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Do the Current Performance-Based Schemes in Italy Really Work? "Success Fee": A Novel Measure for Cost-Containment of Drug Expenditure

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ABSTRACT

Background: Drug costs have risen rapidly in the last decade, driving third-party payers to adopt performance-based agreements that provide either a discount before payment or an ex post reimbursement on the basis of treatments' effectiveness and/or safety issues. **Objectives:** This article analyses the strategies currently approved in Italy and proposes a novel model called "success fee" to improve payment-by-result schemes and to guarantee patients rapid access to novel therapies. **Methods:** A review of the existing risk-sharing schemes in Italy has been performed, and data provided by the Italian National report (2012) on drug use have been analyzed to assess the impact on drug expenditure deriving from the application of "traditional" performance-based strategies since their introduction in 2006. **Results:** Such schemes have poorly contributed to the fulfillment of the purpose in Italy, producing a trifling refund, compared with relevant drugs costs for the National Health System : €121 million out of a total of €3696 million paid. The novel risk-sharing agreement called "success fee" has been adopted for a new high-cost therapy approved for idiopathic pulmonary fibrosis, pirfenidone, and consists of an ex post payment made by the National Health System to the manufacturer for those patients who received a real benefit from treatment. **Conclusions:** "Success fee" represents an effective strategy to promote value-based pricing, making available to patients a rapid access to innovative and expensive therapies, with an affordable impact on drug expenditure and, simultaneously, ensuring third-party payers to share with manufacturers the risk deriving from uncertain safety and effectiveness.

Keywords: cost-containment, performance-based, reimbursement, risk-sharing.

Introduction

During the last decade pharmaceutical expenditure has rapidly increased, and burdens more than other health care costs in many European countries and in the United States [1]. Oncological care is one of the fields in which spending increased faster, growing up to 21% per annum in recent years [2], because of the introduction of novel high-cost therapies, together with the increase in the prevalence of cancer [3].

Many treatments introduced in clinical practice are molecularly targeted agents [4], whose costs vary between an average of approximately $5,000 (€3,700) to more than $10,000 (€7,400) per month [5], most often exceeding $25,000 (€18,500) per year. These treatments, however, often result in benefits measured in months of survival [6]. In a recent analysis published in *Blood* [7], a large group of experts in chronic myelogenous leukemia pointed out examples of dramatically high costs for antineoplastic drugs such as bosutinib, ponatinib, and omacetaxine, concluding that for many clinical conditions, drug prices do not reflect objective benefits in terms of survival prolongation, degree of tumor shrinkage, or improved quality of life because drug prices for new medicines are mostly set on the basis of price of the most recent similar compound commercially available.

High costs, questionable efficacy, and long-term results of new medicines raised questions about their affordability, application in clinics, and cost-effectiveness [8], leading to the need of adopting cost-containment measures, aimed at reducing expenditure for public health. In Europe, third-party payers have introduced different cost-containment strategies to overcome the problem of public health expenditure, leading to reimbursement agreements in which the burden is shared with pharmaceutical companies and the third-party payer. In an official

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report, the "Good Practices for Performance-Based Risk-Sharing Arrangements (PBRSAs)" Task Force of the International Society for Pharmacoeconomics and Outcomes Research defined such agreements as schemes that "involve a plan by which the performance of the product is tracked in a defined patient population over a specified period of time and the amount or level of reimbursement is based on the health and cost outcomes achieved" [9]. In other words, in a PBRSA, the final remuneration or reimbursement of a pharmaceutical is linked to a previously agreed objective, based on effectiveness or budget impact [10].

The aim of this study was to overview the current PBRSAs approved in Italy so far, where such schemes exist since 2006, and to critically evaluate the impact of their application on drug expenditure. The study also proposes a novel tool for the improvement of cost-containment strategies, called "success fee," an evolution of the performance-based reimbursement concept, already adopted in Italy for the drug pirfenidone, approved for the treatment of idiopathic pulmonary fibrosis.

Reimbursement Schemes in Europe

Although in Europe several reimbursement schemes have been adopted and differently recognized, they can be classified into two broad categories: financial-based schemes and performance/outcome-based schemes [1]. The former category includes "price per volume" (focused on controlling financial expenditure, with pharmaceutical companies refunding overbudget situations) and "patient access scheme" (including free drugs or discounts for an agreed period to enhance the value of new medicines and improve the possibility of their funding/reimbursement). PBRSAs are established "between a payer and a manufacturer of pharmaceuticals, devices or diagnostics, where the price level and/or the revenue is related to the future performance of the product in either a research or a real-world environment" [11].

