Performance-Based Managed Entry Agreements for Medicines: Much Needed, but Not Feasible?

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KEY POINTS . . .

Performance-based managed entry agreements are tools that can bridge the gap between the urgent need for value-based approaches and the reality of pricing and reimbursement systems that are slow to change.

These agreements are most appropriate for innovative and promising drugs that genuinely meet a medical unmet need, but substantial uncertainty exists at launch regarding the therapy's clinical effectiveness.

Despite clear implementation challenges, performance-based managed entry agreements are feasible provided that payers and end-users are sufficiently engaged in the development of the scheme, the approach is simple and with a clear rationale, and data capture relies on existing systems or the pharma company supports data infrastructure.

When payers see new and expensive therapies come to market with immature outcome data, they increasingly want to 'pay for value'. That is, pricing and reimbursement (P&R) conditions should reward actual clinical performance and any potential cost savings should be achieved in real-world conditions. Despite increasingly frequent commentaries on the topic in the literature, progress towards value-based P&R is slow across the major markets.

Managed entry agreements (MEAs) encompass a diverse range of contracts between drug manufacturers and payers, aimed at addressing payers' concerns about clinical performance and/or budgetary aspects. This article focuses on a subset: performance-based MEAs. These can be viewed as tools that bridge the gap between the urgent need for value-based approaches and the reality of P&R systems that are slow to change. Such approaches are often described as valuable in the industry and payer circles. After two decades of patchy experimentation in various countries, typically driven by a few companies and open-minded payers, what makes these types of agreements work well is still not well understood.

This article analyses the drivers of and barriers to performance-based MEAs, and suggests ways to make them work.

What are Performance-Based MEAs?

Performance-based MEAs can be defined as "schemes between health care payers and medical product manufacturers in which the price, level, or nature of reimbursement are tied to (future) measures of clinical or intermediate endpoints ultimately related to patient quality or quantity of life" [1]. Inasmuch as these schemes link actual cost of the drug with the observed therapeutic value, they are one of the ways to apply 'value-based pricing.'

These schemes can operate at the 'patient level' or the 'population level,' as will be explained. Patient-level outcome-based MEAs are also called 'pay-for-performance,' 'payment by results' or 'outcome guarantee' schemes. In this scenario, every patient is monitored for their response to the therapy, usually within a timeframe of one to six months (sometimes up to 12 months). The therapy is normally reimbursed during this period, but this cost is refunded (fully or partially) by the manufacturer if the patient has not met the response criteria; reimbursement also ceases for these 'non-responders.' These schemes tend to use a short-term surrogate endpoint (e.g., simple lab test or functional test) to define the lack of response to the therapy, although some link pay back to an adverse, 'hard' outcomes such as need for surgery, bone fracture, organ failure or death. Table 1 provides examples across various countries.

Population-level performance-based MEAs, also often called 'coverage with evidence development' (CED), involve granting initial P&R under the condition that the manufacturer will conduct a further study to confirm/expand the evidence of the therapy's benefits; a subset of the patient population will thus be monitored for the purpose of the scheme. In principle, the methodology of the study must be agreed *ex ante*, and the results be linked concretely to revised P&R conditions if appropriate. The study is designed to address the relevant areas of uncertainty, which may be related to use in appropriate patients, actual dosing regimen, clinical effectiveness/long-term outcomes, cost savings to the health care system, etc. When the study results are available, the reimbursed price and/or breadth of reimbursement may be decreased, stay the same, or be increased. Table 2 provides examples of this type of agreement.

When Are Performance-Based MEAs Appropriate?

Performance-based approaches are appropriate under specific conditions, as follows. One is that the new therapy addresses a genuine medical need and has the potential to make a clear cut difference to patients; hence payers are truly interested in granting access and willing to discuss a non-conventional, potentially complex agreement. An additional condition is that the clinical benefit of the treatment is too uncertain to inform an adequate price and reimbursement decision. For example, let

Table 1. Examples of patient-level performance-based MEAs

Product Disease	Country, date of MEA introduction	Outcomes measured triggering pay back to the health care system
bortezomib (Velcade®) Multiple myeloma [2]	UK, 2007	Less than a partial response after 4 cycles (as defined by a reduction of 50% or more in serum M protein or an appropriate alternative biochemical, where serum M protein is not measurable)
eculizumab (Soliris®) Atypical haemolytic uraemic syndrome [3]	Australia, 2014	Failure to achieve a >25% improvement in renal function, death within 6 months, or established end-stage renal disease
finasteride (Proscar®) Benign prostatic hyperplasia (BPH) [4]	Canada, 2010	Surgery for BPH after 1 year of therapy
brentuximab (Adcetris®), Hodgkin lymphoma [5]	Italy, 2012	Disease progression or drug not tolerated during first 4 cycles
simeprevir (Olysio®) Hepatitis C [6]	Sweden, 2014	Not public, but likely to be based on reduction in viral load. The scheme was combined with a an agreement around patient numbers
fampridine (Fampyra®) Multiple sclerosis [7]	Spain, 2013	Less than 20% improvement in walking ability based on two simple tests at 2 weeks

