Performance-Based Risk-Sharing Arrangements for Pharmaceutical Products in the United States: A Systematic Review

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ABSTRACT

BACKGROUND: Value for money is a growing necessity in today's U.S. health care system in which drug spending is expected to increase by an average rate of 6.7% yearly through 2025. In response to uncertainty about real-world clinical and economic outcomes for many drugs, health insurers and pharmacy benefit managers (PBMs) have implemented various contracts and arrangements with drug manufacturers that can collectively be described as performance-based risk-sharing arrangements (PBRsAs). Little is known about U.S.-specific PBRsAs for drugs.

OBJECTIVES: To conduct a systematic review of U.S.-specific PBRsAs for drugs to describe (a) trends over time and (b) key aspects including outcome measures and terms of arrangements between stakeholders.

METHODS: A systematic review was conducted in MEDLINE (January 1, 1946–April 1, 2017), Embase (January 1, 1988–April 1, 2017), and the grey literature (up to April 1, 2017) to identify publicly disclosed PBRsAs. Articles and conference abstracts were included if they were published in English and described a U.S.-specific PBRSA for a drug. Articles and conference abstracts were excluded if they only described a PBRSA similar to a money-back guarantee to patients. They were also excluded if they only described a PBRSA between a PBM and a health insurer in which the latter would receive a discount for patients nonadherent to a drug. Results were summarized as counts and percentages.

RESULTS: From the literature review, 26 publicly disclosed PBRsAs were identified. Of these, 16 (62%) were announced or initiated from 2015 to 2017, and 10 (38%) were announced or initiated from 1997 to 2012. Thirteen (50%) PBRsAs involved cardiometabolic indications; 5 (19%) involved oncology indications; and 8 (31%) involved other indications. Categorized by health insurer or PBM, 10 (38%) PBRsAs involved large multistate insurers; 5 (19%) involved the Centers for Medicare & Medicaid Services; 7 (27%) involved regional insurers; 3 (12%) involved PBMs; and 1 (4%) involved multiple unspecified insurers. Regarding the most active drug manufacturers, Amgen initiated 5 (19%) PBRsAs and Novartis initiated 4 (15%). Relative to the initial FDA approval of a treatment, 15 (58%) PBRsAs were announced or initiated within 5 years, and 11 (42%) were announced or initiated more than 5 years later. For data collection, electronic medical record (EMR) data would have been an appropriate source for 12 (46%) PBRsAs; claims data would have been an appropriate source for 11 (42%) PBRsAs; and EMR and claims data would have been appropriate sources for 2 (8%) PBRsAs; no description of the outcome measures was available for 1 (4%) PBRSA.

CONCLUSIONS: The number of publicly disclosed U.S.-specific PBRsAs for drugs has increased over the years. This review's findings confirm the interest of stakeholders in such arrangements and their confidence in the use of the selected outcome measures. Each PBRSA represents a timely collaboration among stakeholders to provide access to a drug while generating evidence to better elucidate its clinical and economic value.

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What is already known about this subject

- Because of uncertainty about real-world clinical and economic outcomes for many drugs, health insurers and pharmacy benefit managers have implemented various contracts and arrangements with drug manufacturers that can collectively be described as performance-based risk-sharing arrangements (PBRsAs).
- A 2010 international review of PBRsAs identified 8 U.S.-specific PBRsAs for the drugs oxaliplatin, irinotecan, cetuximab, bevacizumab, erythropoiesis-stimulating agents, simvastatin, sitagliptin and sitagliptin-metformin, and risedronate sodium.

What this study adds

- This systematic review identified 26 U.S.-specific PBRsAs for drugs announced or initiated from 1997 to 2017.
- This review summarized information related to corresponding drugs, factors surrounding the PBRsAs, stakeholders involved in the PBRsAs, and outcome measures used in the PBRsAs.

Value in health care can be defined in its simplest form as health outcomes achieved per dollar spent on medical care.¹ As an extension of this concept, value-based pricing is the price of health care services that reflects clinical and economic benefits.^{2,3} Although prices of drugs are determined at their launch, finite health care resources and uncertainty around real-world clinical outcomes often limit the uptake of new, innovative treatments.^{4,5} Pharmaceutical companies have identified these issues as key factors contributing to less-than-expected usage and revenue for newly launched drugs.^{4,5} With an increase in drug spending over time, especially for specialty drugs,⁶ health care decision makers have placed great importance on understanding the value of drugs in order to inform purchasing decisions, manage drug spending, and improve the delivery of care.⁷