PBRSAs link the reimbursement or price of the new technology/medication to the health outcomes derived from its utilization in the "real world": reimbursement thus depends on future assessment of clinical end points [12].

Within the European Union, several countries are currently using some form of PBRSAs, most of them financially-based, because the performance-based schemes adopted so far have shown critical difficulties in terms of applicability [10]. United Kingdom, The Netherlands, France, and Italy reported a larger use of PBRSAs than did other countries within the European Union [9].

Reimbursement Schemes in Italy

The Italian National Health System (NHS) has adopted several instruments to manage budget impact, uncertain clinical outcome, and appropriate use of medicines. These instruments include discounts (possibly hidden discounts), price-volume agreements, performance-based schemes, therapeutic plans, "AIFA notes," that is, restriction of prescribing centers, and monitoring registries used to collect data about drug safety and effectiveness [9]. The AIFA notes limit reimbursement of the relevant drugs to population subgroups. The monitoring registries have represented, since 2005, an advanced tool to ensure not only prescription appropriateness but also the applicability of PBRSAs [13]. Most of the drugs included in the registries were approved under a centralized marketing authorization (often rapid and/or conditional approval) and are specifically biologics and/or high-cost drugs. Reimbursement strategies are made to ensure not only a rapid patient's access to drugs but also cost control. In fact, the adoption of a PBRSA is commonly associated with a faster patient's access [14]. When price and reimbursement are negotiated by AIFA and the relevant company, the choice of the type of PBRSA to be adopted depends on the data available on the efficacy and safety of drugs, as well as on pharmaceutical products' characteristics and on the availability of alternative therapies [10].

Italy has its own classification system for PBRSAs, which includes the following three categories:

- "cost sharing," which is a discount for initial cycles of treatment for all eligible patients;
- "risk sharing," which sets a partial reimbursement for eligible nonresponders only, after a clinical evaluation; and
- "payment by results," which sets a total reimbursement by the manufacturer for nonresponders.

The system of applying an initial discount to all eligible patients used in the "cost-sharing" scheme is simpler to manage than the system of reimbursement for nonresponders used in the "risk-sharing" and "payment-by-results" schemes, and it is applied when reliable data on the efficacy and safety of the medicine are available. Usually, risk-sharing and payment-by-results schemes are applied in the case of medicinal products whose risk-benefit ratio has a greater degree of uncertainty, thus requiring a definition of nonresponders that derives from the characteristics and the results of pivotal clinical trials [13]. For each eligible patient, a file is opened in the registry and followed up until reevaluation. To be considered eligible for reimbursement, it is critical that every patient's file is full and closed at the end of treatment. The distinction between responders and nonresponders is based on the outcome recorded in the patient's file, according to the respective negotiation agreement.

Table 1 lists the drugs subjected to PBRSAs in Italy at the date of December 31, 2012. Most of these drugs have been approved for oncological care.

Analysis of Data Available in Italy

We based our analysis on the data published in the annual report "Drug Use in Italy: National Report 2012" by Osservatorio Nazionale sull'impiego dei Medicinali [13]. Table 2 describes the total amount of money that has been reimbursed by the companies, as of 2012, for the 22 drugs for which risk-sharing schemes have been activated since their establishment in 2006. Despite the application of the three schemes adopted in Italy, it appears that the amount of money refunded through the reimbursement procedures is trifling: €121 million out of a total of €3696 million (i.e., 3.3%) [15].

Focusing on expenditure/reimbursement data relative to the market of drugs under PBRSAs for the year 2012, we see that €823 million has been paid by the NHS for the treatment of patients. Out of this amount, only €46.3 million (5.6%) underwent the reimbursement procedures, which means that 94.4% of the expenditure was not considered for refund. Reasons accounting for such a high percentage of unrequested reimbursements may be found, at least in part, not only in the high percentage of patients still under treatment and in interruptions of treatment for reasons other than the ones provided in the negotiation agreement but also in patients' files that have not been closed because of the health care center inefficiencies, thus preventing the activation of the reimbursement procedure. Moreover, out of €46.3 million expected to be refunded after the reimbursement procedure activation, only €31.3 million (67.7%) has actually been refunded by the companies (Fig. 1) [13], while the remaining €15 million (32.4%) was not reimbursed because of lack of refund request by hospitals, inefficiency of administrative centers or management/treatment errors (5 million; 10.8%), and rejection of refund requests by the companies (10 million; 21.6%) likely because of other unspecified formal issues.

