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The Six Stages to a Successful Value-Based Risk-Sharing Agreement

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Contents

Certara Market Access Guide
The Six Stages to a Successful Value-Based Risk-Sharing Agreement

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Methodology

This paper is part of a series based on 15 semi-structured interviews with managed care experts and pharmaceutical executives, a comprehensive review of secondary research, survey data and grey literature including more than a dozen contract case studies and industry presentations.

Data analysis was supported by an innovative contracting team of Certara consultants with experience in the design of performance agreements in the US, Italy, France and UK. To preserve confidentiality, the managed markets interviewees for this research are not quoted in this release of the report. Any specifically attributed statements in this document are sourced from media reports or other material already available in the public domain.

A Six-Stage-Journey to the Successful Agreement

Against the background of our relevant payer contracting experience, we have found that the pursuit of a systematic six-stage-process can boost the chances of achieving a successful OBA. In this chapter we will illustrate each stage with concrete business applications and examples. The experiences are based on practitioners' insights and abstracted from our insights on the implementation of recent OBAs – some disclosed, most of them kept out of the public domain.

KEY FACTORS

Six Stages to enhance OBA success

1 Choose simple yet specific outcomes, time horizon, and performance reference

2 Predict outcomes within the health plan population and identify key risks

3 Adapt agreement and payment structures to identified risks

4 Clarify data sources and methods to measure the performance

5 Anticipate deal governance and approach to issue resolution

6 Consider enhancing your OBA with "beyond the pill" interventions

Situation: Type of uncertainty	Payer goals	Manufacturer goals
Clinical benefit in the real-life	Avoid overpaying for uncertain outcomes	Avoid arbitrarily high rebates and potentially allow for premium payments; generate new evidence
Economic impact	Prevent negative budget impact and limit volatility	Secure premium price based on projected economic benefits
Market penetration	Gain savings from competitive play	Ensure robust market uptake or limit erosion

FIGURE 16
What payers and manufacturers are typically trying to solve when pursuing an OBA

For anyone considering the pursuit OBAs, it is fundamentally important to be clear on the exact rationale behind the approach. As we have argued earlier, OBAs are an effective tool to manage uncertainty, but as such they are not required for just any product. Let's revisit three typical situations where OBAs are particularly relevant:

■ When there is significant uncertainty around a meaningful clinical benefit in the real-life

■ When there is significant concern around the potential economic impact

■ When there is significant uncertainty around the ability of the product to penetrate the market.

Identifying these situations is key, as it will provide the source for the internal support in your organization but will also be the foundation of a continuous alignment with your counterparts, making sure there is a shared interest in seeing the agreement come to fruition. Figure 16 offers a summary of core interest for payers and the manufacturers to implement an OBA in each of these situations.

These situations can be the result of different root causes. For example, the uncertainty on real-life clinical benefits can arise from limited data collected in the pivotal studies (e.g., accelerated approvals or rare disease products).

It can also be triggered by a difference in expectations between regulatory agencies and payers for what the outcomes of interest should be (e.g., use of surrogate endpoints for approval). Additionally, the patient characteristics and conditions of use can often differ significantly from those in the clinical studies and can potentially lead to poorer or better effectiveness and safety. The uncertainty on the economic impact can be a result of the uncertainty on the outcome (e.g., reduction in myocardial infarctions for cardiovascular products), but also more simply because of the lack of robust long-term data (e.g., reduction in liver transplant for HCV).

Another common cause is the high volatility in the case of rare diseases, where treatments typically target a limited number of patients, but with a high unit price. Finally, the uncertainty on market penetration is often the result of either two similar products entering the market simultaneously (e.g., anti PCSK9 antibodies), a late entrant position with limited clinical differentiation and/or a highly competitive environment (e.g., diabetes market). While the specific root causes are not critical to initially decide on whether to pursue an OBA, their identification is paramount to ensure the design and implementation of the OBA will be tailored to the specific situation at hand.

Once you have gathered clarity of purpose and the confidence that it might be of benefit to explore an OBA, the question becomes "how to go about it". What we proceed with in this chapter are practical suggestions that can guide you in the design and implementation of an OBA that is robust and set up for success.

KEY FACTORS

Where does OBA leadership originate in the pharmaceutical organization?

There are of course various entry-points for the OBA discussion. But we have observed four common trajectories for how OBAs emerge:

1 A principal mandate by senior management, and thus priority focus for the BU and/or particular assets

2 Initiated or sponsored by a brand lead, as potential contracting scenario

3 Explored by the market access or designated innovative contracting team

4 Recommended by strategically-minded HEOR leaders identifying potential uncertainty around effectiveness.

Those four sources often interlink in the OBA journey. Still, the experience of internal stakeholders at manufacturers with OBAs in the market suggests that an OBA project is very unlikely to become a serious consideration without an internal champion (a "sponsor") to drive the process from one of these functional areas to the other groups.

Here, the impact of a public commitment by senior executives cannot be understated: It shows that contracting innovation is culturally endorsed and incentivizes pro-active exploration of non-traditional approaches as a genuine commercial opportunity. Or, in other words, that value-driven pricing has become a top-management priority.

Healthcare utilization rates (e.g., inpatient hospitalizations, observation stays, emergency department visits)	*Adverse event rates*
Hard clinical endpoints (e.g., myocardial infarction, cardio-vascular composite endpoints, death)	*Laboratory values (e.g., hemoglobin A1c for patients with diabetes)*
Cancer-free survival, progression-free survival	*Quality of life, activities of daily living (i.e. patient-reported outcomes)*
Cure rates	*Medication adherence / Medication persistence*

FIGURE 17
Outcome measures to consider for OBA

STAGE 1

Choose Simple Yet Specific Outcomes, Time Horizon, and Performance Reference

The first decision to be made in the design of an OBA is the choice of outcome against which performance and payments will be indexed. Manufacturers and payers often rely on the primary endpoint of the pivotal clinical study. Still, a few considerations need to be taken into account before jumping to that conclusion. First, the endpoint has to be relevant from a payer perspective. This relevance can be driven by significant population health benefits, significant quality of life improvements for the patients, or the promise of healthcare cost reductions. Second, the partners have to make sure that the outcome will have enough specificity to ensure

the observed performance can be attributed to the treatment without any doubt. For example, in oncology, disease-specific mortality should be preferred to overall mortality and for cardiovascular or respiratory conditions, disease-related hospitalizations (e.g., myocardial infarction- or stroke-related, asthma exacerbation-related) is a better choice than overall hospitalizations. Third, the selected outcome has to be measurable with reasonable effort, so that the cost of implementing the OBA does not become a significant roadblock. The typical data sources include health insurers' claims data, readily available electronic health records, and dedicated data collection

through a targeted ad-hoc study or registry. While simplicity is often an important driver, it is interesting to note that some contracts have been successfully implemented with relatively sophisticated outcomes and measures. One example is the agreement between Genentech and Priority Health for Avastin (bevacizumab) in first line treatment of non-small-cell lung cancer (NSCLC). It was based on PFS, which was measured through EHR data acquired primarily through a third party exchange platform, completed with ad-hoc direct request to the provider when needed (see Section 4 for further discussion about measure and evaluation of the outcome).

