and different prescribing criteria to the AD indication. This expansion into a new indication has confirmed the possibility of using this process to manage drugs with multiple treatment indications across various therapeutic areas.

Between April 2021 and November 2023, 1066 applications for treatment with dupilumab and the other medicines for the treatment of AD subsequently included under the MAPs, have been reviewed by the MMP (Fig. 1b). Of these, 995 (93 %) have been approved for reimbursement, with additional information outstanding for 52 applications. Expenditure in this time interval has been growing steadily, and stands at just under €13.1 million between April 2021 and October 2023 (excluding fees, VAT and any confidential commercial arrangements) (Fig. 2).

3.3 Calcitonin Gene-Related Peptide Monoclonal Antibodies for the Prophylaxis of Chronic Migraine

Calcitonin gene-related peptide (CGRP) monoclonal antibodies (mAbs) are therapeutic agents targeting the CGRP ligand or receptor involved in migraine pathophysiology and are indicated for the prophylaxis of migraine in adults who

have at least four migraine days per month [40–43]. Available agents in this pharmacological class include erenumab, fremanezumab, galcanezumab and eptinezumab.

The NCPE carried out a HTA, which found that erenumab was likely to be cost effective in a treatment-resistant cohort of patients with chronic migraine (CM) who had an inadequate response to three or more prophylactic treatments, with ICERs ranging from €24,780 to €71,073 per QALY [44]. The NCPE considered that cost effectiveness in the patient cohort with episodic migraine was more uncertain and did not recommend reimbursement. Similarly, fremanezumab was considered likely to be cost effective in treatment-resistant CM, but not for episodic migraine [45]. The NCPE highlighted significant uncertainty in the estimated numbers of eligible patients, and estimated a gross budget impact over 5 years of between €27.3 and €49.6 million for these drugs, depending on estimates of the size of the treatment-resistant cohort and market share assumptions, with negligible cost offsets within the drugs budget.

Reimbursement of erenumab was recommended by the HSE Drugs Group in January 2020, as they considered erenumab "appeared to be a cost-effective treatment option" in the cohort of patients with CM who have failed three or more prophylactic treatments [23]. The positive reimbursement recommendation was conditional on the development of an individual patient approval system to enable reimbursement for patients meeting predefined criteria via a MAP. Subsequently, fremanezumab was recommended for reimbursement in the same cohort subject to the same MAP in March 2021 [46], and galcanezumab was added to the Reimbursement List and MAP in March 2022 [47]. These three agents are available through community pharmacies via the High Tech Arrangement. Eptinezumab was added to the MAP via hospital pricing approval in June 2023 as it is administered via intravenous infusion [48].

The MAP for CGRP mAbs was developed by the MMP and launched in September 2021. Eligible patients are aged ≥ 18 years, are under the care of a consultant neurologist for a confirmed diagnosis of CM as per International Classification of Headache Disorders diagnostic criteria, and have demonstrated evidence of trialling at least three prophylactic treatments for migraine [48]. By including these criteria for reimbursement, the MAP reflects the cohort where the treatment had the greatest likelihood of being cost effective. Patients who are pregnant or breastfeeding, aged ≥ 50 years at migraine onset where alternative causes of headache have not been excluded, and patients with a recent history of clinically significant cardiovascular disease, vascular ischaemia or thromboembolic events are not eligible for reimbursement. This reflects the characteristics of patients recruited to the pivotal licensing trials, and the SmPC for these medicines [40–43].

By November 2023, the MMP had reviewed 1828 applications for reimbursement approval for CGRP mAbs, 1746 (95.5 %) of which had been approved, with outstanding information awaited for 46 (2.5 %) applications (Fig. 1c). Total expenditure to date (September 2021 to October 2023) was €10.05 million (excluding fees, VAT and any confidential commercial arrangements) (Fig. 2). Patient numbers are significantly higher than projected in the HTA submission for this refractory cohort.

4 Discussion

We have described how HTA outputs are used to develop MAP processes in Ireland. Across the three case studies outlined, over 3000 patients were accessing novel treatments for chronic illnesses in September 2023 (Fig. 3). In total, 9757 applications for individual reimbursement approval for all drugs reimbursed subject to MAPs were received and reviewed by the MMP in 2023.

By December 2023, there were 28 medicines reimbursed subject to MAPs under the remit of the MMP, with others currently undergoing addition to this list. These drugs are delivered across community and hospital settings, cover a broad range of therapeutic areas and include a number of gene therapy products and other medicines for rare diseases. While the case studies provided here focus on novel treatments coming through the reimbursement process, HTM strategies have previously been applied to medicines already reimbursed in Ireland, such as a reimbursement application system for lidocaine patches [17], and continuous glucose monitoring sensors [49]. As such, HTM strategies form part of a dynamic life-cycle approach to product reimbursement, enabling the payer to react to trends in product utilisation and prescribing behaviour.