Excluding the amount eligible for refund of two of the drugs included in the PBRSAs (sorafenib and temsirolimus) that are subject to a mixed mechanism of reimbursement (based on

Table 1 – Performance-based schemes approved in Italy per drug.

Product	Indication	Reimbursement scheme
Azacitidine	Myelodysplastic syndrome, acute myelogenous leukemia	Cost sharing
Bevacizumab	Metastatic colorectal cancer, non–small cell lung cancer, metastatic breast cancer, renal cell carcinoma	Cost sharing
Bortezomib	Multiple myeloma	Cost sharing
Brentuximab	$CD30^+$ Hodgkin's lymphoma relapsed or refractory	Payment by results
Catumaxomab	Malignant ascites, EpCAM+	Cost sharing
Cetuximab	Squamous cell carcinoma of the head and neck, metastatic colorectal cancer (EGFR+ and WT KRAS)	Payment by results, risk sharing
Dasatinib	Newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to previous therapy including imatinib, Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to previous therapy	Cost sharing
Eribulin mesylate	Advanced or metastatic breast cancer	Payment by results
Erlotinib	Metastatic non–small cell lung cancer	Cost sharing
Everolimus	Renal cell carcinoma, neuroendocrine tumor pNET	Payment by results
Gefitinib	Non–small cell lung cancer (mutated EGFR-TK)	Payment by results
Lapatinib	Hormone-positive and HER2+ advanced breast cancer	Payment by results
Lenalidomide	Multiple myeloma	Cost sharing
Nilotinib	Philadelphia chromosome-positive chronic myelogenous leukemia resistant or intolerant to previous therapy that included imatinib, newly diagnosed patients with chronic myelogenous leukemia	Payment by results, cost sharing
Ofatumumab	Chronic lymphocytic leukemia	Cost sharing
Panitumumab	Metastatic colorectal cancer EGFR+ and KRAS WT	Risk sharing
Pazopanib	Renal cell carcinoma	Payment by results
Pegaptanib	Age-related macular degeneration	Payment by results
Plerixafor	Mobilization of hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma	Payment by results
Ranibizumab	Age-related macular degeneration, diabetic macular edema, and macular edema following retinal vein occlusion	Payment by results
Sorafenib	Hepatocellular carcinoma, renal cell carcinoma	Payment by results, cost sharing
Sunitinib	Renal cell carcinoma	Cost sharing
Temsirolimus	Renal cell carcinoma, mantle cell lymphoma resistant to treatment	Payment by results, cost sharing
Trabectedin	Soft tissue sarcomas, relapsed ovarian cancer	Payment by results
Trastuzumab	HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	Payment by results
Vinflunine	Advanced or metastatic transitional-cell carcinoma of the urothelial tract	Payment by results

ALL, acute lymphoblastic leukemia; CD30+, Cluster of Differentiation 30 positive; CML, chronic myeloid leukemia; EGFR+, Epidermal growth factor receptor positive; EGFR-TK, Epidermal Growth Factor Receptor - Tyrosine Kinase; EpCAM+, Epithelial Cell Adhesion Molecule positive; HER2+, Human Epidermal-growth-factor Receptor 2 positive; KRas, Kirsten Rat sarcoma; Ph+, Philadelphia positive; pNET, primitive Neuro-Ectodermal Tumor; WT, Wild-Type.

therapeutic indications), €28.2 million (~68.6%) rely on the discount provided by "cost-sharing" schemes and the rest is accounted for by reimbursement for nonresponders provided by "risk-sharing" (€0.6 million; ~1.5%) and "payment-by-results" (€12.3 million; ~29.8%) schemes.

Considering the high number of registries and the heterogeneity of the mechanisms through which regions/companies/pharmacies/hospitals are actually refunded, the complexity of this system is remarkable. Moreover, health care professionals are not prompted to update the registries, close the patients' files, and submit refund requests on a regular basis, possibly because the actual money to be refunded does not come to the prescribing center itself, but rather to the hospital general budget, thus producing a responsibility gap between the stakeholder that will receive the refund (in this case, the hospital) and the actual person in charge of the reimbursement procedures (the prescribing center).