Once the outcome has been selected, the partners need to define specifically on what basis the payments will be triggered. For this a time horizon must be set, potentially along with a reference for population-level outcomes. While the time horizon must remain reasonably short (typically within 1-2 years), multiple options exist and should be thought through carefully. For patient-level outcomes, a minimum duration of treatment can be included (e.g., cancer-specific deaths arising after at least 3 months on treatment). A maximum duration can also be included but is less common. For population-level outcomes a specific duration of treatment is typically selected (e.g., average LDL-C level after 1 year on

treatment in the health plan population). Additionally, a reference has to be provided to determine whether or not the outcomes are met. Oftentimes the reference is the outcome observed in the clinical trial, but there are other options such as the possible interest in using a comparator treatment in the plan population. The latter can be particularly relevant when there is uncertainty around the relative effectiveness of the new treatment vs. the standard of care in real-life. Another important situation is the case of combined interventions (drug combinations or drug/disease management program). In that case the reference could potentially be the outcome observed in patients receiving only one of the two interventions.

STAGE 2

Predict Outcomes within the Health Plan Population and Identify Key Risks

Therapies often perform differently in the real-life compared to the clinical trial setting. The phenomenon has been described as the "efficacy-to-effectiveness" gap mentioned earlier. A commonly-held belief is that performance is always reduced in the real-life, but there are numerous examples of treatments performing better than in the RCT (e.g., long acting dopamine agonists in schizophrenia, anti-IgE mAb in asthma). There are several factors that can influence real-life effectiveness, and they can be grouped into two categories: drug use

factors and patient population factors. Drug use factors include patterns of use, dose, duration of treatment, past history of exposure, co-prescription, and adherence to treatment. Patient population factors include age, gender, behaviors, co-morbidities, disease stage and severity, genetic and risk factors relevant to the disease. Furthermore, these factors are in turn influenced by the health system (e.g., coverage/reimbursement, medical practice, or screening policies influence which patients receive a treatment and how it is used). The so-called "Drivers of

Effectiveness" (DoE) framework, which originated from Analytica Lasers' participation in "GetReal", part of the EU Innovative Medicines Initiative, is illustrated in Figure 18.

FIGURE 18

Drivers of effectiveness: Framework of factors influencing effectiveness of therapies in the real-life
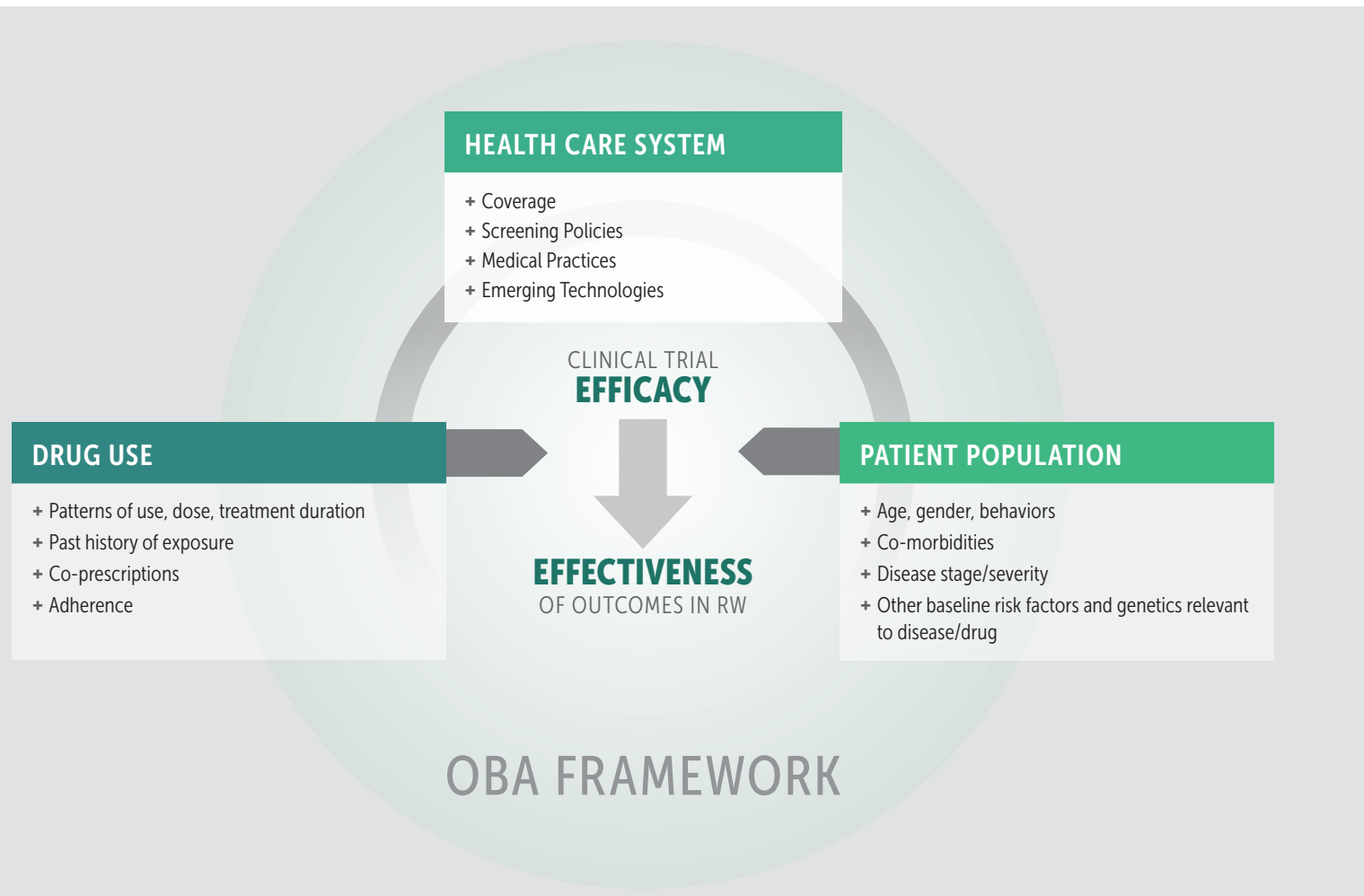
For real-life effectiveness to differ from clinical efficacy, the distribution of patients along some of these factors has to differ significantly in the real-life compared to the clinical trial setting and there needs to be a meaningful interaction between the factor(s) and the outcome. Based on our experience, there is usually a limited set of factors that truly influence effectiveness and the interacting effects are mostly universal. The relevant factors can be identified through previous studies reported in the literature, sometimes based on your own clinical data, or by setting up ad-hoc studies.

What needs to be remembered is that the interaction between these factors and the drug efficacy is actually the same – whether you are looking at pivotal clinical trials or the real world. While the drug properties don't change from population to population, the distribution of risk factors and effect modifiers does.

That is why drug effectiveness appears different in the OBA context. A clear understanding how this framework plays out in the relevant context enables robust estimates of effectiveness as we concentrate on exactly these interactions. Of course, the more data that can be integrated, both 'on the drug' and on informing the characteristic of the population in real life, the better.

Once the factors are identified and their effects understood, it becomes possible to build a model that will be able to predict the real-life effectiveness. This model can then be used for different countries and health plans, provided the distribution of the influencing factors is understood in the populations of interest. The key benefit of the predictive approach is that it enables the manufacturer to quantify the multiple sources of variance and uncertainty that will be encountered in the execution of an outcomes-based agreement, which are related to:

- the difference between the real-life versus clinical trial setting discussed above

- the inter-patient variability

- the effect of time, including both the intrinsic evolution of the disease and outcome, as well as potential changes in how, or by whom, the drug is being used.