In response to uncertainty around clinical outcomes for specific drugs, health insurers have implemented various contracts and arrangements with drug manufacturers, which can collectively be described as performance-based risk-sharing arrangements (PBRsAs). Such arrangements include, but are not limited to, value-based contracts, outcomes-based contracts, risk-sharing agreements, coverage with evidence development (CED), and managed entry schemes.⁸ Using the Performance Based Risk Sharing Database, which is

available at the University of Washington School of Pharmacy, a 2014 review of publicly disclosed PBRsAs revealed that Italy had the most arrangements (n=36), followed by the United Kingdom (n=29), Netherlands (n=23), United States (n=18), and Sweden (n=17) from January 1993 to June 2013.⁹ Among these arrangements, the most represented therapeutic areas were oncology (n=77), endocrinology (n=14), neurology (n=10), and cardiology (n=10), and the majority (92%) were for drugs rather than devices or diagnostic tests.⁹

In contrast to other countries in the years leading up to 2013, PBRsAs in the United States focused primarily on CED.⁹ In addition, the majority of these PBRsAs focused largely on devices and surgical procedures as opposed to drugs.¹⁰ CED involves an agreement by a health insurer to provide broader coverage for a promising treatment despite evidence gaps and is contingent on the facilitation of additional collection of data.¹¹ In recent years (2015 to present), however, U.S. interest in drug-related PBRsAs appears to have been revived, driven largely by the launch of new therapies with high price tags for potentially large patient populations (e.g., sacubitril-valsartan, evolocumab, and alirocumab) or for smaller populations but with potentially larger budget impacts (e.g., sofosbuvir and ledipasvir-sofosbuvir).

In response to these demands on the health care system, professional organizations such as the American Society of Clinical Oncology, National Comprehensive Cancer Network, and the Institute for Clinical and Economic Review have developed frameworks and reports that focus on the value of drugs while taking into account economic burden.¹²⁻¹⁴ Memorial Sloan Kettering Cancer Center also released DrugAbacus, which incorporates inputs such as dollars per year, toxicity, novelty, rarity, population burden of disease, cost of development, prognosis, and unmet need to estimate the appropriate prices of oncology drugs based on their perceived value.¹⁵ With specialty drug spending expected to account for approximately 50% of total annual pharmacy spending by 2018,¹⁶⁻¹⁸ in combination with the lack of real-world evidence and robust comparative information of the benefits of many drugs,⁷ PBRsAs can serve as an option to facilitate better value for health care dollars.

Value for money is vital to a health care system that continues to trend upwards in terms of overall drug spending, despite finite health care resources—prescription drug spending is expected to increase by an average rate of 6.7% yearly through 2025, exceeding that of total health care spending (i.e., 5.8%).¹⁹ In view of the lack of a systematic review of U.S.-specific PBRsAs for drugs, the objectives of this review were to (a) provide a greater understanding of PBRSA trends over the years and (b) describe key aspects, including outcome measures and terms, of the arrangements between stakeholders

Methods

Search Strategy and Selection Criteria

A systematic review was first conducted in MEDLINE (January 1, 1946-April 1, 2017) and Embase (January 1, 1988-April 1, 2017) using the following search terms and their nonhyphenated versions (when applicable) as key words: *value-based pricing*, *value-based contract**, *value-based agreement**, *performance-based agreement**, *performance-based scheme**, *price-volume agreement**, *price-volume arrangement**, *outcomes-based contract**, *outcomes-based agreement**, *coverage with evidence*, *conditional coverage*, *conditional reimbursement*, *risk-sharing agreement**, *risk-sharing arrangement**, *outcome guarantee**, *health impact guarantee**, *pay back scheme**, *denial of payment*, *paying for outcomes*, and *no cure no pay*. These search terms were selected based on a review of published literature and grey literature in order to maximize the sensitivity of the search strategy to identify PBRsAs. Articles and conference abstracts were evaluated to minimize any loss of relevant information.

To ensure completeness of the literature review, and using the same search terms, a search of the grey literature (up to April 1, 2017) was performed using Google; the Centers for Medicare & Medicaid Services website; 2015 annual reports of the top 20 pharmaceutical companies by revenue (Pfizer, Roche, Merck, Gilead Sciences, Sanofi, Johnson & Johnson, Novartis, GlaxoSmithKline, AstraZeneca, AbbVie, Amgen, Eli Lilly, Bristol-Myers Squibb, Novo Nordisk, Bayer, Takeda, Boehringer Ingelheim, Astellas, Biogen, and Otsuka)²⁰; 2015 annual reports of the top 10 health insurance companies by market value (UnitedHealth Group, Cigna, Anthem, Humana, Aetna, Molina Healthcare, Centene Corporation, Magellan Health, WellCare, and Health Net)²¹; and 2015 annual reports of the top 3 pharmacy benefit managers (PBMs) by covered lives (Express Scripts, CVS Health, and OptumRx).²²

