

Pilots of multi-country, multi-stakeholder consultations in drug development: from proof of concept to tangible benefits

Executive summary

European health systems face significant fiscal constraints in meeting the increasing needs of their citizens at a time of intensifying austerity. Drug developers also face increasing competition for funds to invest in research and development of innovative products to treat unmet needs.

European healthcare leaders from eight Member States have completed six pilots of multi-country, multi-stakeholder consultations in drug development from mid-2010 through early 2012. The pilots have tested the feasibility and benefits of a novel approach to identifying the potential value of a new medicine along with the evidence required to demonstrate that value. The pilots have brought together the key constituencies along a drug's path from the laboratory to the patient – including regulators, health technology assessors, budget holders, clinical experts and patient representatives – in an early dialogue addressing the most significant questions facing the drug developer. The pilots evolved over the six consultations from a process similar to traditional early advice to a forum where stakeholders can address the total health system value proposition of the treatments under discussion. This report synthesises the lessons learned through completion of the pilot consultations, addressing drugs in five therapeutic areas from the pipelines of three pharmaceutical companies.¹

- **Tapestry and healthcare leaders co-designed the pilot consultations to reduce the risks of drug development and to increase its responsiveness to health system needs.** In order to avoid what one pilot participant described as *“losing access to good drugs simply because we don't have a system of rewarding them”* in the current economic climate, the dual objectives of the pilots have been to facilitate more effective research and development (R&D) spending and to generate more relevant data for assessments. Each consultation has focused on one or two pipeline medicines presented by a single company. The content of each pilot has been confidential, while process findings have been shared openly.
- **The pilot consultations improved the focus of drug development programmes and increased clarity regarding the value of new treatments.** Benefits to pharmaceutical innovators have included the reaffirmation or termination of development programmes based on feedback regarding the pipeline drug's potential value; the redesign of studies to better meet stakeholder requirements; reduced cost through the elimination of unnecessary studies; and enhanced alignment within companies regarding stakeholder requirements. Benefits to advice-givers have included the opportunity for improved assessments by influencing what evidence is generated about a medicine and mutual education through increased interaction with other healthcare institutions.

¹ This paper reflects the Network's use of a modified version of the Chatham House Rule, whereby names of participants and their affiliations are a matter of public record, but comments made during meetings are not attributed to individuals or organisations. Quotes in italics are drawn directly from comments made by members and guests participating in the pilots.

- **Multiple factors contributed to the effectiveness of the pilot consultations.** Those factors included effective project management within an agreed organisational structure; participation by a diverse and knowledgeable group of sitting officials, patient representatives and domain experts; adequate resourcing and preparation to support meaningful contributions to the discussion; equal standing among participants; and active co-chairing.
- **The pilot consultations highlighted commonalities and differences among participating stakeholders.** Commonalities included perspectives regarding the proper sizing of proof-of-concept studies; the importance of treatment pathways in the choice of comparators; the validation of surrogate endpoints and the importance of starting outcome studies early; and the importance of patient outcomes data. Differences included perspectives regarding requirements for active trial comparisons; consideration of anticipated future clinical practice; and demonstrations of patient and economic outcomes.
- **The pilot consultations evolved from proof of concept for multi-country, multi-stakeholder early advice into a more candid and open forum for addressing strategic questions.** This evolution was reflected in an increased open-mindedness and comfort among participants through repeated interactions; an increased willingness to address strategic issues and to propose novel solutions, rather than limiting responses to a narrow reading of the development teams' questions; and improved presentation of the pipeline medicine and consultation questions through the company's briefing book.
- **Pilot participants identified the multi-country, multi-stakeholder forum as being most appropriate for addressing the total health system value of new treatments that raise complex questions of health policy.** As distinct from and complementary to traditional scientific advice, they noted the opportunity through a multi-multi forum to steer the entire clinical development plan and shape the total value proposition package for a new medicine. Participants agreed that this form of advice is most likely to be appropriate in the case of truly novel or transformational drugs or therapeutic areas that elicit different approaches among stakeholders, and development programmes seeking an integrated, multi-stakeholder strategy to obtain relevant data in clinical trials.
- **Pilot participants support a sustained mechanism for applying their experience with multi-country, multi-stakeholder consultations to further drug development issues.** The pilot experience suggests the need for an infrastructure of institutional linkages to support collaboration among healthcare institutions, patient representatives and clinical experts. Necessary components of such an infrastructure are likely to include an agreed governance model, effective integration of operating practices, and appropriate resourcing.

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Introduction

European healthcare leaders representing drug developers, public institutions, academia and civil society have completed six pilots of multi-country, multi-stakeholder consultations in drug development from mid-2010 through early 2012. The primary goal of these pilots was to test the feasibility of engaging a diverse group of senior decision-makers to improve clarity and alignment on the questions of what constitutes a pipeline medicine's value and what evidence is required to demonstrate that value most effectively.