While any model in itself does not reduce the uncertainty (without which an OBA would be rather pointless), it is essential to understand source and magnitude in order to frame and provision the contract adequately and manage the risk properly. Once the model offers a solid foundation of your understanding on real world performance, it can be useful to set up a baseline pilot for a preliminary discussion of mutual perspectives, data management and financial implications (paid for under "Fair Market Value" fees for staff time and resource needs to analyze data). This would precede the execution of the full-fledge agreement and can enhance further stages of the implementation.

HEALTH CARE SYSTEM

+ Coverage
+ Screening Policies
+ Medical Practices
+ Emerging Technologies

CLINICAL TRIAL
EFFICACY

EFFECTIVENESS
OF OUTCOMES IN RW

DRUG USE

+ Patterns of use, dose, treatment duration
+ Past history of exposure
+ Co-prescriptions
+ Adherence

PATIENT POPULATION

+ Age, gender, behaviors
+ Co-morbidities
+ Disease stage/severity
+ Other baseline risk factors and genetics relevant to disease/drug

OBA FRAMEWORK

> *The interaction of risk factors with drug efficacy is not what varies from one population to another – it is the distribution of these factors that does. This is why drug effectiveness may be different from country to country, or from one healthcare system to another.*
>
> **PROF. LUCIEN ABENHAIM**, Pioneer of Pharmacoepidemiology

STAGE 3 — Adapt Agreement and Payment Structures to Identified Risks

When drafting the terms of the agreement, multiple considerations are required from a legal, operational, and strategic risk management perspective. The set of legal ambiguities encountered within different countries, and especially in the US (e.g., anti-kickback laws, Medicaid's "best-price" rule, 340B ceiling price, among others) are certainly challenging but can still be navigated as we have argued in the second part of this report. It is important to also note that many of the operational concerns are second-order challenges, meaning that our willingness to dedicate time and significant resources to address them should be predicated upon the likelihood of success, based on the best estimates of performance under real world conditions. No matter how well we navigate the legal and operational hurdles in the implementation, an OBA that fails to deliver due to miscalculated real world performance is one that can and should be avoided. Thus, our core interest here is in advancing guidance as it relates to the question how to

make an agreement perform in the first place. At the outset, it is important to look at the strategic risk management component, which should be the very core of the agreement. Many of the initial agreements that have been negotiated aimed simply at guaranteeing the same performance in actual practice as was observed in the clinical trial, with partial or full refund when this performance is not reached. While this structure is convincingly simple, it might be inadequate from a risk management or a population health perspective.

For example, a common risk to which manufacturers are exposed with OBAs in chronic diseases is the so-called channeling effect. In these conditions, early adoption of newly launched treatments tend to happen disproportionately among patients with more severe disease as they are the ones with the highest switch rates and because these are the ones for which physicians often have no alternative treatment. As a result, in the first year

of launch of a new chronic treatment, we can often expect to see a high share of severe patients receiving the new treatment (at a higher proportion than in the clinical trial and a higher proportion than other comparator treatments), which will likely decrease progressively over time as the adoption broadens. As observed outcomes tend to be poorer among more severe patients, manufacturers engaging in OBAs for chronic conditions such as multiple sclerosis or cardiovascular diseases face a risk to refund a significant share of their sales in the first years after launch. Anticipating this type of issue is critical to avoid disincentives for manufacturers and potentially provision the agreement to limit risk. For example, a simple cap on the percentage of total refund could be included in the agreements, or patients with specific characteristics could trigger lower refund amounts. Channeling is one among the various uncertainties and risk that need to be managed when embarking on an OBA.
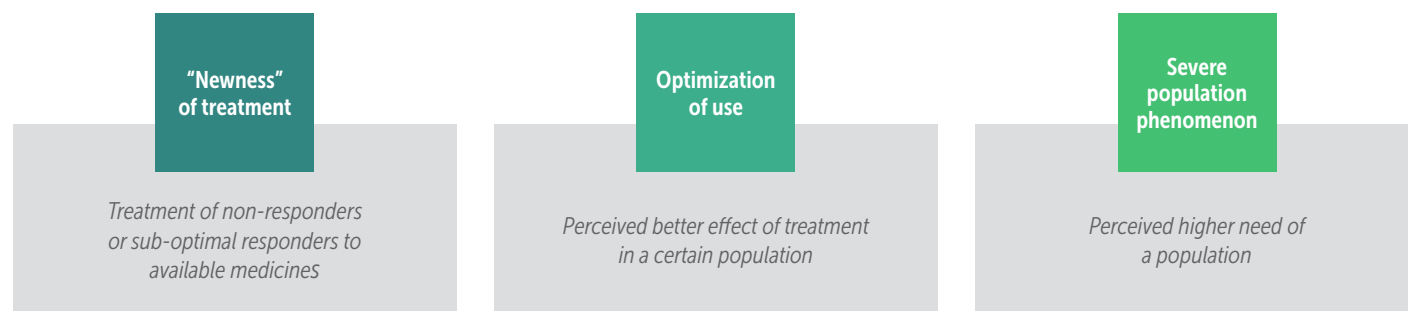
Another interesting example of robust planning and risk management is provided by the two agreements between Amgen and Harvard Pilgrim for Repatha discussed in the previous section. The first agreement, signed in 2015, aimed at guaranteeing the same LDL control in the plan population witnessed in the clinical trial, while in the second agreement signed in 2017 Amgen rebates the cost of Repatha for patients with at least 6 months of treatment who experience a stroke- or MI-related hospitalization. Interestingly, both agreements comprised an exclusion clause of patients that would not meet a minimum level of adherence to treatment, considering that adherence to treatment is in many ways a factor that the health plans do have some ability to influence. This clause was particularly important to secure a fair agreement as one can expect adherence to a cardiovascular

treatment to be lower under real world conditions than in the RCTs, which can be problematic as adherence typically has an impact on effectiveness. Hence, the provision in the contracts was appropriate, as the real world adherence is likely to negatively affect the observed real world effectiveness of Repatha but this represents a shortcoming of the health system and not necessarily of the treatment itself. Another possible approach could have been to further enrich the agreements by adding disease management programs that can enhance patient adherence (cf. section 6). Finally, two other interesting features of these agreements are that the first one also included a traditional clause of rebate on volume and the second one includes a refund of out-of-pocket costs. These show that hybrids of financially-based and outcomes-based agreements are possible and perhaps prominent, and

that the value of the outcomes-based agreements can go not only to the payers, but also reach the patients.

In conclusion, whether your OBA is set up as a population-level or patient-level agreement, modeling the expected outcome in the health plan population is a critical step to identify key uncertainties and to develop a robust sales forecast that can guide decisions regarding the contract, such as timing and target level of the outcome, as well as potential provisions regarding specific use of patient population factors. For more on this stage of the contracting process, please have a look at this guided seminar on the gross-to-net implications of prediction-driven outcomes-based agreements here: **bit.ly/oba-seminar**

"Newness" of treatment	Optimization of use	Severe population phenomenon
Treatment of non-responders or sub-optimal responders to available medicines	*Perceived better effect of treatment in a certain population*	*Perceived higher need of a population*

FIGURE 19
Uptake of new treatment is rarely random: Risk and opportunity of the "Channeling Effect"

STAGE 4 — Clarify Data Sources and Methods to Measure the Performance

While the contract design is a key step in the development of an OBA, it is important to keep in mind that your strategy will only be as good as its execution. Hence, it is critically important to think through where and how the performance will be measured, analyzed, and potentially adjudicated during the implementation phase of the OBA.