Inclusion criteria for this systematic review were defined a priori. Articles (e.g., peer-reviewed manuscripts, press releases, and news articles) and conference abstracts were included only if they were in English and mentioned a U.S.-specific PBRSA. Annual reports before 2015 were only evaluated if a PBRSA was identified in the 2015 report (most recent year available at the time of this review). For the grey literature search, only the earliest-identified articles for PBRsAs and articles with additional information on those PBRsAs were included. Articles and conference abstracts were excluded if they only described PBRsAs that were similar to money-back guarantees to patients. They were also excluded if they only described PBRsAs between PBMs and health insurers, in which the latter would receive discounts for patient nonadherence to a drug (this type of PBRSA focuses more on the value of PBM services than on the value of a drug). Given that this systematic review focused on

FIGURE 1 Flow Diagram of Included Articles and Conference Abstracts

^aConference abstracts that appeared separately from articles in MEDLINE and Embase.

^bEarliest-identified articles for PBRSA and articles with additional information on those PBRSA.

PBM=pharmacy benefit manager; PBRSA=performance-based risk-sharing arrangement.

the identification of PBRSA, the PICOS criteria (participants, interventions, comparators, outcomes, study design) were not considered applicable.

After the articles and conference abstracts were retrieved, 2 of the review authors (JY and LC) independently reviewed each article and conference abstract by first screening the title and abstract to determine eligibility for inclusion in the study results. When it was unclear if an article referred to a PBRSA, the article was scheduled for a full-text review. All disagreements were discussed until a consensus was reached. After identifying relevant articles and conference abstracts, the grey literature was reviewed to understand details on the drugs associated with the PBRSA. The sources of information reviewed included drug prescribing information and the U.S. Food and Drug Administration (FDA) website.

Data Extraction and Analyses

One review author (JY) extracted data from each article and conference abstract that met the selection criteria, including the year the PBRSA was announced or initiated, products, disease state, drug manufacturers, health insurer or PBM, description of the PBRSA, and outcome measures of interest. Data on the drug approval year, trade name, same-class competitors and same disease-state competitors, and time from drug approval since the PBRSA was announced or initiated were also recorded based on a review of the grey literature. In addition, based on the primary uses of electronic medical record (EMR) and claims data (for clinical and billing purposes, respectively) and their widespread use,²³ each PBRSA was classified according to its likelihood of using each data type to assess the outcome measures. Other data sources, however, could also be used and

TABLE 1 Summary of Literature Review

Drug (Trade Name)/ Initial Approval Year ^a	Drug Manufacturers ^b	Disease State	Same-Class Competitors/ Same Disease-State Competitors ^b	Year PBRSA Was Announced or Initiated	Time from Approval Since PBRSA Was Announced or Initiated (Years) ^a	Health Insurer/PBM	Description of PBRSA	Outcome Measures	Outcome Measures Assessable Using Claims Data ^c	References
Epoetin alfa (Epoen, Procrit) 1989	Amgen, Ortho Biotech	Anemia	Yes/Yes	1997	8	Health Care Financing Administration (CMS)	CMS will use a 3-month rolling average Hct level for reimbursement of epoetin alfa claims in hemodialysis patients with Hct greater than 36% in any given month, with denial of payment when the 3-month rolling average exceeds 36.5%.	Hct	No	10, 27, 58
Simvastatin (Zocor) 1991	Merck	Hyperlipidemia	Yes/Yes	1998	7	Patients and insurers	Merck will refund patients and insurers up to 6 months of prescription costs if simvastatin plus diet does not help lower LDL cholesterol to target concentrations identified by their doctors.	LDL	No	25, 58
Oxaliplatin (Eloxatin) 2002	Sanofi- Aventis	Colorectal cancer	N/A (CED)/ N/A (CED)	2005	3	CMS	CMS will cover oxalip- latin, irinotecan, cetuximab, and bevacizumab for the off-label treatment of colorectal cancer in the context of an approved clinical trial.	Survival	No	24, 52, 53, 58
Irinotecan (Camptosar) 1996	Pfizer	Colorectal cancer	N/A (CED)/ N/A (CED)	2005	9	CMS		Survival	No	
Cetuximab (Erbix) 2004	ImClone, Bristol-Myers Squibb	Colorectal cancer	N/A (CED)/ N/A (CED)	2005	1	CMS		Survival	No	
Bevacizumab (Avastin) 2004	Genentech	Colorectal cancer	N/A (CED)/ N/A (CED)	2005	1	CMS		Survival	No	
Sitagliptin (Januvia) 2006	Merck	Type 2 diabetes mellitus	Yes/Yes	2009	3	Cigna	Merck will tie what Cigna pays for sitagliptin and sitagliptin-metformin to how well type 2 diabetes patients are able to control blood sugar.	Blood sugar	No	34, 58
Sitagliptin and metformin (Janumet) 2007			Yes/Yes		2					

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varied based on each PBRSA. After the initial data extraction, the other review authors independently reviewed the data table to ensure accuracy of the findings. Note that the risk of bias was not assessed for each included article, since the objective of this systematic review was to identify PBRsAs rather than to assess the validity of study outcomes. Results were summarized as counts and percentages.