Each consultation engaged sitting healthcare decision-makers, along with patient representatives and content experts, in a discussion of strategic issues raised by a company development team about a pipeline drug. While the drug-specific content of each consultation remains confidential, participants regarded the general process findings from the pilots as a public good to be shared. The pilots have thus given rise to a shared basis of knowledge and experience regarding the benefits and limitations of a multi-constituent approach to informing drug development. Participants noted that the pilots evolved over six consultations from a process similar to traditional scientific advice to a forum informing the entire clinical development path to reflect the overall value proposition of the medicine to health systems. Experience with the pilot process can inform and complement other on-going experiments, including combined regulatory and HTA advice at the country level and combined HTA advice across multiple countries.

This report summarises the learning from these pilots.

Consultation participants and areas of focus

The pilots were designed to engage all the major stakeholder groups on a drug's path from the laboratory to the patient. Participants in the pilot consultations included the following:

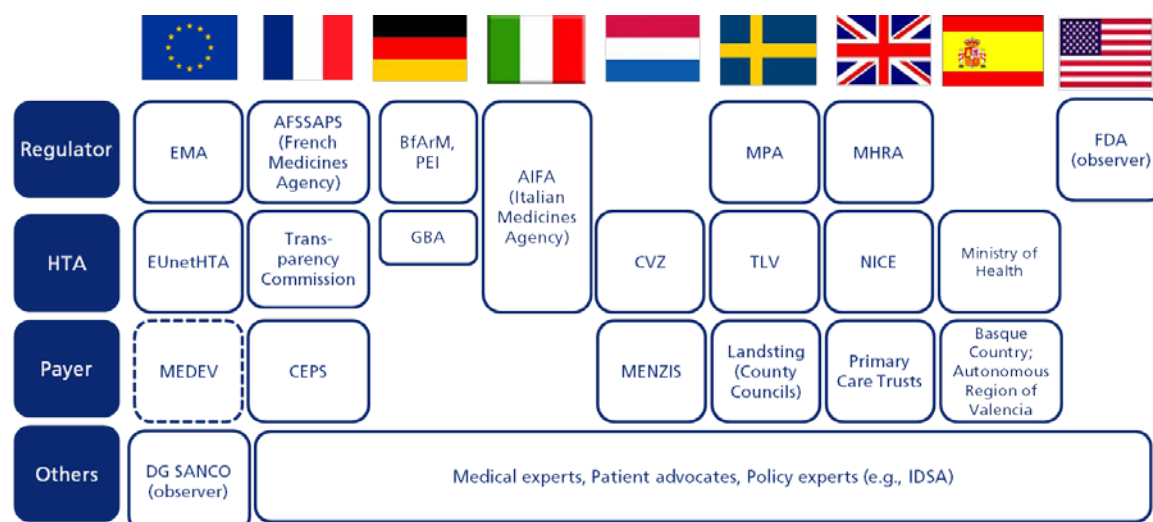
- Regulators, including the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), the latter as an observer for the sixth pilot
- HTAs
- Payers and budget holders
- Pharmaceutical innovators
- Subject matter experts, patients, and patient and policy advocates, as providers of content-specific input appropriate to the therapeutic area and questions raised

As the initiative’s sponsors, AstraZeneca, GlaxoSmithKline and Johnson & Johnson provided pipeline medicines for the consultations. These three companies were joined by Bristol-Myers Squibb in summer 2011. Table 1 below provides an overview of the six pilot consultations.

	Sponsor	Therapeutic area	Approach	Phase
Pilot 1 25 Oct 2010	AstraZeneca	Type 2 diabetes	New strategy to create value in disease area in the context of global risk with multiple risk factors	I
Pilot 2 2 Dec 2010	GlaxoSmithKline	Type 2 diabetes	New mechanism of action with proposed novel endpoints to asses value	IIA
Pilot 3 3 Feb 2011	Janssen (Johnson & Johnson)	Breast cancer	Two development strategies focused on targeted subpopulations with accompanying diagnostic; no precedents for one area	II
Pilot 4 1 July 2011	Janssen AI	Alzheimer’s disease	Strategy for new indication and approach to patient identification	II
Pilot 5 2 Dec 2011	GlaxoSmithKline	Melanoma / NSCLC	Application of data to new indication and development of a companion diagnostic	III
Pilot 6 3 Feb 2012	AstraZeneca	Antibiotics	Approach to new indications for 2 new drugs, valuation of antibiotic stewardship, reimbursement strategy for emerging infections	II

Tapestry Networks co-designed the pilot process with participating institutions and convened each consultation in accordance with its guidelines for public-private collaboration. At the end of this document is a list of Tapestry’s principles and guidelines for public-private networks in the European Union.