Given such caveats, a critical reconsideration of the reimbursement processes must take into account the economic impact of the introduction of expensive therapies on public health. As far as efficacy is concerned, it has been given the first place in the negotiation process of a medicinal drug and is considered the main driver for the therapeutic choice. However with the most critical issues in the application of PBRSAs are represented so far by the lack of first-person responsibility for the prescribing centers in the reimbursement procedures and by the fact that refund from manufacturers comes ex post.

"Success Fee": A New Strategy for Performance-Based Agreements

To respond to such critical issues, a novel mechanism has been proposed in Italy for the improvement of the existing PBRSAs. Named "success fee," it consists of an ex post payment to the

Table 2 – Total cost and reimbursement amounts for the period 2006 to 2012 in Italy.

Drug	Reimbursement scheme	Total reimbursement 2007–2012 (€)	Total cost 2006–2012 (€)	% over total cost per single drug	% over total reimbursement
Bevacizumab	Cost sharing	47,419,548	640,859,288	7.4	39.0
Erlotinib	Cost sharing	25,026,477	209,003,042	12.0	20.6
Sorafenib	Payment by results, cost sharing	11,206,335	183,039,972	6.1	9.2
Sunitinib	Cost sharing	9,779,791	268,536,204	3.6	8.0
Cetuximab	Payment by results	3,997,318	323,324,085	1.2	3.3
Bortezomib	Cost sharing	3,730,158	325,321,155	1.1	3.1
Eribulin mesylate	Payment by results	3,713,984	5,470,192	67.9	3.1
Everolimus	Payment by results	3,203,820	31,363,496	10.2	2.6
Lapatinib	Payment by results	2,272,128	58,099,651	3.9	1.9
Gefitinib	Payment by results	1,937,717	40,177,957	4.8	1.6
Panitumumab	Risk sharing	1,796,097	35,586,365	5.0	1.5
Ofatumumab	Cost sharing	1,426,381	3,693,415	38.6	1.2
Trabectedin	Payment by results	1,281,909	36,616,625	3.5	1.1
Vinflunine	Payment by results	940,371	5,529,130	17.0	0.8
Azacitidine	Cost sharing	852,305	57,904,318	1.5	0.7
Pazopanib	Payment by results	772,340	7,597,587	10.2	0.6
Temsirolimus	Payment by results, cost sharing	606,390	5,783,170	10.5	0.5
Dasatinib	Cost sharing	515,065	71,525,433	0.7	0.4
Plerixafor	Payment by results	422,620	3,822,145	11.1	0.3
Trastuzumab	Payment by results	420,688	1,309,896,209	0.03	0.3
Nilotinib	Payment by results	168,226	73,119,135	0.2	0.1
Catumaxomab	Cost sharing	10,696	113,264	9.4	0.0
Total	/	121,500,364	3,696,381,837	/	100.0

Note. The analysis includes cost and reimbursement amounts calculated for each drug included in a reimbursement scheme. Values for percentages of refunded money over the total cost per drug could be as low because for many products the reimbursement scheme is applied only to some of the approved indications (e.g., trastuzumab).

