Therapeutic Challenges Analysis

ViewPoints

The New Role of Payer Advisory Boards in Shaping Clinical Development Preparation, Structure, Outcomes and Key Success Factors

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Payers Advisory Boards (PABs) During Clinical Development – A Requirement in the New Pharmaceutical Market Environment?

The pharmaceutical industry is beginning to appreciate that it is no longer viable to look at regulatory and Health Technology Assessment/reimbursement/formulary decisions as two separate processes to get a drug to market. The measure of clinical development success is changing from "Time to Regulatory Approval" to "Time to Market Access". As German Pasteris, in charge of Alzheimer's for GlaxoSmithKline Plc, recently told Reuters, "The ultimate goal was not optimal reimbursement and access; today it is". This ongoing evolution will only accelerate as payer demands for differentiating value become more stringent. By addressing both regulatory and payer needs at the same time, companies can increase the likelihood of successful Market Access, achieve significant savings, and increase speed and magnitude of return on development dollars.

Clinical advisory boards are used extensively by the industry to provide input into clinical programs at all stages of the development process. While clinical advisory boards are extremely useful, they do not offer real insight into payer's likely value assessment of novel products, or into the ability of the proposed development programs to answer payer's key questions. As a result, we have seen, and are likely to continue seeing many products meeting the endpoints and efficacy thresholds defined during clinical advisory boards and discussions with regulatory authorities and therefore achieving regulatory approval, but then either failing to gain reimbursement or expected pricing, or failing to achieve formulary listing without severe usage restrictions. These failures are often due to significant payer value uncertainty.

Differences Between Regulatory and Payer Assessment of Value – Example: Arzerra (ofatumumab) for Chronic Lymphocytic Leukaemia (CLL)

EMA (European Medical Agency): "The CHMP considered by consensus that the risk-benefit balance of Arzerra in the treatment of Chronic Lymphocytic Leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab was favourable and therefore recommended the granting of the conditional marketing authorization

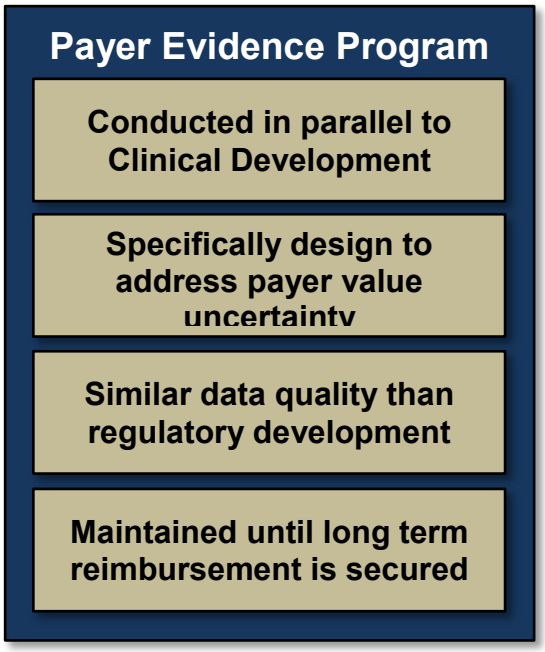
FDA (Federal and Drug Administration): "The majority (10 yes; 3 no) of ODAC members agreed that the results of Protocol Hx-CD20-406 supported the accelerated approval of Arzerra"

HAS (Haute Authorité de Santé – France): "The real efficacy of ofatumumab cannot be assessed with the methodology used during clinical development"

Regence Rx (Leading Pharmacy Benefit Management – U.S.): "The evidence for ofatumumab is poor (not useful)"; "The value of ofatumumab is unknown"

SMC (Scottish Medical Agency - UK): "The robustness of the response shown in this study and its ability to be translated into a clinical benefit is uncertain"

Payers and regulators have very different focus when evaluating new therapies. Regulators concentrate on efficacy or, "The extent to which an intervention does more good than harm under ideal circumstances". Payers, on the other hand, are more concerned with systematically evaluating a therapy's relative effectiveness or, "The extent to which an intervention does more good than harm compared to alternatives for achieving the desired results when provided under the usual circumstances of health care practice". These different points of view create a significant gap between regulators and payers appraisal of the quality and usefulness of clinical data. Payer's relative value perception also changes significantly with events such as the genericization of specific product classes, a significant increase in the number of competitors, or HTA evaluations and reimbursement decisions in other countries, all of whom have no or little impact on the perception of value by regulators or physicians.