Provider claims for the health plan are the simplest and most straightforward data to use to gauge a product's performance in the context of an OBA. Still, it might lack granularity regarding the type of information collected, like in the oncology example cited above where the outcome of interest was PFS. In these instances,

a complementary data collection is required either in a systematic approach or for a representative patient sample. The sampling approach can be considered in the case of a large patient population and for population-level outcomes. When the patient population is more restricted as in the case of OBAs based on patient-level outcomes, systematic data capture is needed. This complementary data collection can rely on various sources and tools such as existing EHR data, laboratory testing provider databases or ad-hoc registries. While the initial setup of such a data collection platform can be burdensome and costly, it is important to note that there is a quick learning curve and economies of scale across OBAs and products.

Regarding the interpretation of the data to determine the actual product performance, it is important to clearly define who will analyze the data: the health plan only, or the health plan and the manufacturer, or a third party? If it is the health plan only, will there be a double coding or validation process to ensure quality of the output? Manufacturers who receive summarized reports about performance from the health plan – which can keep overhead costs lower and be faster – face limitations when it comes to understanding the sources of outcome performance (which would require inclusion of de-identified patient level data). Arbitration would be required if disagreements arise.

Additionally, like for a clinical study a clear analysis plan should be devised, describing the inclusion/exclusion criteria used to select the patients in scope for the analysis, as well as how exactly the outcome will be analyzed. On the latter, multiple technical issues need to be addressed such as patients switching across plans, treatment adherence, crude vs. adjusted analysis if comparing two treatments for example. The analysis plan should also specify the frequency at which the performance will be assessed.

While setting up a clear analysis plan upfront should limit the risks of discrepancies and contentions, it is still important to have a strategy in place for how these issues will be ultimately adjudicated. The two partners should agree on the resources (e.g., joint team, third party...), the timing, and the decision process they will follow to get to a resolution in case of disagreement on the performance and leave the door open to potential amendments of the analysis plan if needed.

Finally, parties would be well-advised to include provisions in their agreement regarding potential exceptional externalities (e.g., new treatment guidelines, discontinuation of a competitor treatment...) that could significantly affect the measure and lead to a renegotiation of the methods to assess the performance or even the whole OBA.

The composition of the committee should be open enough to potentially evolve when the agreement transitions from preparation to execution, as responsibilities and activities will change. In the preparation phase, the committee will focus on designing and negotiating the different items of the OBA, namely articulating the rationale for the agreement, selecting the outcome, defining precisely the patients included in the performance evaluation, the performance threshold or events that will trigger payments or additional rebates, the financial deal structure, the data source(s) and methods to assess the performance, the frequency of performance assessments, and adjudication process in case of disagreement. The steering committee will also ensure that the right capabilities are developed to support the execution, and will manage internal and external communications around the agreement. In the execution phase, the steering committee should primarily focus on reviewing the performance assessments and validating payments/additional rebates.

Additionally, it will be responsible for resolving issues that could arise, which could revolve around disagreement on the performance assessment, but also possibly renegotiating part or all of the agreement in case of exceptional events.

As in any partnership, the steering committee will play a key role in making it a success or failure. Hence, companies should take the time upfront to carefully select the team members they will include and agree on the mandate of the committee.

STAGE 5 — Anticipate Deal Governance and Approach to Issue Resolution

As discussed up to this point, preparing and implementing an OBA requires addressing multiple complex and technical issues. In order for the partners to effectively and successfully tackle these, it is paramount to set up the right governance from Day 1 with a proper steering committee and clear decision-making rules.

First the health plan and the manufacturer should involve appropriate senior leadership to co-chair the steering committee. This will ensure that both parties will set the right vision for the partnership and provide significant decision power to resolve most of the issues within the steering committee. They will also be able to make some recommendations about potential needs for an amendment of the agreement if needed. Each group should then include committee members that represent the key critical skills to set up and manage the agreement.
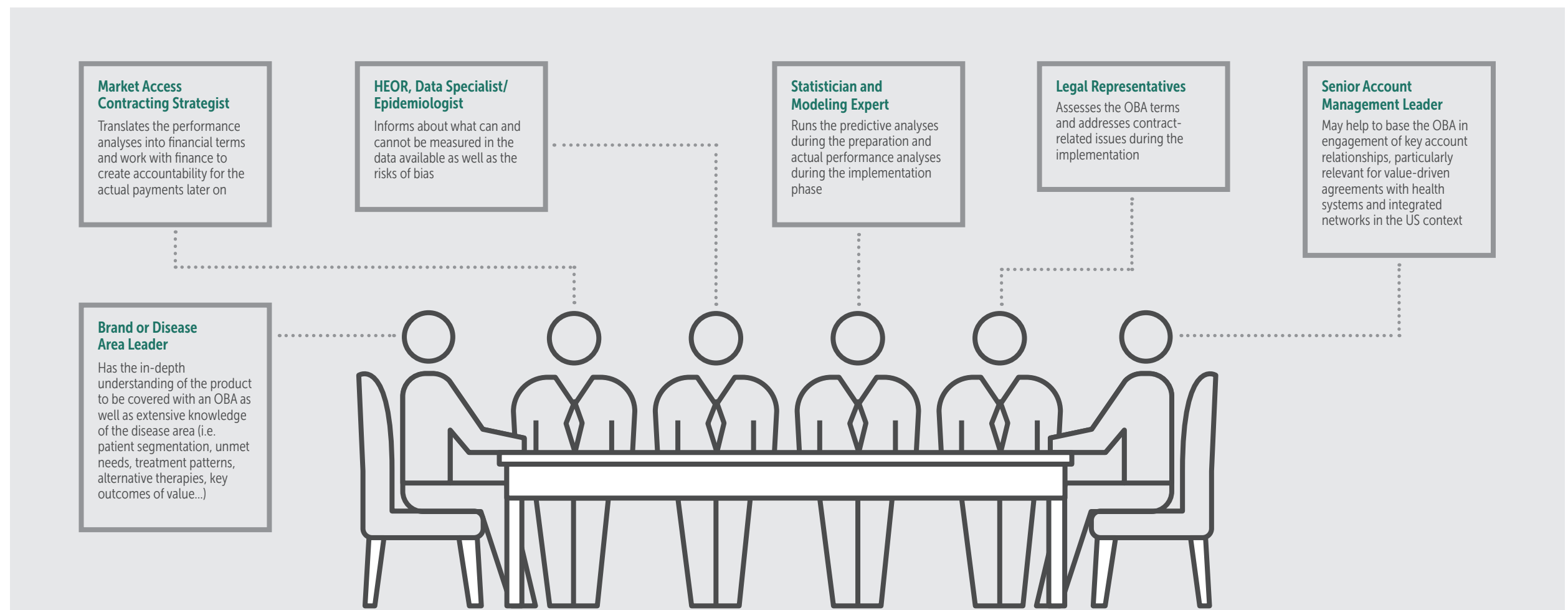
FIGURE 20
Typical selection of members for the OBA steering committee

Market Access Contracting Strategist
Translates the performance analyses into financial terms and work with finance to create accountability for the actual payments later on

HEOR, Data Specialist/Epidemiologist
Informs about what can and cannot be measured in the data available as well as the risks of bias

Statistician and Modeling Expert
Runs the predictive analyses during the preparation and actual performance analyses during the implementation phase

Legal Representatives
Assesses the OBA terms and addresses contract-related issues during the implementation

Senior Account Management Leader
May help to base the OBA in engagement of key account relationships, particularly relevant for value-driven agreements with health systems and integrated networks in the US context

Brand or Disease Area Leader
Has the in-depth understanding of the product to be covered with an OBA as well as extensive knowledge of the disease area (i.e. patient segmentation, unmet needs, treatment patterns, alternative therapies, key outcomes of value...)