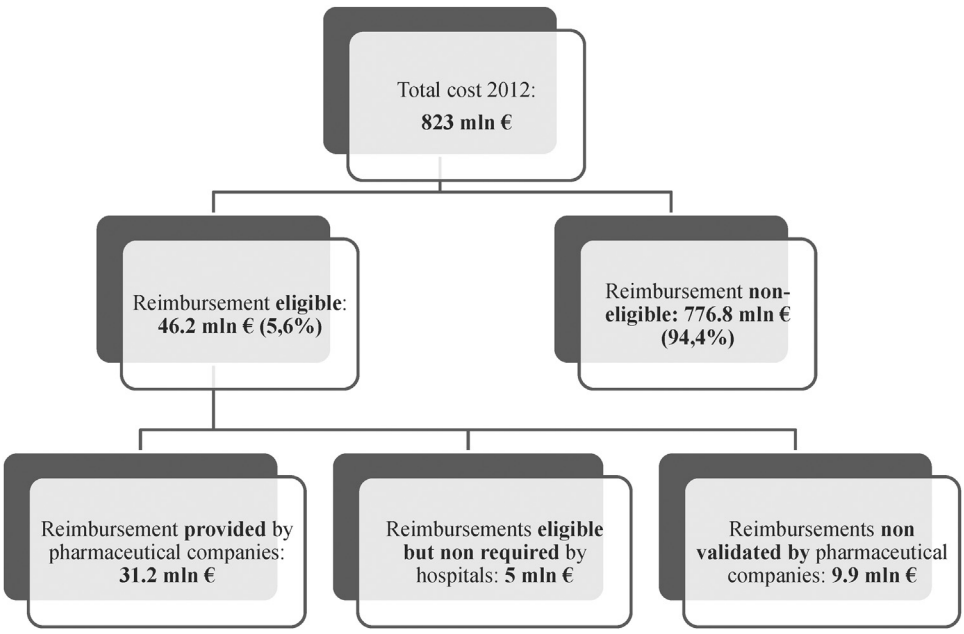

Fig. 1 – Cost and reimbursement amounts for the year 2012. Data are divided into eligible and not eligible for reimbursement. The eligible amount includes reimbursement provided by companies, reimbursement unrequested by hospitals, and nonvalidated.

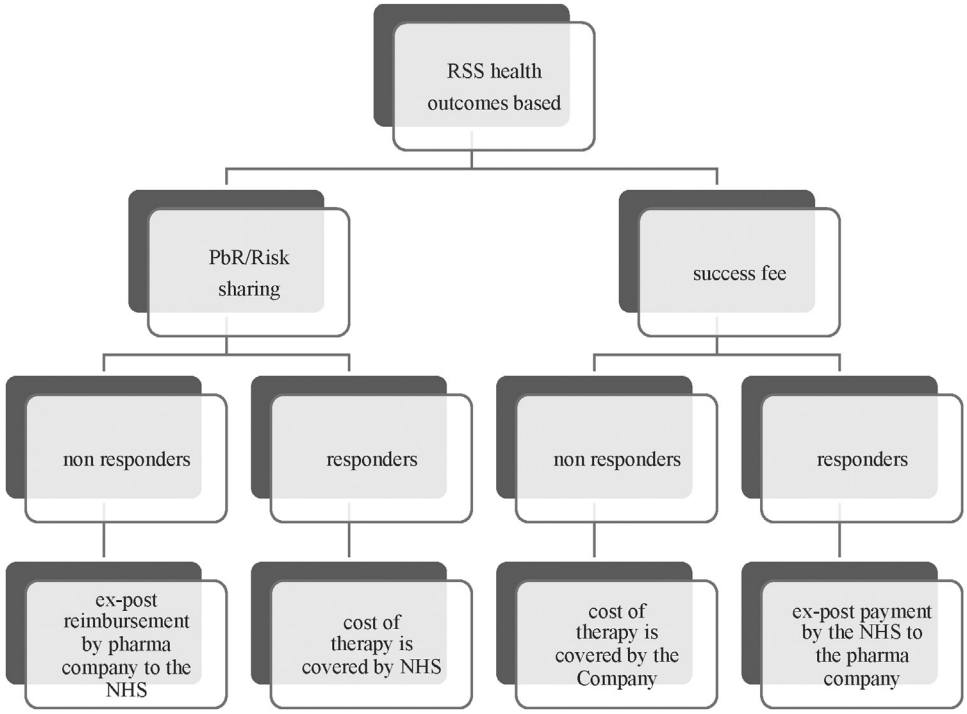

Fig. 2 – Comparison between traditional reimbursement schemes and "success fee." The main feature of "success fee" is the fact that the payment is provided by the NHS only after the evaluation of efficacy. NHS, National Health System.

manufacturer, applied only for those patients receiving a real benefit from therapy. The drug is provided by the company at no initial cost for the NHS. Depending on the disease characteristics, clinical trials data available, and therapy duration, the NHS and the pharmaceutical company establish a temporal threshold for the evaluation of effectiveness to separate responders from nonresponders. Effectiveness is based on clinical outcomes defined specifically for each disease and relies on the efficacy primary end point reported in the registration clinical trial. After the predefined period of treatment, the NHS provides payment only for those treatments that have shown effectiveness. Despite what normally happens with "traditional" PBRSAs, in which reimbursement is made ex post by the manufacturer to the NHS, and is driven by the population of nonresponders, "success fee" consists of an ex post payment instead, made by the NHS to the manufacturer, and is driven by the population of responders (Fig. 2).

Table 3 – Comparison between PBRSAs approved in Italy.