The consultation process and the quality of engagement among participants improved over the course of the pilots, through a natural evolution and an active focus on learning and development. Participants are working to incorporate findings from the pilots into the drug development landscape to provide a focused complement to other forums for early advice. Table 2 below provides an overview of the institutions contributing to the pilots.



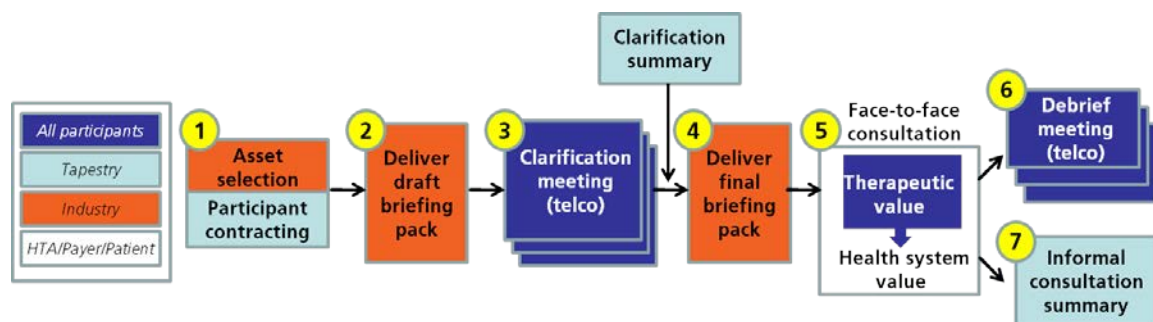
The pilot consultation process

Each pilot followed a multi-stakeholder early-advice process that participants co-designed based on experience with existing advice processes. Each consultation involved a single company and proceeded under an agreement to keep the discussion's content confidential, as it pertained to the development of a pipeline medicine. On the other hand, participants similarly agreed to share findings about the consultation process openly outside the pilots.

A pilot consultation began with a participating pharmaceutical company selecting a pipeline drug that raised questions on which the development team sought an integrated perspective across stakeholders. Tapestry worked with the company to recruit relevant stakeholders and reached agreement on terms for engagement with each participant (step 1 in the diagram below). The drug development team then produced a briefing document to provide background information and to detail specific questions on which the team sought stakeholder perspectives (step 2).

A series of clarification teleconferences enabled participants to clarify the company's questions and to request any additional information required to respond to the questions (step 3). After distribution of the revised briefing document (step 4), the process culminated in a face-to-face consultation, hosted by the EMA (step 5). The focus of the face-to-face meeting was an interactive discussion among all stakeholders present, guided by the questions raised in the briefing document.

After each consultation, Tapestry debriefed pilot participants to gather input to refine the process and distil findings (step 6), and distributed a set of informal minutes summarising key points of the discussion (step 7). The figure below provides an overview of the pilot process.



The pilot consultations were designed to reduce risk to all stakeholders and increase the responsiveness of drug development to health system needs

The pilots were initiated in response to a need for greater clarity and alignment on “value for money” due in large part to the effects of the European debt crisis: “*The current economic climate is accelerating the need to understand value.*” If resources are not allocated to the most valuable drug candidates, one participant said, “*it raises the prospect of losing access to good drugs simply because we don’t have a system of rewarding them.*”

More effective R&D spending

Participants supported the development of the pilot consultations as *“a step to becoming more efficient in drug development and reducing the cost of development programmes.”* The aspiration for drug developers was that *“this process will allow us to focus the resources and better manage the risks for all the parties involved.”*

HTA representatives and payers agreed that the consultations could support *“decisions about how best to use limited healthcare budgets”* and would provide the opportunity *“to help industry choose what society really needs and what health systems will value.”* As one industry representative summarised, the goal is that *“[the company] can make a profit while [health systems] can have access to good drugs at a reasonable price and manage patients better.”*

More relevant data for assessment decisions

Participants also designed the consultations to provide a forum for a drug’s eventual evaluators to consider and convey what evidence they will need to make an informed judgment. HTA representatives and payers agreed that a collaborative process will lead to *“better data on which to base our decisions.”* An HTA participant explained, *“Too often I get an application and cannot make an appropriate decision because the company has not done the right studies.”* A patient representative commented, *“It is such a waste of money when, as we have seen so many times, a medicine is registered through the EMA, but then the reimbursement agency concludes that the data is insufficient to show added therapeutic value.”*

Participants observed that the *“different responsibilities of reimbursement agencies and the registration authorities”* resulted in fragmentation of evidence requirements, emphasising the *“need to build up a common language amongst regulators, reimbursers and payers.”* An HTA participant opined that if a company considers the needs of downstream participants sufficiently early in its programme, it can *“use the opportunity of its trials to collect data for multiple audiences.”*

The pilot consultations improved the focus of drug development programmes and increased clarity regarding stakeholder needs and evidence requirements

The six pilot consultations demonstrated the utility of these forums in making progress on the key challenges of more effectively focusing drug development spending and providing relevant data to decision-makers who assess new medicines. Stakeholders shared tangible examples of how they have addressed these challenges through the pilots, while building collaborative engagement and creating opportunities for mutual education.