Results

We retrieved and screened 472 articles and 297 abstracts (769 records total) from MEDLINE and Embase. After applying the inclusion and exclusion criteria, 11 peer-reviewed articles^{8-10,24-31} and 2 conference abstracts^{32,33} were eligible for inclusion. The grey literature search revealed 22 articles that were eligible for inclusion (Figure 1).³⁴⁻⁵⁵ In the event that

TABLE 1 Summary of Literature Review (continued)

Drug (Trade Name)/ Initial Approval Year ^a	Drug Manufacturers ^b	Disease State	Same-Class Competitors/ Same Disease-State Competitors ^b	Year PBRSA Was Announced or Initiated	Time from Approval Since PBRSA Was Announced or Initiated (Years) ^a	Health Insurer/PBM	Description of PBRSA	Outcome Measures	Outcome Measures Assessable Using Claims Data ^c	References
Risedronate (Actonel) 1998	Procter & Gamble, Sanofi- Aventis	Osteoporosis	Yes/Yes	2009	11	Health Alliance	Procter & Gamble and Sanofi will reimburse Health Alliance for the costs of treating nonspinal fractures suffered by patients taking risedronate.	Nonspinal fracture	Yes	35, 58
Interferon beta-1a (Actonel) 1996	EMD Serono	Multiple sclerosis	Yes/Yes	2011	15	Cigna	Cigna will track the percentage of hospitalization and emergency room visits avoided by people using interferon beta-1a by tracking medical claims in order to determine whether a relapse was the cause. The company will use 2010 as a baseline, looking at data from medical, pharmacy, and lab claims, and measure members' MPR. This represents a multitiered contract where discounts will be based on ranges for medication adherence, and then on customers with multiple sclerosis being relapse-free.	Hospitalization, emergency room visit, adherence	Yes	36, 37, 58
Interferon beta-1a (Rebif) 1996	EMD Serono	Multiple sclerosis	Yes/Yes	2012	16	Prime Therapeutics (PBM)	EMD Serono will pay rebates to Prime Therapeutics for use of interferon beta-1a if patients who are on the drug have a higher overall total cost for their plans than patients on a different multiple sclerosis drug, or if medication adherence rate remains above a specified level. Prime Therapeutics will evaluate data pertaining to health outcomes and medication adherence of patients a number of times throughout the contract in order to determine total cost of care, including medical and pharmacy costs.	Cost, adherence	Yes	38, 58
Fingolimod (Gilenya) 2010	Novartis	Multiple sclerosis	No/Yes	2015	5	Humana	Not available	Not available	Not available	39, 58

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TABLE 1 Summary of Literature Review (continued)

Drug (Trade Name)/ Initial Approval Year ^a	Drug Manufacturers ^b	Disease State	Same-Class Competitors/ Same Disease-State Competitors ^b	Year PBRSA Was Announced or Initiated	Time from Approval Since PBRSA Was Announced or Initiated (Years) ^a	Health Insurer/PBM	Description of PBRSA	Outcome Measures	Outcome Measures Assessable Using Claims Data ^c	References
Ledipasvir and sofosbuvir (Harvoni) 2014	Gilead	Hepatitis C	Yes/Yes	2015	1	Cigna	An innovative outcomes incentive alignment will be developed based on actual SVR results across Cigna's customer population.	SVR	No	40, 58
Evolocumab (Repatha) 2015	Amgen	Hyperlipidemia	Yes/Yes	2015	0	CVS Health (PBM)	Amgen will link the net price of evolocumab to expected LDL cholesterol reductions and anticipated appropriate patient use.	LDL	No	50, 58
Evolocumab (Repatha) 2015	Amgen	Hyperlipidemia	Yes/Yes	2016	1	Harvard Pilgrim	Amgen will provide Harvard Pilgrim with an enhanced discount if the reduction in LDL levels for Harvard Pilgrim members is less than what was observed during clinical trials. In addition to the outcomes guarantee, the agreement will provide for additional discounts if utilization of the drug exceeds certain levels. The contract also contains an adherence provision that conditions discounts on whether patients reliably take the drug.	LDL, adherence	No (LDL), Yes (adherence)	26, 51, 58
Alirocumab (Praluent) 2015	Sanofi, Regeneron	Hyperlipidemia	Yes/Yes	2016	1	Cigna	Sanofi/Regeneron will further discount the cost of alirocumab if Cigna's customers are not able to reduce LDL levels at least as well as what was experienced in clinical trials.	LDL	No	41, 58
Evolocumab (Repatha) 2015	Amgen	Hyperlipidemia	Yes/Yes	2016	1	Cigna	Amgen will further discount the cost of evolocumab if Cigna's customers are not able to reduce LDL levels at least as well as what was experienced in clinical trials.	LDL	No	41, 58
Sacubitril and valsartan (Entresto) 2015	Novartis	Chronic heart failure	No/Yes	2016	1	Cigna	The arrangement ties financial terms to how well sacubitril-valsartan improves the relative health of Cigna's customers. The primary outcome measure is the reduction in proportion of customers with heart failure hospitalizations.	Hospitalization	Yes	42, 43, 58