Reimbursement scheme	Positive features	Negative features
Cost sharing	Applied for all treatments; easy to apply (no follow-up required)	Not based on safety/efficacy outcome
Risk sharing	Based on efficacy outcome	Partial reimbursement of the cost for nonresponders; difficult to apply (requires follow-up and notification to the company); no incentive to start and follow up the refund procedure for prescribing centers (refund does not go to the prescribing center but to the hospital)
Payment by results	Based on efficacy outcome; theoric total reimbursement of cost for nonresponders	Difficult to apply (requires follow-up and notification to the company); no incentive to start and follow up the refund procedure for prescribing centers (refund does not go to the prescribing center but to the hospital)
Success fee	Based on efficacy outcome; no cost for nonresponders; prescribing centers are more incentivized (money for nonresponders treatment remain within the center)	Difficult to apply (requires follow-up and notification to the company), but easier than other PBRSAs: no risk to pay for nonresponders; requires a tax bill to be provided by the company to give the drug with initial no payment (solved with a pro forma tax bill at the beginning of treatment, followed by proper tax bill only for responders)

PBRSA, performance-based risk-sharing arrangement.

Moreover, given the application difficulties of traditional PBRSAs, due to the gap between the prescribing center notifying the ineffective treatments and the hospital receiving the refund, with "success fee" the prescribing centers are incentivized to check for ineffective treatments because the eventual savings come directly to the centers.

"Success fee" has been applied for the first time in Italy to negotiate the price of a novel drug indicated for mild-to-moderate idiopathic pulmonary fibrosis, pirfenidone (Esbriet). The drug is provided by the company at no initial cost for the NHS. Between day 165 and 195 after the onset of therapy, the prescribing center certifies the successful or unsuccessful outcome and gives notice to the company promptly. The outcome is considered unsuccessful when a decline in forced vital capacity overcomes a specific absolute value after the first 6 months of treatment. A failure (of any nature) in delivering the certificate to the company is interpreted as a successful treatment and money has to be paid to the manufacturer. This represents probably the most critical issue of "success fee" and requires further improvement. In fact, the NHS will also have to pay for ineffective treatments if the patient's file is not closed within the time point agreed with the manufacturer. One way to overcome this issue could be to couple the possibility to continue drug prescription for a patient after the agreed time point only if the certification about successful or failed therapy has been provided to the manufacturer.

Conclusions

Cost-containment strategies aim to overcome the issue of the adoption of high-cost therapies, such as anticancer drugs, but they represent the final step of a complex process of negotiation.

Our analysis of the application of cost-containment strategies approved in Italy shows several mismanagement and procedural problems deriving from the application of "traditional" PBRSAs such as "payment by results" and "risk sharing." The total amount of money that is actually refunded through the application of such schemes is really trifling, and the larger portion of that amount comes from discounts that are not based on the assessment of an outcome ("cost sharing").

Considered that every procedure may present some limitations in terms of application and overall control, a strategy such as "success fee" may represent a stronger method to ensure both the access of patients to novel therapies and the NHS to share with the manufacturer the risk derived from uncertain efficacy. "Success fee" introduces the concept of an ex post payment to the company applied only for patients receiving a real benefit from therapy, with an initial no cost for the NHS. The most critical difficulties met in the application of the traditional PBRSAs come from the lack of a direct incentive for the prescribing center in notifying ineffective treatments, considering that the potential refund does not go to the center itself but rather to the hospital general budget. In the case of "success fee", prescribing centers are incentivized to check for ineffective treatments (and to notify them to the manufacturer), because they would have to pay for effective treatments only, thus saving money in their own budget in case of inefficacy. "Success fee" may then be proposed for the negotiation processes of other treatments already in the market or yet to come, not only in Italy but also in other countries where the final payer is the NHS. Table 3 presents points of strengths and weaknesses of each of the PBRSAs analyzed in this study.

Finally, because it is accepted that pricing and reimbursement negotiation processes are aimed at linking payment to health outcomes, it would be of benefit to define precise and meaningful end points to be used in clinical trials so that decision makers could adopt strategies that pursue real benefits for patients at an affordable and appropriate cost. The American Society of Clinical Oncology is working to set such end points, taking into account not only the overall survival but also the quality of life and the safety profile of treatments [16]. Based on these considerations, having a clinically meaningful end point in a clinical trial would make it easier to define the value and the consequential price of a drug, thus reducing uncertainty about treatment efficacy.

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