Many pharmaceutical companies routinely conduct payer research. However, in most cases this research is used primarily to:

- Test payer reactions to a specific set of data produced during clinical development
- Assess likelihood of positive Market Access and reimbursement based on these data
- Test various pricing ranges or pricing schemes
- Define specific elements of the value proposition to emphasize in value dossiers
- Evaluate the "technical" elements of the reimbursement process (coding, DRG,…)
- Develop proposals and program outlines for HEOR research or models

The resulting insight intelligence has limited strategic value and allows at best for local tactical and "technical" adjustments in obtaining reimbursement, and in negotiating pricing.

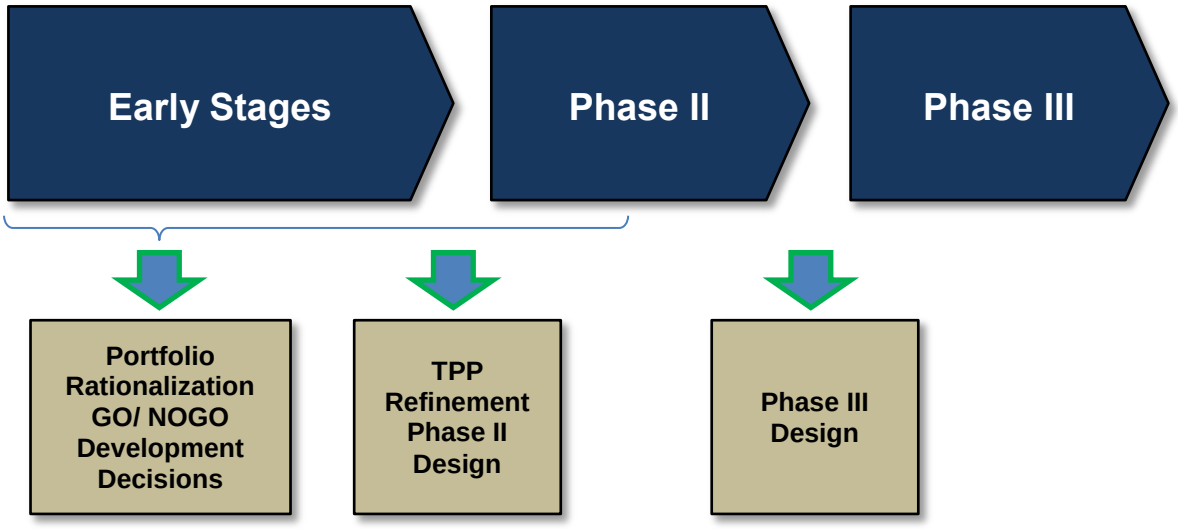
This approach suffers from a fundamental flow: while payer value perception is impacted by HEOR data, its primary driver remains the strength and the quality of the clinical evidence produced during clinical development. Therefore the strategies and activities required to positively shape future payer perceptions must be defined several years prior to Market Access and reimbursement decisions, during the design of clinical development programs, on order to impact the structure and outcomes of these trials.

As the pharmaceutical market evolves toward a value-based pricing environment, in different forms and in different countries, successful pharmaceutical companies will be those that are best at optimizing payer value perception and reducing payer value uncertainty throughout their development programs, either by integrating payer needs in the regulatory development program or by conducting a parallel, high quality payer evidence program. Payer Advisory Boards (PABs) are a critical tool in that process. They should be used to define, analyze and develop solutions to address potential payer value uncertainty. They should be combined with clinical advisory boards to optimize the design of clinical trials, identifying potential conflicts between different stakeholder groups and addressing these conflicts proactively while planning development, rather than reactively when trials are complete.