We have emphasized some of the benefits of MAPs. Each process is individual to the relevant medicine, with its basis in the conditions and uncertainties highlighted in the HTA report. The data collected through MAPs is useful in characterising patient populations and could be used to inform future economic evaluations and reimbursement decisions. The flexibility of the process has been demonstrated, where reimbursement support can be extended to a broader population or where additional drugs can be added to an existing MAP without requiring HTA, e.g., upadacitinib and tralokinumab for the treatment of AD. This can be done on an "approved for one, approved for all" basis, minimising the administrative burden for clinicians, and allowing for treatment choice for clinicians and patients. We have also seen how new drugs can be added to a MAP regardless of funding stream, e.g., eptinezumab is funded through hospital pricing approval as it is an intravenous product, whereas the other

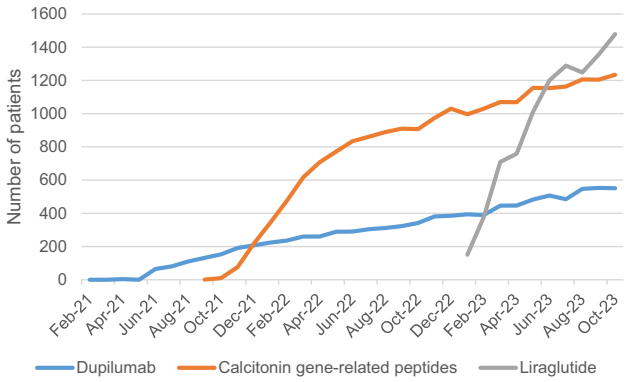

Fig. 3 Numbers of patients accessing dupilumab, calcitonin gene-related peptide monoclonal antibodies (CGRP mAbs) and liraglutide each month under the managed access protocols

CGRP mAbs are reimbursed from the primary care budget as they are self-administered subcutaneous injections.

A consideration in the development of these processes is the issue of patient access. Where medicines are reimbursed in a subgroup of the licensed population, there is a cohort of patients clinically eligible for treatment where reimbursement is not supported. In the case of dupilumab, the subgroup reimbursed is likely to include the majority of the estimated eligible population as per the product license. The projected differential in expenditure between both cohorts gives some indication of the difference in size between the licensed population and the refractory cohort; assuming the same treatment cost in both cohorts, then the refractory cohort would represent 74 % of all eligible patients having access to treatment. In the case of CGRP mAbs and liraglutide (Saxenda®), there is a significant proportion of the population covered by the product license who are not eligible for treatment, although estimates of the size of this population were not included in the HTA reports. The HSE Drugs Group must, by law, consider the opportunity cost of reimbursing a medicine when making reimbursement recommendations [2]. Neither liraglutide (Saxenda®), dupilumab nor CGRP mAbs were cost effective in the full licensed population as assessed by the NCPE; thus, reimbursement in the designated sub-populations supports the cost-effective allocation of resources.

As a measure of the success of MAPs in containing utilisation of a medicine, we can compare the actual utilisation with that projected in the HTA report. For the three case studies detailed here, the number of patients approved for treatment to date is in line with or in excess of the numbers projected during the HTA process. For dupilumab, utilisation and expenditure trends appear aligned with those published in the HTA. In the case of CGRP mAbs, between 568 and 744 patients were predicted in year 1 in the HTA, whereas reimbursement claims were submitted for 1063 patients in that time frame. The higher patient numbers are potentially due to large early access programmes operated by the marketing authorisation holders prior to reimbursement, and the restriction of reimbursement support to patients with highly treatment refractory disease, which may lead to higher than expected treatment adherence and persistence [50]. While a counterfactual scenario for the full licensed population was not described in the published HTA, it is likely that the number of patients treated in the absence of a MAP would be significantly higher based on the prevalence of chronic migraine in the population. For liraglutide (Saxenda®), patient numbers are far in excess of that predicted in the HTA report, which is at least partially attributable to the assumption in the HTA that treatment would be available only in specialist weight management clinics, whereas under the MAP liraglutide (Saxenda®) can be initiated in the primary care setting. The higher-than-projected numbers of eligible patients accessing treatment with CGRP mAbs and liraglutide suggests that MAPs are not a barrier to access for eligible patients. They also provide certainty that the greater-than-expected utilisation is due to a higher number of eligible patients, rather than utilisation outside of the reimbursed indication.

Managed access protocols can allow for the collection of outcome data, where relevant. The liraglutide case study, where reimbursement support is discontinued for patients who do not attain a pre-specified outcome, in this instance a percentage reduction in body weight, is an example of this. Other MAPs include a requirement for the submission of outcome data, and for treatment discontinuation where patients meet pre-specified discontinuation criteria. These features help to manage uncertainty in the underlying clinical or cost-effectiveness evidence, while providing some measure of cost certainty and cost containment to the decision maker. This also illustrates the potential of MAPs to be utilised to operationalise performance-based managed entry agreements. The use of MAPs to manage utilisation of dupilumab across multiple indications highlights the use of this mechanism as an option for the reimbursement challenge of operating value-based pricing for medicines with multiple indications, and as a possible alternative to other proposed mechanisms such as multi-year–multi-indication deals. Having established the principal of the use of MAPs to confine reimbursement to specific patient populations, other potential uses for MAPs can be envisaged, for example to encourage the prescribing of preferred drugs within a therapeutic area, the implementation of step-therapy or hierarchal treatment paradigms, or applying MAPs in the interests of medication safety.