STAGE 6 — Consider Enhancing your OBA with "Beyond the Pill" Interventions

While the discussion above has focused on fairly straightforward OBAs structured around new therapies, there is tremendous interest in including non-pharmacological interventions that can enhance the performance and value of therapies.

As we've seen in practice, several factors can influence the effectiveness and safety of treatments in real-life and partners should investigate early-on what are these factors, how they are distributed in the health plan population, and what is their expected impact. Once the partners have this basis of shared understanding, there is a common interest in trying to add interventions that can steer the use of the therapy towards patients where it is most effective and safe, so that performance is maximized for the health plan's members and the financial risk is minimized for the Biopharma company.

For example, contracts for therapies in diabetes or hypercholesterolemia consider including a disease management program to reinforce adherence, which is known to be a key driver of effectiveness in these diseases. As we have seen, an alternative is to include a provision where non-adherent patients are out of scope of the contract. Still, even with this type of provision, there is interest to minimize the proportion of these patients so that the OBA can deliver its full value to each partner and ultimately to the patients. Other interventions can include physician support programs to ensure that the treatment is given to patients who benefit the most from it (e.g., based on severity profile, prior treatment history, specific biomarkers, co-morbidities...)

Merck has reached agreements with Aetna for Januvia (sitagliptin) and Janumet (metformin/sitagliptin): If Aetna members with type-2 diabetes don't meet certain clinical goals – such as hitting their hemoglobin A1C or blood-sugar targets – Merck pays a rebate which increases depending on the number of patients who miss the targets, measured by analyzing data from Aetna's claims. But in addition to such a classic performance contract, Merck/Aetna also worked out an agreement for commercial patients that involves predictive analytics to identify 500 at-risk patients diagnosed with hypertension or diabetes. The objective was to identify at-risk members with commercial insurance coverage who are participating in two accountable care organizations (ACOs) in northern New Jersey. For the payer, the data will be analyzed to create improved-care procedures that are aimed at helping patients improve adherence to therapy with social support such as phone calls and in-person visits from Aetna nurses on a regular basis. Merck agreed to provide adherence tools and educational resources.
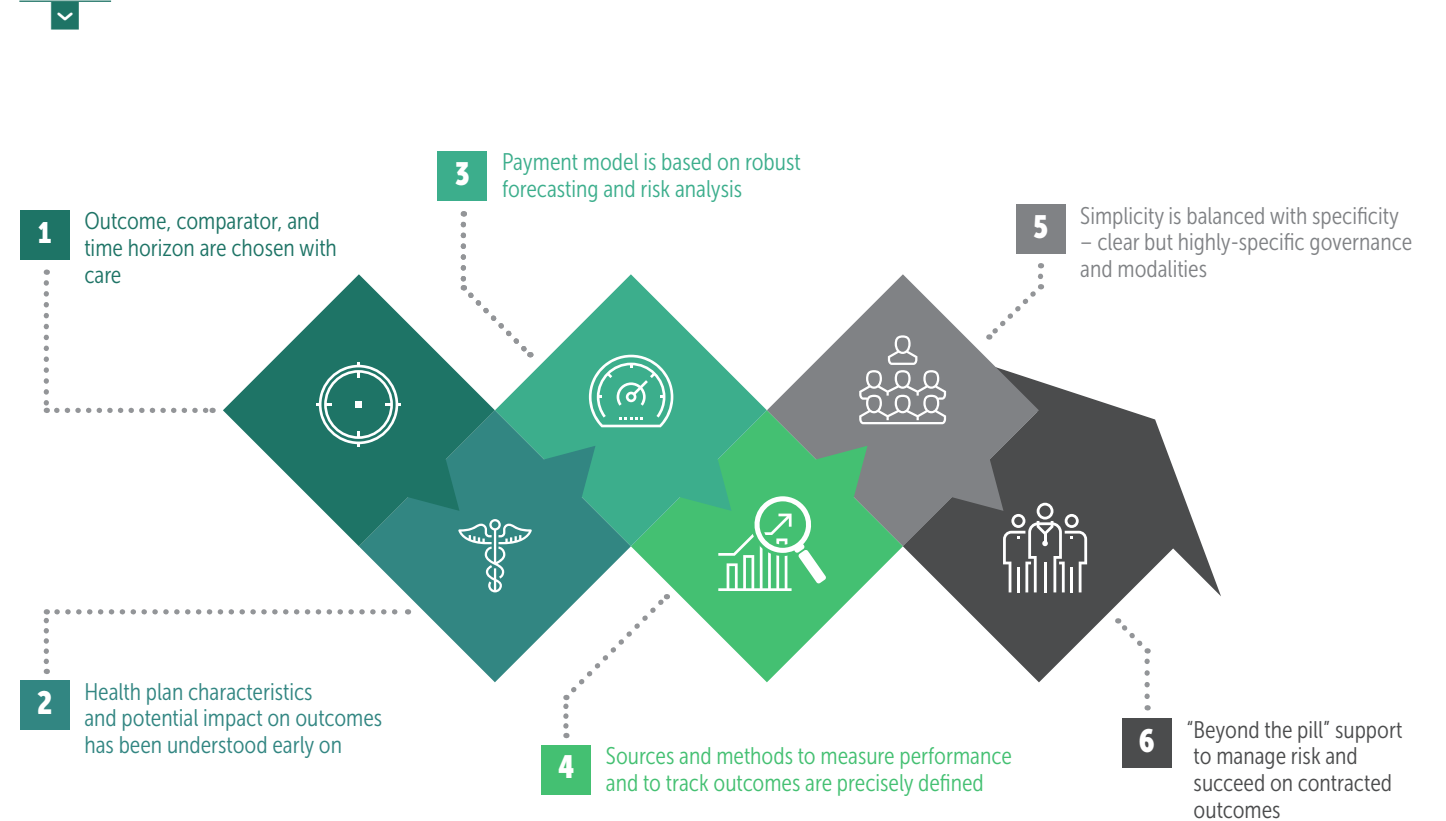
So-called "beyond the pill" interventions are a key opportunity for insurers to maximize the outcomes in their patient population, while paying for the actual value of the treatment through the OBA. At the same time, they represent an opportunity for manufacturers to minimize their financial risk on the OBA, as well as to possibly enhance their volumes by optimizing adoption and use of their treatment by physicians and patients.

FIGURE 21
The six stages of the OBA journey

1 Outcome, comparator, and time horizon are chosen with care

2 Health plan characteristics and potential impact on outcomes has been understood early on

3 Payment model is based on robust forecasting and risk analysis

4 Sources and methods to measure performance and to track outcomes are precisely defined

5 Simplicity is balanced with specificity – clear but highly-specific governance and modalities

6 "Beyond the pill" support to manage risk and succeed on contracted outcomes

Key Takeaway: Following an Integrative Approach Across Each Stage

Deal or no Deal? There is little doubt that to pursue an OBA is a journey, but we believe that it doesn't have to be a journey into the unknown. Once the rationale and goals behind the approach are articulated internally, we recommend that manufacturers pay close attention to six stages of success for the OBA partnership with a health plan or provider organization. To be clear, these don't represent a simple checklist but rather a series of strategic considerations that should be answered in an integrative approach (Figure 21).