They should allow defining and comparing routes to successful Market Access and reimbursement and helping companies make educated decisions when weighting the benefits and drawbacks of different trial designs. We advocate that PABs are actually as important as their clinical counterparts and should be given equal attention during product development. As the role of PABs increases and evolves, so does their structure, their preparation and their key success factors.

At Which Stage(s) of Development Should Payer Advisory Boards be Conducted?

In a perfect world, Payer Advisory Boards should be conducted prior to any decision leading to significant investment or to significant impact on the development program. In practice, PABs should be considered at three critical junctures in development: Questions and objectives will be different for each of these three decision points:



- Early stage: Understand how payers define differentiated value. Develop potential target product profiles addressing payer requirements in the targeted indication

⇨ Estimate of likelihood that the asset can deliver differentiated value to payers. Input into portfolio rationalization

- Prior to Phase II: Confirm initial belief that the asset can deliver differentiated payer value? Identify key endpoints and comparators of interest to payers. Recognize and address potential red flags for payers in terms of activity and tolerability

⇨ Refinement of TPP and design of Phase II / IIb trial(s) to start addressing payer needs

- Prior to Phase III: Assess the ability of the Phase III trial to answer payer questions. Identify needs for additional data to support payer value assessment

⇨ Design the Phase III to optimize likelihood of Market Access (reimbursement and favorable pricing). Initiate additional required studies

- We usually advise against conducting PABs to discuss existing phase III data. Payers are engaged when they feel that they can influence product development and study design but are less attracted to PABs whose main objective is about getting the best possible price, not about answering their needs

The most important decisions are those leading to the design of Phase III pivotal trial(s) program. As a result, we strongly advocate organizing a PAB prior to entering into discussions with regulatory authorities. In most cases meeting payer needs is more challenging than meeting regulatory requirements. Payers are likely to ask for a harder primary endpoint, or for co-primary endpoints. They may demand an additional study arm or a more selected patient population. It is important to enter regulatory discussions with a clear understanding of the impact of different trial designs on likely payer perceptions, to help guide potential outcomes. While there are no guarantees that regulatory authorities will agree to meet payer requirements, and this is clearly not their function, our experience has taught us they are often open to clear rationale supported by well-structured arguments.

Conversely, when regulatory authorities have already given advice on a specific trial design, it becomes very difficult to change this pivotal trial to integrate payer's requirements. Payer needs must then often be addressed through a separate, payer directed trial, which is clearly not the most economical or rapid approach. Another important use of Payer Advisory Boards is in development portfolio rationalization. There is no point in developing assets through Phase I and Phase II if they do not stand a realistic chance of achieving reimbursement and favorable pricing. Few companies reach out to payers in these early stages, and we advocate a much greater use of PABs to include a proper assessment of Market Access risk, along with development, regulatory and commercial risks in pipeline Go / No Go decisions.

Key Elements of Payer Advisory Boards Preparation

Advisory Board Composition

To make the most of PABs, our approach relies on inviting "real payers", participants who hold true budget responsibilities and participate in Market Access and reimbursement decisions. While this seems obvious, it is often easier said than done. In many countries it is difficult to convince these people to participate, as they are government employees and express, in theory, little interest in direct contact with the pharmaceutical industry during product development. However, with the appropriate effort in recruitment, the right approach to payers and the development of long-term, trusting relationships, we have been successful in recruiting Advisory Board members who are either current payers or HTA members or were part of these organizations in a very recent past. As the payer world evolves rapidly, participants whose experience as a payer dates from more than 18 months are probably not best suited. The number of participants is often a matter of debate. As with all Advisory Boards there is a need to find the right balance between obtaining a variety of opinions and allowing each participant ample opportunity to express and detail these opinions to participate in constructive debates. In Europe this issue is often compounded by the need to have representatives from at least EU4 or EU5, due to different reimbursement systems. We suggest limiting the numbers of payers to 7 or 8, even if several countries are left out. However since the countries involved are likely to represent the bulk of the market opportunity, it is also those whose input will generate the largest return.