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TABLE 1 Summary of Literature Review (continued)

Drug (Trade Name)/ Initial Approval Year ^a	Drug Manufacturers ^b	Disease State	Same-Class Competitors/ Same Disease-State Competitors ^b	Year PBRSA Was Announced or Initiated	Time from Approval Since PBRSA Was Announced or Initiated (Years) ^a	Health Insurer/PBM	Description of PBRSA	Outcome Measures	Outcome Measures Assessable Using Claims Data ^c	References
Sacubitril and valsartan (Entresto) 2015	Novartis	Chronic heart failure	No/Yes	2016	1	Aetna	The arrangement is based on sacubitril-valsartan replicating results achieved in clinical trials (i.e., reduction in hospitalizations and cardiovascular deaths related to heart failure).	Hospitalization, survival	Yes (hospitalization), no (survival)	43, 58
Dulaglutide (Trulicity) 2014	Eli Lilly	Type 2 diabetes mellitus	Yes/Yes	2016	2	Harvard Pilgrim	In exchange for preferred status for dulaglutide on Harvard Pilgrim's formulary, Harvard Pilgrim will pay Eli Lilly a lower net price for dulaglutide if fewer patients taking it achieve an HbA1c value of less than 8% compared with patients taking other GLP-1 receptor agonists, and a higher net price if patients taking dulaglutide have better outcomes than patients taking other competing drugs.	Blood sugar	No	44, 45, 58
Sitagliptin (Januvia) 2006	Merck	Type 2 diabetes mellitus	Yes/Yes	2016	10	Aetna	Merck will pay rebates if certain portions of patients in the insurer's population who are prescribed the drugs do not achieve treat- ment goals and require further therapy, as deter- mined by their physicians.	Further therapy	Yes	46, 47, 58
Sitagliptin and metformin (Janumet) 2007					9					
Sacubitril and valsartan (Entresto) 2015	Novartis	Chronic heart failure	No/Yes	2016	1	Harvard Pilgrim	Novartis will provide Harvard Pilgrim with a discount if sacubitril- valsartan does not reduce hospitalizations for congestive heart failure by a given level.	Hospitalization	Yes	48, 58
Gefitinib (Iressa) 2015	AstraZeneca	Lung cancer	Yes/Yes	2015	0	Express Scripts (PBM)	AstraZeneca will reim- burse costs of gefitinib if a patient stops treatment before third prescription fill.	Prescription fill	Yes	49, 58
Prasugrel (Effient) 2009	Eli Lilly	Acute coronary syndrome	Yes/Yes	2016	7	Humana	Eli Lilly will tie reimbursements for prasugrel to the rate of hospitalizations among patients who take it.	Hospitalization	Yes	49, 58

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TABLE 1 Summary of Literature Review (continued)

Drug (Trade Name)/ Initial Approval Year ^a	Drug Manufacturers ^b	Disease State	Same-Class Competitors/ Same Disease-State Competitors ^b	Year PBRSA Was Announced or Initiated	Time from Approval Since PBRSA Was Announced or Initiated (Years) ^a	Health Insurer/PBM	Description of PBRSA	Outcome Measures	Outcome Measures Assessable Using Claims Data ^c	References
Ticagrelor (Brilinta) 2011	AstraZeneca	Acute coronary syndrome	Yes/Yes	2016	5	University of Pittsburgh Medical Center's regional health plan	AstraZeneca will cover a portion of the costs of treating patients who have additional heart attacks after taking ticagrelor if the rate of heart attacks exceeds a threshold.	Heart attack	Yes	49, 58
Teriparatide (Forteo) 2002	Eli Lilly	Osteoporosis	No/Yes	2017	15	Harvard Pilgrim	Eli Lilly will reduce the cost of teriparatide for Harvard Pilgrim if mean- ingful improvements in the drug's persistence are achieved compared with the baseline level of adher- ence observed in Harvard Pilgrim's population.	Persistence	Yes	54, 58
Etanercept (Enbrel) 1998	Amgen	Rheumatoid arthritis	Yes/Yes	2017	19	Harvard Pilgrim	The 2-year contract for etanercept is based on an effectiveness algorithm consisting of 6 criteria (including patient compli- ance, switching or adding drugs, dose escalation, and steroid interventions) that serve as a global mea- sure of the drug's impact. Harvard Pilgrim will pay less for etanercept if patient scores are below a specified level. The contract also specifies the tracking of patient adher- ence to the drug.	Compliance/ adherence, switching drugs, adding drugs, dose escalation, steroid interventions (Last criteria not stated)	Yes	55, 58