We have noted that OBAs can serve as a valuable tool for some (but not all) therapies, and they may arguably be the best way for manufacturers and payers to address the challenge of achieving adequate access for the next wave of medical innovations that are just beyond the horizon. As such they represent an opportunity to create a shift in the incentive structures that drive current decision-making in our healthcare system and better encourage all players to work towards the appropriate goal of improving patients' outcomes.

Outcomes Prediction & Modeling as a Core Activity for OBA Success

Today, OBA pioneers are leveraging advanced modeling and simulation to help remove some of the uncertainties between clinical trial efficacy and real world effectiveness. The goal is to enable robust outcomes predictions during their payer engagements. Our experience shows that, in the interest of feasibility, stakeholders tend to identify those data sources that can be affordably accessed, monitored and analyzed.

> *We are analyzing historical claims data to define certain benchmarks that would aid its discussions with payers when negotiating these deals. As an industry we're still working through ways to truly tie price to the value that's realized by the patient, building a model that's thorough, that's measurable, that's objective, and to figure out how to measure that value is the critical step where we're at today.[1]*

JEN NORTON, VP, Market Access, *Biogen*

Whereas the financial modeling component is practically well-established today (in terms of 'If we get X result, we pay Y...'), carrying out the complex modeling that is required to predict clinical outcomes across a range of potential scenarios is much harder. A primary challenge arises in that the types of real world data of greatest value are also inherently heterogeneous and often difficult to gather. For the modeling, it is critical to leverage fit-for-purpose data in the same disease category and with similar drugs. Important types include recognized clinical endpoints, relevant quality-of-life (QoL) factors, the impact of variable time horizons,
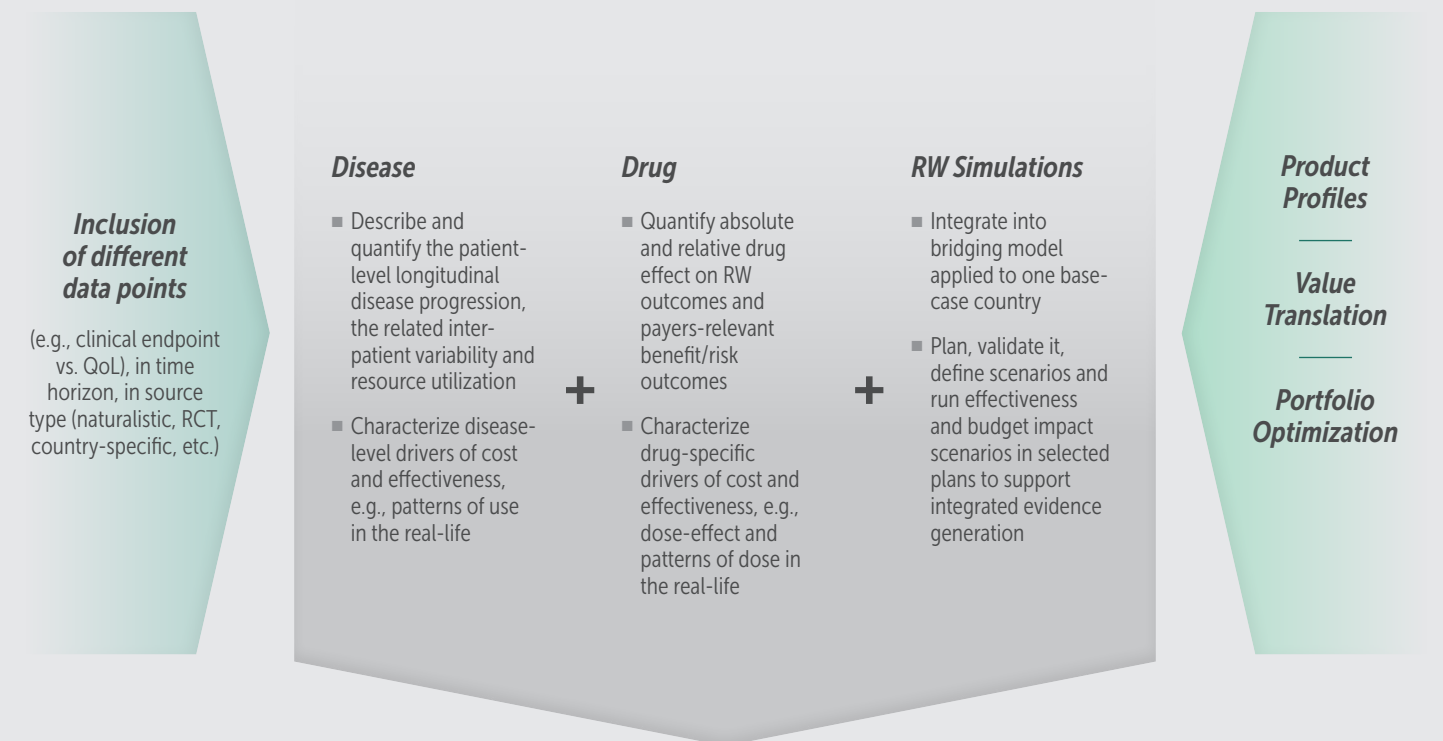
factors impacting patient adherence to therapy, and more. You look at historical claims data and registry data from third-party sources. It varies a lot from disease to disease, so when devising the model, manufacturers need the confidence to make some assumptions.

The drug's clinical trials provide invaluable data for how the drug performed within the defined and tightly controlled patient population enrolled in the trials. But as has been noted before, RCTs are carried out under real world conditions, typically screening to identify optimal patients for participation and managing patients more closely

than in typical clinical practice and often leading to greater than normal adherence to therapy. By contrast, in actual practice, medication use – and its success in terms of health benefits – are subject to variable prescribing patterns, follow up and patient management, and often broader indications or larger variability in the patient cohort etc.

The goal for those facing an OBA should be to devise an approach that considers all of these intertwined factors in a way that allows them to predict effectiveness in individual patients and patient cohorts of interest in this clinical practice setting and to try to quantify those uncertainties. A simplified concept of an integrated modeling platform is shown in Figure 22.

FIGURE 22
Leveraging integrated modeling platforms to assess OBA performance

Inclusion of different data points

(e.g., clinical endpoint vs. QoL), in time horizon, in source type (naturalistic, RCT, country-specific, etc.)