Payer Advisory Boards or payer research often includes academic health economists or "KOLs advising payers" as those are easier to recruit than "real payers". We advocate inviting one or two health economists to the PAB to provide input in potential HEOR models, but they should not represent the majority of participants. To repeat our earlier position, reducing payer uncertainty is not about HEOR data, but about the development of strong and relevant clinical data.

When conducting PABs, we also recommend separating the U.S from Europe. Differences in Health Care and reimbursement systems are such that it is virtually impossible to conduct discussions leading to global consensus. Regulatory requirements can also vary across the geographies, thereby changing the potential impact of the outcome of the Payer Advisory Board and its integration in overall design and investment decisions.

In our PABs, we also routinely invite 2-3 clinical KOLs with three main objectives:

- It helps provide clinical context and ensure that payers understand unmet clinical needs, and the potential impact of diseases and therapies on all elements of health outcomes and patient quality of life. Despite being prepared prior to the advisory board (see next section) payers often have limited understanding of the real impact of diseases and hearing it directly from KOLs and through specific patient examples proves very useful
- It mirrors real-life reimbursement decision process, where payers very often use clinician advisors during product assessment. To mimic that situation, expert clinicians should attend the PAB
- When generating input in Phase III trials, it is crucial to provide a dimension of "reality check". Designing a trial that meets payer expectations but is rejected by clinicians because it does not correspond to clinical practice is deemed unethical or patients are impossible to recruit, has little value.

Participant Motivation

An important element of every advisory board success is the motivation of participants. In our experience, financial compensation is often not the main motivation. Payers aspire to contribute to the development of novel products with a positive impact on patient outcomes. Payers across the world are striving to change the negative image often associated to them in the pharmaceutical industry, or in the general public. As a result they are very willing to participate to PABs as long as this participation is and part of a real partnership. Following clinician advisory boards, participants are often involved in the resulting development program as investigators. They thus see the direct impact of their contribution through the definition of the trial protocol and the trial progress. This is very different for payers who may not be exposed to the product again for 3 or 4 years and it is important to give them regular feedback. This ongoing relationship needs to be nurtured. When the Advisory Board recommendation is not followed, it is also important to explain why. We have often been in contact with payers complaining that their input into PABs was not followed: "We had a payer consensus on the choice of a comparator and kept repeating to the company clinical development team that their product would not be reimbursed using the proposed trial. They still went ahead against our advice". Payers accept that companies integrate the outcome of PABs in their business decision process including and weighting other factors and potentially reaching conclusions that are contrary to payer's opinions. However, it should be explained and rationalized to participants, within the limits of confidentiality.

Participants Knowledge Packages:

Payers are not experts in specific therapeutic areas. While it is possible to screen participants to ensure past involvement into P&R decisions in the specific therapeutic area, it should be assumed that knowledge is incomplete, and potentially biased by past experiences. Therefore we suggest preparing a concise but complete briefing package for each asset to be evaluated. This briefing package should include:

- An overview of the target indication, including its clinical features and outcomes, effect on patient QoL, and functional and societal impact
- An unbiased view of clinical and economical unmet needs (unbiased in the sense that it should not serve as a validation of the asset in development)
- A description of current therapies, including data supporting these therapies
- A description of products in the pipeline, detailing ongoing clinical studies (with comparators and endpoints)
- A review of pricing and pricing schemes for existing products in key countries
- A description of "objective" and "trustable" Health Economic studies in the indication, supporting the value of health care savings associated to changes in outcomes or in the treatment pathway
- TPPs for the assets to be discussed

These knowledge packages should be sent to payers at least 2 weeks prior to the advisory board, giving them an opportunity to review and to ask questions about the market environment and the product(s) to evaluate. Investing time with payers prior to the Advisory Board is highly valuable and allows focusing meeting time on discussions rather than education / clarification. A common mistake is also to assume that payers know all the details about prices, reimbursement decisions and HTA or health economic evaluations in the target indication. While they certainly have a detailed knowledge of the decision processes leading to these prices and evaluations, it is not realistic to expect them to know all outcomes and rationales. It is also important to give payers from each country some background knowledge of the situation in other countries. The discussion time during the Advisory Board must not be spent discovering and debating differences across countries, but on finding global or at least cross country solutions. We cannot stress enough the need to be unbiased in the development of this preparation package. The objective is not to convince payers of the value of the asset but to allow them to have an educated discussion leading to conclusions that will be useful in tackling the challenges created by the P&R process.