^aBased on the first indication approved by the U.S. Food and Drug Administration.^bAt the time the PBRSA was announced or initiated.^cBased on the assumption that claims data would be an appropriate data source; electronic medical record data were assumed to be an appropriate source for all other outcomes.

CED=coverage with evidence determination; CMS=Centers for Medicare & Medicaid Services; GLP-1=glucagon-like peptide-1; HbA1c=hemoglobin A1c; Hct=hematocrit; LDL=low-density lipoprotein; MPR=medication possession ratio; N/A=not applicable (drug not approved at the time for treatment of the corresponding disease state and thus had no actual competitors); PBM=pharmacy benefit manager; PBRSA=performance-based risk-sharing arrangement; SVR=sustained virologic response.

multiple sources presented the same information on a PBRSA, the earliest-published source was included in Table 1, which summarizes the results; other sources were also included in Table 1 if they provided additional information on a PBRSA beyond that of the earliest-published source.

In total, 26 PBRsAs were identified. Among them, 16 (62%) were announced or initiated from 2015 to 2017, and 10 (38%) were announced or initiated from 1997 to 2012. In relation to disease state, 13 (50%) PBRsAs involved cardiometabolic indications (i.e., type 2 diabetes mellitus, acute coronary syn-

drome, hyperlipidemia, and chronic heart failure); 5 (19%) involved oncology indications (i.e., colorectal cancer and lung cancer); and 8 (31%) involved other indications (i.e., anemia, osteoporosis, multiple sclerosis, hepatitis C, and rheumatoid arthritis; Table 1).

Categorized by health insurer or PBM, 10 (38%) PBRsAs involved large multistate insurers (Cigna, n=6; Humana, n=2; and Aetna, n=2); 5 (19%) involved the Centers for Medicare & Medicaid Services; 7 (27%) involved regional insurers (Harvard Pilgrim, n=5; Health Alliance, n=1; and University

of Pittsburgh Medical Center's regional health plan, $n=1$); 3 (12%) involved PBMs (Prime Therapeutics, CVS Health, and Express Scripts); and 1 (4%) involved multiple unspecified insurers. The drug manufacturer most actively involved with initiating PBRsAs was Amgen ($n=5$, 19%), followed by Novartis ($n=4$, 15%), Sanofi ($n=3$, 12%), Merck ($n=3$, 12%), and Eli Lilly ($n=3$, 12%; Table 1).

As for FDA approval date for a treatment, 15 (58%) PBRsAs were announced or initiated within 5 years after approval, and 11 (42%) were announced or initiated more than 5 years after approval. For PBRsAs in which the drug had a same-class competitor and/or same disease-state competitor at the time, 17 (65%) had a same-class competitor and same disease-state competitor; 5 (19%) had only a same disease-state competitor (i.e., drugs had novel mechanisms of action); and 4 (15%) were unique in that reimbursement was based on coverage with evidence development (CED), meaning that the drugs were not yet approved for the treatment of the corresponding disease states and thus had no actual competitors (Table 1).

For the data collection method, EMR data would have been an appropriate source for 12 (46%) PBRsAs; claims data would have been an appropriate source for 11 (42%) PBRsAs; and EMR and claims data would have been appropriate sources for 2 (8%) PBRsAs. An appropriate data source could not be determined for 1 (4%) PBRSA because a description of its outcome measures was not available.

Outcomes that could be measured using claims data include hospitalizations ($n=5$), adherence/compliance ($n=5$), persistence ($n=1$), switching drugs ($n=1$), adding drugs ($n=1$), dose escalation ($n=1$), steroid interventions ($n=1$), emergency room visits ($n=1$), nonspinal fractures ($n=1$), cost ($n=1$), further therapy ($n=1$), prescription fills ($n=1$), and heart attacks ($n=1$). Outcomes that could be measured using EMR data include low-density lipoprotein ($n=5$), survival ($n=5$), blood sugar ($n=2$), hematocrit ($n=1$), and sustained virologic response ($n=1$; Table 1).