Disease
- Describe and quantify the patient-level longitudinal disease progression, the related inter-patient variability and resource utilization
- Characterize disease-level drivers of cost and effectiveness, e.g., patterns of use in the real-life

Drug
- Quantify absolute and relative drug effect on RW outcomes and payers-relevant benefit/risk outcomes
- Characterize drug-specific drivers of cost and effectiveness, e.g., dose-effect and patterns of dose in the real-life

RW Simulations
- Integrate into bridging model applied to one base-case country
- Plan, validate it, define scenarios and run effectiveness and budget impact scenarios in selected plans to support integrated evidence generation

Product Profiles

Value Translation

Portfolio Optimization

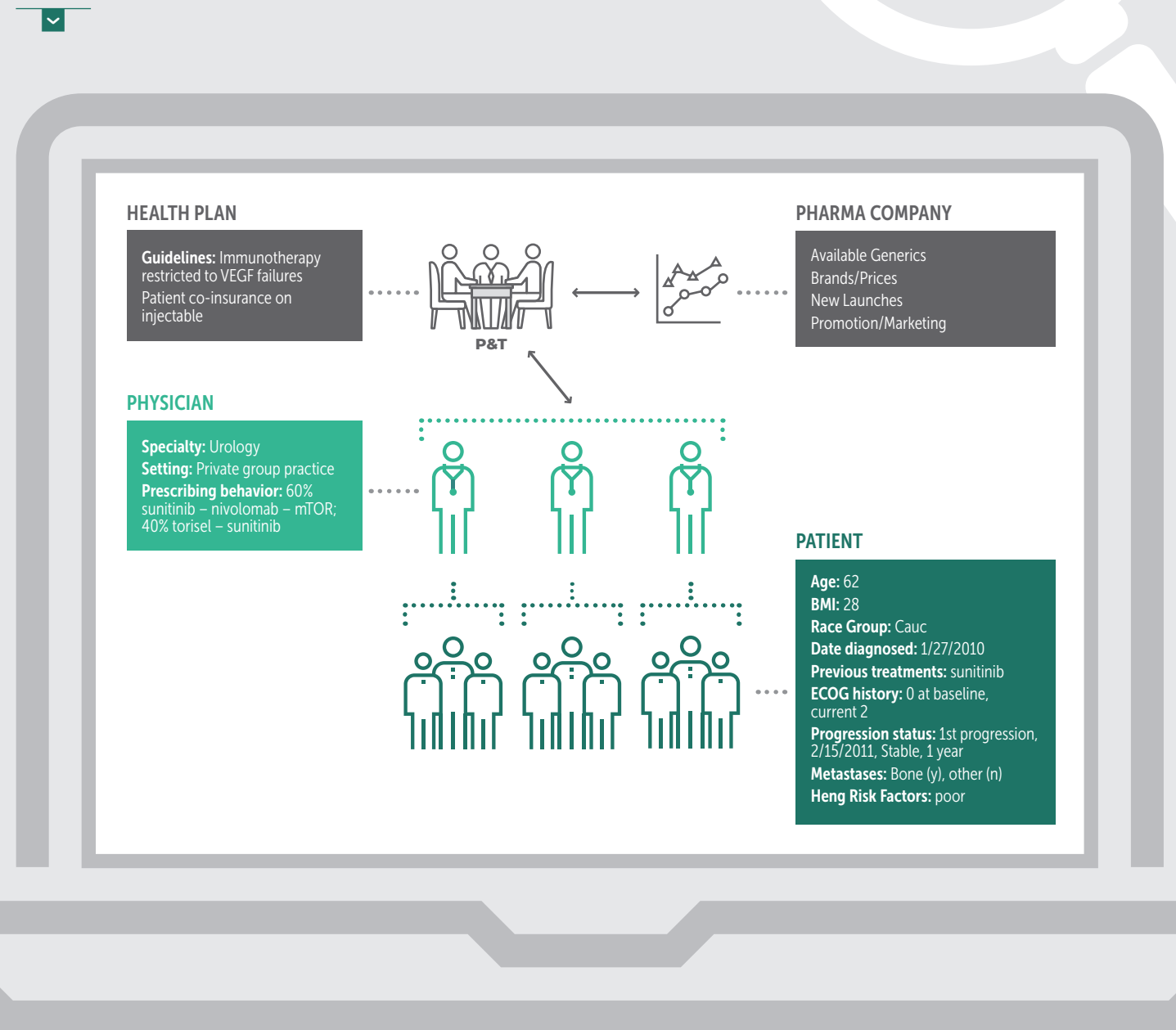*Optimize deal parameters by reducing uncertainty around performance*

> *Typically, we start with taking a look at the Phase III trial and imagine: Will it be the same in the real world. But we know it's not going to be the same in the real world, between messy conditions, and the inherent variability of the population and all the other controls in the clinical trials not being at work under real world conditions. You need to have a robust model, good techniques and then pick the right data, and re-equilibrate and extrapolate those factors that you may not have measured in the clinical trial. There may be circumstances where the clinical trial showed relatively little variability (for instance, 95% progressed as predicted between 5-6 months of PFS), but with modeling the scenarios under real world conditions, you may expect 95% progressed PFS in the first 3 months but then it falls off. Given this insight, you'll want to structure the rebate to really take advantage of the spread of outcomes that you would expect in the real population. If you set up terms that are more progressive in nature, you need to know how the distribution of outcomes (PFS) will vary in real world vs. clinical trial and then make sure you are rewarded along the way and not just punished if it falls off at 6-month mark.*

BILLY AMZAL, Senior Vice President, Decision and Real world Data Analytics, *Certara*

Pivotal trials should provide important insights about which subpopulations of patients are likely to benefit most from the medication. When embarking on the data analytics and modeling needed to support OBA contract negotiations, the question is what types of real world patients will likely take the medication once it is on the market (above and beyond the controlled sub-populations that were described in the clinical trial setting). In the inquiry, key questions are: "What are the factors that will shift the clinical trial outcomes in my real world populations?" and "How will I make best use of those factors?". Answers to the integrated modeling may often go down to the patient-level, as illustrated in Figure 23.

FIGURE 23
Connected approaches: Real world effectiveness simulations from the plan to the patient-level

HEALTH PLAN

Guidelines: Immunotherapy restricted to VEGF failures
Patient co-insurance on injectable

PHARMA COMPANY

Available Generics
Brands/Prices
New Launches
Promotion/Marketing

P&T

PHYSICIAN

Specialty: Urology
Setting: Private group practice
Prescribing behavior: 60% sunitinib – nivolomab – mTOR; 40% torisel – sunitinib

PATIENT

Age: 62
BMI: 28
Race Group: Cauc
Date diagnosed: 1/27/2010
Previous treatments: sunitinib
ECOG history: 0 at baseline, current 2
Progression status: 1st progression, 2/15/2011, Stable, 1 year
**Metastases:** Bone (y), other (n)
Heng Risk Factors: poor

Leveraging a Dedicated Analytics Platform as Decision-Support Tool

Pioneers in the OBA space feed their experience and data into a decision-support platform. The teams at Analytica Laser have distilled our experience from numerous studies bridging the gap between efficacy and effectiveness into a proprietary platform called HOPE (Health Outcomes Performance Estimator) which translates clinical trial results, observational sources and population-specific health knowledge into expected real world impact scenarios for individual pharmaceutical therapies under OBA consideration (Figure 24). We would encourage manufacturers to employ such a cloud-based platform that enables them to:

■ **Carry out joint simulation.** Based on a dynamic Bayesian inference modeling engine to predict a drug's performance in real life, the tool allows for the simulation of potential patient outcomes under specific real world settings. This is based on knowledge of these outcomes in RCTs, summary statistics (for instance, obtained via literature review), patient-level data, and various drivers of effectiveness (DoE) – which are any factor that may impact real world performance of a treatment

■ **Test highly complex scenarios and visualize results over time.** Such modeling enables an understanding of how the dynamic interactions of outcomes, exposure and other effectiveness drivers influence outcomes in any user-defined "virtual cohort." Such scenarios may include launch of new products in a crowded therapeutic area or a change in medical practice, for example.

An OBA modeling platform like HOPE™ analyzes a variety of complex, interrelated factors that ultimately impact how a given therapy will perform under real world conditions. Taken together, these insights offer insightful decision support as to select and define the most appropriate methods to measure the anticipated clinical outcomes of the therapy conditions, and to model the OBA's financial implications, across the range of different real world scenarios the agreement will face.