There are a number of enablers for MAPs. There is a clear basis in legislation for HTM practices, under Section 20 of the Health (Pricing and Supply of Medical Goods) Act, 2013 [2]. A dedicated unit within the HSE, the MMP, develops

and operates HTM initiatives including MAPs, with support from the CPU and PCRS. A bespoke IT infrastructure, linked with the national claims reimbursement system, has been developed to support MAPs for drugs delivered through the Community Drug Schemes.

There are both technical and operational challenges involved in translating aspects of the HTA into clinical eligibility criteria for reimbursement approval, not least that the chosen parameters must be readily verifiable, and that chosen subgroups must be relevant to clinical practice. There is also the challenge of limiting the administrative requirements for prescribers. A key lesson learned to date is the importance of early consideration of HTM during the HTA process, in terms of feasibility, identifying relevant subgroups and developing clinical criteria for reimbursement. Earlier consideration of these issues could reduce the time required to develop a MAP following a positive reimbursement recommendation.

Significant resources are required to develop and operationalise these protocols. The operation of MAPs involves the individual review and assessment by a pharmacist and clinician where required, of every application submitted. There is an administrative burden in assessing applications, which is only partially offset by the use of the online application system. There is also a necessity for ongoing review and audit of MAPs, and consideration of circumstances where MAP criteria could be reviewed, or potentially removed, in light of material changes in the reimbursement circumstances, such as patent expiry or large cost reductions, significant changes in clinical practice, including additional efficacy or safety information, or the advent of therapeutic alternatives. There is an additional workload for clinical staff in gathering the required information and submitting the application for reimbursement approval, and clinician acceptability is a challenge.

In a number of studies from the USA, prescribers have criticised the implementation of drug utilisation management systems requiring prior reimbursement approval, mainly focusing on timeliness of patient access, lack of transparency and out-dated and fragmented systems. However, there are key differences in the operation of MAPs in the Irish setting. The majority of applications are submitted and reviewed within a single, centralised IT infrastructure, which is directly linked to the pharmacy claims system with live visibility of approval status available. The patient pharmacy claims reimbursement history is frequently available to the MMP, which lessens the administrative burden in the clinic. Developing the MAP using the information available in the HTA report ensures that the criteria applied are evidence based and linked to cost effectiveness, ensuring transparency in the process. A full appeals process is provided. Finally, there is ongoing engagement with the network of national clinical programmes, which provides a platform for clinicians concerns to be addressed and ameliorated where possible.

There are limitations to this work. Currently, follow-up data of sufficient length is not available from all MAPs to determine their success over a 5-year period in maintaining budget in line with allocated funds. We have not elicited the views of clinicians or patients regarding the implementation of MAPs, specifically on the impact on administrative workload, or patient access issues. The influence of MAPs on marketing authorisation holders strategic positioning of their products in the Irish market has yet to be elicited. Predictive factors for reimbursement recommendations with HTM controls such as MAPs are unknown, and research is underway to identify the parameters most likely to result in a recommendation for reimbursement with a MAP.

5 Conclusion

Managed access protocols, developed utilising HTA outputs to impose eligibility criteria for reimbursement support for a medicine, can provide some cost certainty for the payer by aligning utilisation and expenditure with committed funds, while enabling patient access where unmet need is greatest. Managed access protocols have successfully enabled the managed entry of high-cost medicines to the Irish market, and have been successfully applied as a tool for active HTM in the post-reimbursement phase of the product lifecycle.

Acknowledgements The authors would like to acknowledge the contribution of all the staff in the Health Service Executive Medicines Management Programme and the Health Service Executive Primary Care Reimbursement Service who devised, supported and implemented the health technology management initiatives outlined in this paper.

ADeclarations

Funding Open Access funding provided by the IReL Consortium.

Conflicts of interest The authors have no relevant financial or non-financial interests to disclose. The authors have no competing interests to declare that are relevant to the content of this article.

Data availability Data on managed access protocol criteria (www.hse.ie/mmp) and technical summaries of HTA reports (www.ncpe.ie) are publicly available. The pharmacy claims data used to inform this research is not available from the research team as it was specifically obtained for use by the named authors for the purpose of inclusion in this research paper.

Ethics approval This was an observational study conducted using reimbursement claims data. Ethics approval was not required for this study.

Author contributions Conceptualisation (Claire Gorry); methodology (Claire Gorry); formal analysis and investigation (Claire Gorry, Amelia Smith); writing—original draft preparation (Claire Gorry); writing—review and editing (all authors); resources (Michael Barry); supervision (Michael Barry).

Consent to participate Not applicable.

Consent for publication (from patients/participants) Not applicable.

Code availability Not applicable.

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