Discussion

This systematic review identified 26 U.S.-specific PBRsAs for drugs that were announced or initiated from 1997 to 2017. More than half occurred from 2015 to 2017, suggesting a change from what appeared to be a slowing pace of initiation of PBRsAs worldwide in 2012 and 2013.⁹ Furthermore, these U.S.-specific findings are unique in that only 15% of the identified PBRsAs involved CED, and only 19% involved oncology indications. These findings compare with 41% and 52% of PBRsAs worldwide (92% which were for drugs) that involved CED and oncology indications, respectively.⁹ These observed differences between the United States and other countries reflect the priorities of regional stakeholders and the extent to which they publicly disclosed PBRsAs.

At a basic level, PBRsAs create access to drugs for patients, while addressing uncertainty in clinical and economic outcomes, and can thus function as effective coverage and reimbursement mechanisms.⁹ Drug manufacturers benefit from PBRsAs by ensuring coverage for specific drugs, while health insurers and PBMs benefit by linking a drug's price to its real-world performance or clinical efficacy (in the case of CED). With drug pricing under increased scrutiny from the public, health insurers, and PBMs, in conjunction with the recent launch of high-cost specialty agents and the aggressive pricing practices of several generic drug manufacturers,⁵⁶ it is likely that this upward trend in PBRsAs will continue.

Factors Associated with PBRsAs

Various factors are associated with the implementation of the PBRsAs identified in this review. Examples of such factors include the recent launch of a high-grossing treatment (i.e., sofosbuvir),⁵⁷ same-class competitors, and same disease-state competitors. With the 2013 launch of sofosbuvir, one of the best-selling drugs in its first year on the market,⁵⁷ health insurers likely became much more sensitized to the budget impacts associated with the inclusion of costly drugs on their formularies, which may have influenced the uptick in PBRsAs in 2015 and 2016.

Also, among drugs in which PBRsAs were identified, most had competitors (within the same class, for the same disease state, or both) at the time of initiation of the PBRsAs.⁵⁸ Competitive pressure creates competition for drug access to patients, especially for costly agents; for example, the initiation of a PBRSA for ledipasvir-sofosbuvir in 2015,⁴⁰ 1 year after its approval and the introduction of its competitor ombitasvir-paritaprevir-ritonavir.⁵⁸ Furthermore, many drugs for which we identified PBRsAs appear to lack head-to-head clinical trials with the standard of care for their approved indications.⁵⁸ At the time of approval for these drugs, and before the PBRsAs were initiated, there was likely considerable uncertainty with regards to their efficacy and safety versus the standard of care. Combined with a lack of real-world evidence at the time of drug approval, the previously mentioned factors represent compelling reasons for health insurers and PBMs to engage with drug manufacturers to initiate PBRsAs.

The high per-member-per-year (PMPY) spend on various therapeutic areas contributes to the needs of health insurers for more value-based approaches to cost management. In the context of Express Scripts's 2016 spend for its commercially insured population and the PBRsAs that were identified in this systematic review, diabetes (\$108.80 PMPY), hyperlipidemia (\$38.45 PMPY), high blood pressure/heart disease (\$34.52 PMPY), multiple sclerosis (MS; \$58.63 PMPY), oncology (\$60.70 PMPY), and hepatitis C (\$25.26 PMPY) ranked in the top 15 therapy classes.⁵⁹ Among traditional drugs, sitagliptin ranked sixth in PMPY spend in 2016 (\$8.66 PMPY).⁵⁹

Based on the assumption of similar trends for other health insurers in diabetes drug spending in previous years and the availability of other approved dipeptidyl peptidase-4 inhibitors, this assumption may explain Merck's willingness to engage in a PBRSA for sitagliptin and sitagliptin-metformin with Aetna in 2016.^{46,47} Furthermore, among specialty drugs, ledipasvir-sofosbuvir ranked fifth in PMPY spend in 2016 (\$9.86); fingolimod ranked seventh in PMPY spend in 2016 (\$8.48); and among MS drugs, interferon beta-1a ranked fourth in PMPY spend in 2016.⁵⁹ Assuming similar spending trends for other health insurers in previous years, and given the availability of other competitors for the 3 previously mentioned specialty drugs, PBRsAs were likely initiated for each of them in order to manage drug costs.

Drug spending appears to be associated with the initiation of specific PBRsAs, which will most likely continue trending upwards as health insurers and PBMs attempt to separate drug spending from prescription volume. In addition, a lack of transparency among all stakeholders involved in PBRsAs will likely persist into the future.⁹ Unless stakeholders publicly disclose PBRsAs, their relation to costly therapy classes, costly drug classes, and other factors will be unknown.