Against the background of a real world understanding around the gross-to-net impact, this approach enables drug developers to identify appropriate payment-reconciliation methods. After all, gaining greater insight into all of these factors is crucial for optimizing OBA negotiation processes and ultimate contract design with the plan.
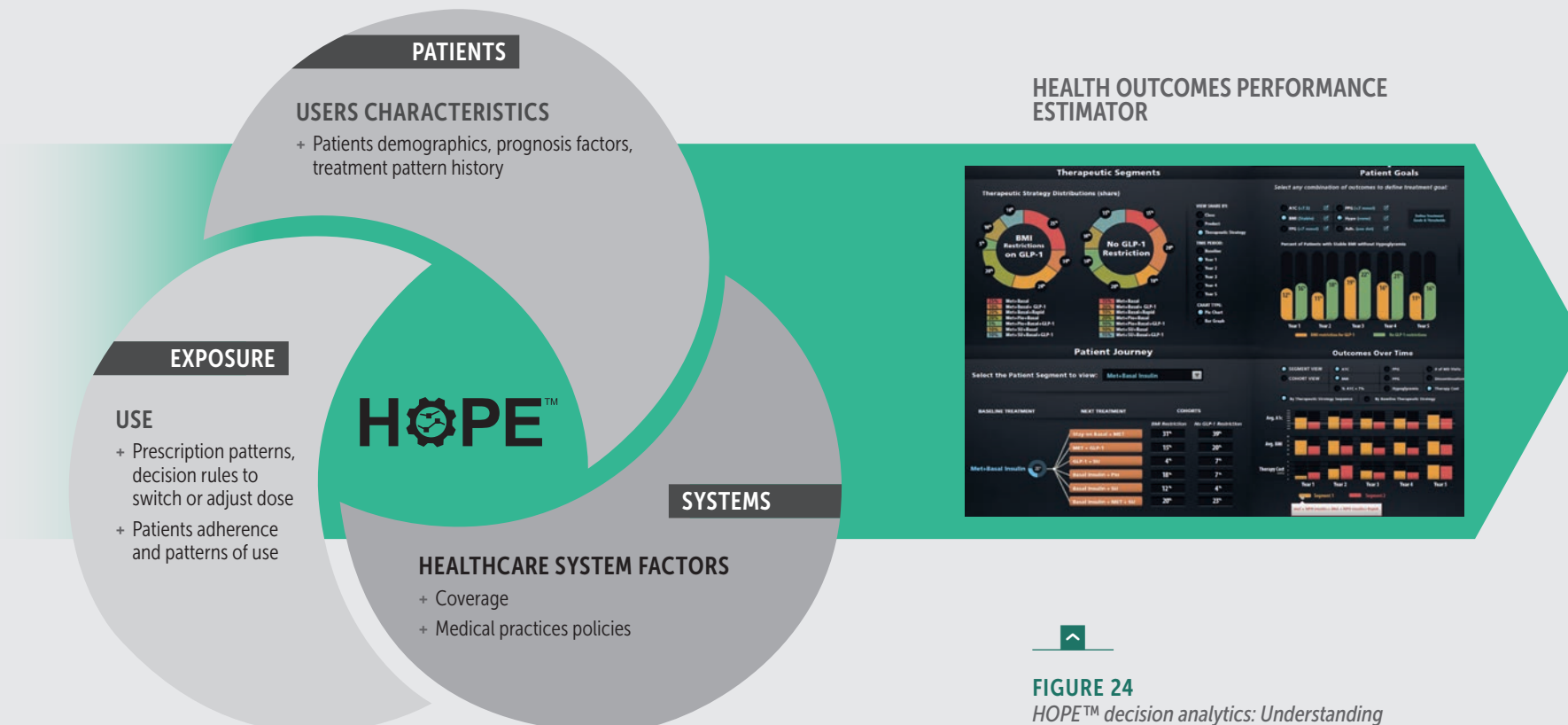
Key Features

Bayesian model of disease

- *Combination of mechanistic and probabilistic models*
- *Competing-risk modelling of multiple outcomes*
- *Joint time-to-event and continuous outcomes, binary outcomes*
- *Patient cohort simulations under user-defined RW scenarios*
- *Automatic input detection and standardization*
- *Synthesize modelling uncertainty and population variability*
- *Fast, cloud-enabled, probabilistic computation of complete patient history*
- *Flexible visualisation and reporting features to accompany the models*

During modeling and simulation of real world drug-utilization scenarios, experience with advanced bridging methodologies will help you to derive time-to-event model estimates, identify links between drivers and outcomes, consider the influence of risk factors on the resulting predictions, understand potential outcomes, comparators and corresponding time horizons. From a customer perspective, it is crucial to keep outputs of the platform simple and user-friendly: All inputs should be able to be imported from Excel spreadsheets, and all outputs exported into an automated report or visualized presentations, animated interactive and customizable dashboards.

On the visualization of value-vased contracting tools, Analytica Laser partners closely with its sister company BaseCase, the customer engagement platform for the life sciences industry. Their software-as-a-service (SaaS) data visualizations combine integrated content creation, adaptibilty, sales enablement and integrated compliance and legal validation processes, all on one integrated platform powered by HOPE™ decision analytics.

PATIENTS

USERS CHARACTERISTICS
+ Patients demographics, prognosis factors, treatment pattern history

EXPOSURE

USE
+ Prescription patterns, decision rules to switch or adjust dose
+ Patients adherence and patterns of use

SYSTEMS

HEALTHCARE SYSTEM FACTORS
+ Coverage
+ Medical practices policies

HOPE™

HEALTH OUTCOMES PERFORMANCE ESTIMATOR

REAL WORLD IMPACT

FIGURE 24
HOPE™ decision analytics: Understanding product performance in the real world

CERTARA

| EVIDENCE & ACCESS

Analytica Laser, leader in scientific value assessment and population health intelligence, and **BaseCase**, pioneer of cloud-based value communication technology, are now part of Certara.

Together, we're providing unparalleled end-to-end analytics and strategy to define, capture, and communicate the value of therapies.

We combine strong technical capabilities in real world evidence development, health-economic analysis and advanced analytic methods with our deep relationships in the payer community.

analytica LASER

BASECASE COMMUNICATE VALUE

www.certara.com/evidence-access

CERTARA'S PROVEN TRACK RECORD
EXPERT LEADERS IN INNOVATIVE CONTRACTING AND PRICING AGREEMENTS

Assessed financial impact of innovative contracting schemes for treatment in multiple myeloma

Simulated outcomes of 15 performance plans across multiple disease areas for global PharmaCo

Conducted prediction and monitoring of real world outcomes for new lipid-lowering treatment

Evaluated the real world risk of hospitalization for the implementation of innovative contract in asthma

Prepared and facilitated senior management workshop on design and implementation of OBAs for top 5 global PharmaCo

Measured real world outcomes in the context of an OBA for new treatment in schizophrenia

Evaluated new price structures and financial risk-sharing scenarios for treatment in multiple solid tumors

Led various educational symposia, i.a. ISPOR 21st (2016) and 22nd Annual Meeting (2017)

References

[1] McCaffrey, K. (2017), Biogen, Merck Use Predictive Modeling to Better Negotiate Value-Based Contracts, Managed Care magazine. http://www.mmm-online.com/commercial/biogen-merck-use-predictive-modeling-to-better-negotiate-value-based-contracts/article/681709/