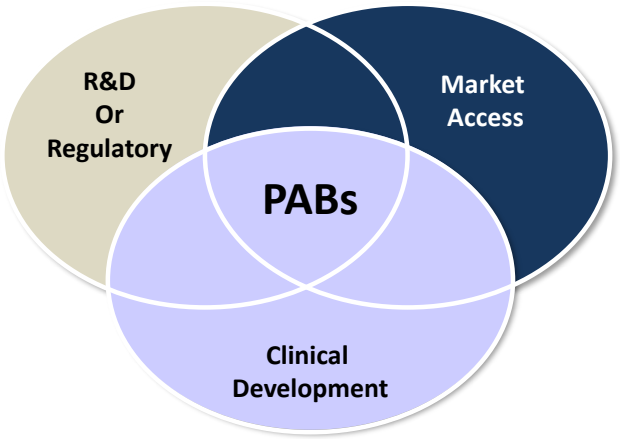
Conducting the Advisory Board

While there are clearly differences in clinical practice across countries, those variations are often limited and rarely have a strong impact on decisions pertaining to clinical development. However the differences between countries across payers and HTA decisions are much more significant. The risk is thus to have payers from different countries expose their own point of view in a succession of opinions and statements without developing consensus. The discussion should be focused on the perception of value of the product and how different elements can contribute to that perception of value. These various elements will have different "weights" across countries but it is the combination of these value elements that will drive pricing and reimbursement decisions.

The objective of the debate should not be to build the ideal development program, but rather a development program that will answer the main questions for all participants / countries. It can then be complemented by additional tactical country activities that can be defined separately through additional payer research. It is also very important to establish a real dialogue between physicians and payers. Participating to PABs remains an unusual experience for many physicians. While physicians are interested in hearing the opinions of payers, it is necessary to avoid conflicts and situations where physicians feel that payer do not understand patient needs. Ample time should be given to physicians to expose their current treatment paradigms and their needs in order to promote partnerships with payers in achieving the best outcome

Company Audience

PABs should be attended by a broad company audience, as they serve to educate functional teams that may not have a detailed understanding of the needs of the payers. It is crucial for regulatory and clinical development to hear first-hand the opinion of the payers and the required adjustments to the clinical development plan. When PABs are conducted at an early stage, Regulatory should be substituted by Research and Development. However company audience should be prepared to hear a message that is contrary to internal beliefs. Indeed there are many more products / clinical development plans that do not meet the needs of the payers than products that do. Company audience should not take that as a direct criticism of their work, but as constructive feedback helping them and their company allocate resources productively.



Expected Outcomes from Payer Advisory Boards

There are four main outcomes that can be expected from payer advisory boards:

- A clear definition of what "value" and "differentiating value" mean to payers in the target indication
- A recommendation on elements of clinical developments that are important in demonstrating that value to payers and in reducing the value uncertainty remaining after regulatory trials
- An understanding of the payer thought process and belief systems, and how those will be applied during HTA, reimbursement and pricing decisions
- A clear definition and evaluation of potential "comparators" for pricing decisions

These four outcomes alone are justification enough to conduct PABs. It is equally important to understand what cannot be expected:

- Payers cannot make future commitments of course, nor can they make future predictions. While clinicians can easily state during advisory boards: "If you show X or Y, I will use your product", the same cannot be expected from payers. There are too many unknowns affecting future reimbursement and pricing decisions

- Payers cannot design clinical trials or write protocols. They can express what is important for them, but their insights have to be "translated" into activities by the Market Access and Clinical Development teams
- PABs are not an alternative to consulting services provided by organizations such as NICE or IQWiG. Those are very useful and informative tools but are country specific and are more applicable to the preparation of value dossiers than to decisions on global trial designs
- PBAs will help frame questions for additional payer and / or commercial market research but will need to be supported by such research

One thing that can be expected however is honesty. Payers have nothing to lose or gain from the decisions that are made by the company following the advisory board, beyond making their work easier several years down the road. This is contrary to clinicians whose participation to the advisory board often ensures participation to the resulting clinical trials with the associated benefits both financials and academic prestige. As a result, payers can be "brutally honest" in their assessments.