Over half of the PBRsAs identified in this systematic review involved drugs with cardiometabolic indications. Given the large number of Americans affected by diabetes (30.3 million) and coronary heart disease (15.4 million, inclusive of myocardial infarction, angina pectoris, heart failure, stroke, and congenital cardiovascular defects),^{60,61} it is not surprising that health insurers and PBMs are interested in managing the high costs associated with these disease states.⁵⁹ As the American population continues to age and the proportion of individuals aged 65 years and above continues to grow, health insurers and PBMs will increasingly focus on managing costs of drugs with the potential for high budget impact. PBRsAs can offer an attractive alternative to traditional rebates for high-cost drugs or those with large target populations. Health insurers can align payments for drugs with the value they create, while drug manufacturers in turn will receive incentives to continue developing new treatments.

Implementation of PBRsAs

To establish viable PBRsAs, stakeholders should evaluate key factors such as the availability of existing data systems, existence of mutually acceptable measures (ideally with short-term responses), and reasonable proxies for clinical outcomes (if needed).⁹ Low administrative burden and acceptable monitoring and evaluation costs are also critical to the successful implementation of PBRsAs.⁸ Based on the outcome measures, multiple PBRsAs with certain health insurers, and data collection methods that were identified in this systematic review, it appears that many of the previously mentioned barriers to implementation have been overcome

by stakeholders. Given the availability of claims data,⁸ the frequent use of claims data by PBMs and health insurers,²³ and the frequent use of real-world evidence by manufacturers,²³ the following discussion will focus on outcome measures available in claims data to better understand the considerations and implications of their use in PBRsAs.

The number of prescription fills for a drug and persistence on a drug (i.e., whether a patient's length of therapy meets or exceeds a specified threshold⁶²) represent measures contained in claims data that can serve as proxies for drug effectiveness. These measures are based on the assumption that patients who continue taking specific drugs do so because the drugs are working for them. Claims data also allow for an evaluation of adherence (also referred to as compliance⁶²). Although it is not explicitly stated for most of the PBRsAs identified in this systematic review, adherence provisions (e.g., using medication possession ratio) likely exist for many arrangements where outcomes can be influenced by whether a patient reliably takes a drug²⁶; this is observed in the cases of evolocumab,²⁶ interferon beta-1a,³⁶⁻³⁸ and etanercept.⁵⁵ Despite the utility of measuring adherence in PBRsAs, interpretations of adherence will always be subject to the limitation of unknown timing of doses and whether patients actually took their doses.⁶²

Other measures contained in claims data that can serve as proxies for actual outcomes include hospitalizations, emergency room visits, further therapy, switching drugs, adding drugs, dose escalation, and steroid interventions. These measures estimate disease worsening in the absence of claims data for the clinical stage of a disease. In the case of hospitalizations and emergency room visits, these outcomes also have direct cost implications that are of interest to health insurers. In the context of costs, however, no PBRSA identified in this review evaluated the performance of a drug based on costs before and after treatment initiation. Such an approach would directly address concerns of health insurers regarding the budgetary impact of treatments but would not incorporate other important aspects of value such as comparative effectiveness, comparative safety, cost-effectiveness, mechanism of action, indirect costs, and mode of administration.

Limitations

This systematic review has some limitations to consider. The main limitation is the lack of publicly available data on every PBRSA between drug manufacturers and health insurers or PBMs. Taking into account the PBRsAs identified in this review, it should be noted that they likely represent a minority of the total number in place between drug manufacturers and health insurers or PBMs. Anthem, for example, does not publicly disclose its PBRsAs, along with many drug manufacturers.⁶³ Humana had 15 PBRsAs for drugs in effect as of November 2016, but only 2 were identified in this review; UnitedHealth Group had 1 in effect as of May 2016 but did not provide

details; and Aetna only confirmed 2 as of November 2016 but would not disclose possible others.⁶³ This lack of public disclosure is further reinforced by a search of the 2015 annual reports of pharmaceutical companies, health insurance companies, and PBMs (see Methods section for details), which yielded no specific data on PBRsAs and thus supported previous findings that many are not publicly disclosed.⁹

Conclusions

The number of publicly disclosed U.S.-specific PBRsAs for drugs has increased over the years as the need to demonstrate value for money has become more important in paying for health care. The findings of this systematic review likely underestimate the total number of PBRsAs but, nonetheless, confirm the interest of stakeholders in such arrangements and their confidence in the use of the selected outcome measures. Also, our results suggest that barriers to initiating PBRsAs have decreased over time. Finally, each PBRSA represents a timely collaboration among stakeholders to provide access to a drug, while generating evidence to better elucidate its clinical and economic value.

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