Table 2. Examples of population-level performance-based MEAs

Product Disease	Country, date of MEA introduction	Agreed study
risperidone (Risperdal® Consta®) Schizoprenia [8]	France, 2005	A naturalistic, cohort observational study of 1,859 patients receiving Risperdal Consta or any other antipsychotic drug, to demonstrate decreased rate of hospitalisation
crizotinib (Xalkori®) Previously treated anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer [9]	Sweden, 2014	By 2016, company to submit updated health economic analysis for Xalkori, including patient profiles, patterns of drug use and clinical effectiveness
cetuximab (Erbitux®) First-line treatment of metastatic colorectal cancer patients with EGFR expression and the wt-RAS gene in combination with FOLFOX, CAPIRI/CAPOX [10]	The Netherlands, 2015	By 2019, company to submit new evidence on overall survival, tolerability, quality of life, treatment patterns and health care resource utilisation
pazopanib (Votrient®) Advanced renal cell carcinoma [11]	UK, 2011	Part A of the patient access scheme provided a 12.5% discount from the list price. Part B of the patient access scheme offered a future rebate linked to the outcome of the head-to-head COMPARZ trial (non-inferiority on progression-free survival vs. sunitinib (Sutent®)

us assume that clinical data indicate that some patients clearly benefit from the therapy while others are non-responders or low responders, but it is difficult to predict which patients will be the high responders in the indication population. In this scenario, refunding the drug costs for non-responders (patient-level MEA) should be considered. If, however, a diagnostic marker exists to predict a good response before starting therapy, reimbursement could be restricted patients testing positive or price be higher for these patients. Another scenario is that the drug's clinical value shown in the clinical trials might not predict the actual benefit in real-world conditions because of differences in patient profiles or care patterns, or because benefits may be difficult to measure with a clinical trial (e.g., compliance). In those cases, coverage with evidence development may be appropriate.

A further consideration for accepting an MEA is that the conventional route of expanding the phase III program is not an option. This could be the case for rare disease drugs with no effective treatments, when improved compliance is a key benefit or when the commercial risk of delaying launch is too high. Lastly, the viability of the schemes must be taken into account. For example, a pay-for performance scheme is practical only if a clear not confounded measure of the drug's performance exists, and can be done in daily clinical practice within a relatively short time frame (preferably less than a year). Lastly, the cost of implementing the performance-based MEA should be low in relation to the cost of therapy (e.g., a high-cost drug targeting a not-too-large population would be a good candidate, as would be a drug used in a hospital or in an integrated hospital system where efficient data and financial processes are in place).

A strong clinical and practical rationale is key in developing a performance-based MEA. But country-specific legal frameworks and payer preferences will determine what MEAs are likely to be accepted. For example, MEAs are negotiated with central authorities in the Netherlands (where CED has been preferred) or Italy (where patient-level performance-based schemes have been preferred). In other countries, such as the UK and Spain, MEAs can be negotiated at the national level or subnational level.

The Challenges of Implementation
In the past, commentators have highlighted various reasons why performance-based schemes can be difficult to implement or even not acceptable:

- the administrative burden of collecting and processing data may be unacceptable to the health care providers or payers
- the payback mandated by the scheme may not reach the appropriate budget holder (if local), or be delayed or not happen at all
- the contract may be too complicated

or not have foreseen complications (e.g., disputes, exceptional cases)

• the evidence generated is of poor quality, so that uncertainty about the drug's performance may persist.

However, all these challenges can be resolved through analysis and preparation, and early engagement with payers, HTA bodies, and other health care stakeholders as appropriate.

Success Factors and Outlook

Successful negotiation of an MEA requires strategic thinking and preparation sufficiently ahead of time, proposing schemes that:

• have a clear rationale and truly address payer concerns

• are simple and have a minimal burden on the health care system, relying on data that are normally tracked by the health care system

• tap into the incentives of the users to ensure good quality of data entry

• take confounders into account, so that payback is genuinely related to the performance of the drug

• can be monitored and arbitrated by independent, trusted third parties.

Although it is difficult to predict the future, performance-based MEAs are likely to be used more often in future for various reasons: (1) the need to manage access to an influx of innovative therapies going through fast-track regulatory approval, and thus having immature data at launch; (2) an emerging 'appetite' of payers for real-world evidence; and (3) the better integration of databases and improving sophistication of pharma market access teams.

References

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Additional information:
The preceding article is based on an issues panel given at the ISPOR 18th Annual European Congress.

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