Overall PABs are a small investment for a very high return, providing substantial business value and helping generate consensus around hard portfolio rationalization or clinical development decisions.

Using the Insight Gained During Payer Advisory Boards – Input from the PAB on Business Decisions

While PABs provide highly valuable input, this input is only useful if it impacts future business decisions. Changing trial designs, or conducting new ones, should be based on a rigorous risk benefit analysis built upon detailed clinical, pricing and reimbursement hypotheses. PABs can help define the scenario to be evaluated, and can provide significant input on Market Access assumptions, but by themselves they do not allow to build the full models.

Case Study – Payer Advisory Board Leading to Another Phase III trial to Complement the Regulatory Trial

Our client was a mid-sized European company developing an innovative product in a highly competitive therapeutic area. The product is designed to be positioned between a relatively inexpensive but complex to manage first line, and highly expensive second line biologics. Our client has already approached regulatory authorities in Europe who have suggested a three-arm trial including placebo and an active control. We organized a PAB with representatives from 7 countries to validate that trial design and understand the impact on payer value perception. However it rapidly became clear that the active control discussed with regulatory authorities had little relevance in the majority of the countries represented, leaving payers with a significant uncertainty on the value of the product and demanding a second trial. We then discussed several trial designs against different active comparators to understand the impact of different designs for this second trial on potential pricing and reimbursement, ultimately coming to a clear recommendation for a non-inferiority study vs. a product priced significantly higher than the target price for our client product.

The next step was to analyze the costs and risks of this "payer specific trial", and the business implications of success and failure. Our client then make a fully educated decision on whether or not it wanted to fund the development of the product and with which combination of Phase III trials.

As a result PABs are the initial step in a process that includes many other internal stakeholders leading the optimal production of payer valued evidence.

Similarly, when used for portfolio rationalization, PABs are only one element leading to Go/NoGo decisions. We are not advocating stopping development programs based purely on PABs, but every asset whose potential value and differentiation are not clearly perceived by payers should be carefully re-evaluated with a very critical eye.

Key Success factors to Payer Advisory Boards

- PABs should be run from a business standpoint. They are impacting business decisions and investments, not technical decisions. All discussions and outcomes should be analyzed within the overall brand strategy
- Do not restrict company attendance to the Market Access team. Invite the clinical development team to the PAB. They need to hear first-hand the requests of the payers to understand the impact on product success. It is very beneficial and very sobering for clinical development teams to hear a group of payers from various countries clearly state: "If you conduct this trial, we will not reimburse your product"
- Provide feedback and build long standing relationship. Having a team of motivated payers that like to work with your company and can provide reliable advice regularly on the development portfolio is a critical capability
- Make sure that the rationale behind opinions is clear and well captured. In Payer advisory Boards the Why is often more important than the "what"

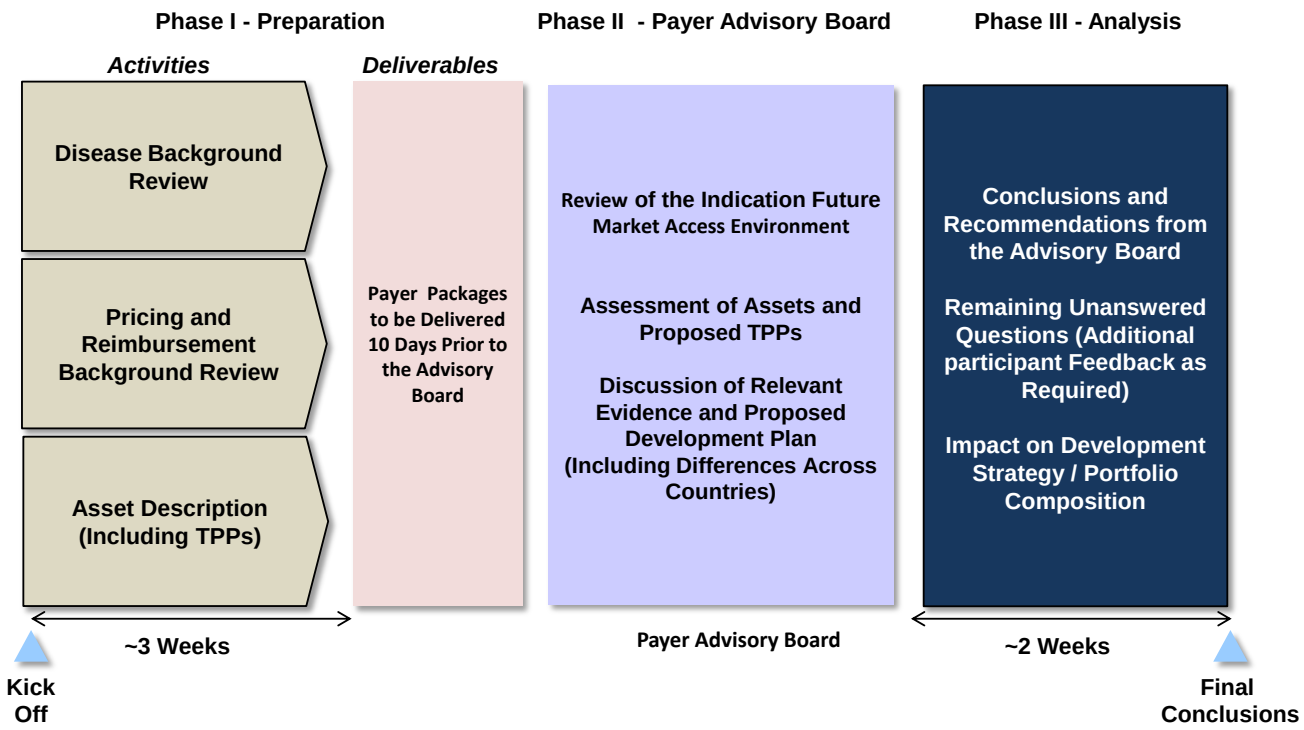
Our Approach

TCA and Mr. Ali have joined forces to organize and conduct efficient, informative and actionable Payer Advisory Boards. We are managing the full process from definition of the PAB objectives and composition, to the writing of the final report and the development of conclusions. We offer one point of contact with an experience pharmaceutical strategy consultant and an active payer / HTA member.

Mr. Ali chairs these advisory boards and leads the recruitment of participants. The "peer to peer" or "payer to payer" invitation process allows a strong likelihood of response and ensures high quality of participants. Mr. Ali runs the discussions bringing his strong understanding of the UK Health Technology Assessment and reimbursement processes, his perception as a payer, along with his insight on the development of value based pricing across European countries.

TCA is responsible for the preparation of the background and education material prior to the Advisory Board, for helping facilitate the discussion and for capturing the outcome of these discussions in clear recommendations and in consulting format. This approach, combining a leading Payer with a strong consulting firm allows for high quality participants and top level payer discussions, while ensuring that the outcomes are expressed and framed in a way that is directly applicable by the company management to make clear business decisions.

Payer Advisory Board Methodology



About Us: **Therapeutic Challenges Analysis** is an expertise-based management consulting firm dedicated to the business of healthcare. Founded in 2012 by former executives of Easton Associates and The Wilkerson Group, we bring decades of experience to our clients. We are leaders in the analysis of the impact of Market Access requirements on clinical development, business development, and portfolio management decisions.

About TCA ViewPoints: This white paper is part of a continuing series of TCA and Dr. Nicolas Touchot reports on the life science industry. For a complete list of our publications, and to subscribe to future publications, please visit our website at www.therapeuticchallenges.com.

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