Benefits to pharmaceutical innovators: valuable feedback to focus development programmes

Companies viewed the multi-stakeholder consultations as an important vehicle to reduce waste and to increase the likelihood of success in their development programmes: *“It is absolutely key*

to have this interaction not with one body at a time but to get everyone into the same room to see the total picture of the best strategy for developing a new drug.”

Stakeholder advice to companies ranged from confirming the value of pursuing a programme, recommending that a study be redesigned and advising that a study not be pursued. Additionally, the consultations helped companies to achieve internal alignment on the best way to address the demands of their multiple stakeholders.

Confirmation of potential value

The consultations provided some development teams with feedback on whether stakeholders saw value in their development programmes and would support the end product, given appropriate evidence. For some, as one participant described, *“[the most valuable] input was not about what I needed to do next; rather, I needed to know if something I perceived to be important was perceived as such by others.”*

- In one case, *“The pilot kept alive the indication [that we were working on] ... It was an ‘out there’ idea that gained legitimacy and momentum.”* A colleague concurred, *“The consultation showed how to develop novel molecules that have different clinical profiles to meet unmet needs and address endpoints that other molecules don’t ... The stakeholders gave support for moving the molecule forward.”*
- In another case, the development team terminated development of the medicine, *“partly on the basis of the consultation feedback.”* A member of the development team explained, *“The advice provided extremely important information. Knowing early that the medicine’s target profile would not give it any better position in reimbursement than existing drugs was very helpful.”*
- After a different pilot consultation, a company representative noted that even though *“some endpoints were acceptable to regulators but not to HTAs,”* the company received *“clear approval of the specific phase”* of the disease that it was targeting for treatment, supporting continuation of the programme.

Redesign of studies based on stakeholder feedback

Development teams redesigned studies in their programmes or incorporated additional analyses based on stakeholder consultation.

- Based on one pilot consultation, the development team altered the proof-of-concept study to lay the groundwork for performing future confirmatory trials. A payer advised the company, *“At this stage ... you ought to invest in getting an important answer right at the beginning rather than potentially waste huge amounts of money later. It sounds financially sensible to take the approach of longer and bigger studies at the beginning.”*
- A different pilot team altered its choice of comparator: *“What we learned was that our choice of comparator is not the standard of care in many countries ... and some people were not even interested in the standard of care, but rather a cost comparator arm in the trial ... It*

made us think long and hard about how we will design trials to show that the medicine is not just effective but is also the most cost-effective option.”

- Another development team was able to incorporate additional statistical analyses into its evidence package to support and explain the drug’s value. A team member explained, *“We performed extra statistical analyses to provide information on the standard-of-care comparator in our study ... The consultation shaped our launch strategy [particularly with regard to] how to present [the product] to payers.”*
- Yet another development team gained insight about how to account for the cost of diagnostics in the use of its medicine: *“One of the interesting learnings that came out was how many patients you have to apply the [diagnostic] test to who would not receive your treatment. [That number] gets added onto the global healthcare assessment in terms of cost. That was a very, very important point.”*

Reduced cost by eliminating unnecessary studies

Other companies decided to forego costly studies that particular stakeholders did not find valuable.

- One team was able to scale back its real-world evidence programme: *“We thought we needed real-world evidence [for one issue], but an HTA leader told us he needed something else instead ... It was an ‘aha!’ moment that allowed us to scale back some of our requirements and take those costs out.”*
- Another development team was able to eliminate an imaging study that participants *“did not see as an added benefit.”* This allowed the company to cancel a study that *“could run from 40 million euros and [would be] very long and very complicated. Understanding that the end customer’s view is that this is not very valuable ... We would not do [the trial] and [would] rather invest in studying clinical outcomes.”*

Enhanced internal alignment

Participating in the consultations made it easier for companies to align internally on how best to meet the needs of their various stakeholders.

- One company representative said, *“What I found unique is that [everyone] made an investment in the briefing package and that led to broader adoption of the advice received ... Instead of the market access folks beating the drum of payer value, that value is internalised ... It helped the programme to be more oriented not just toward regulatory approval.”*
- A representative from a different company added, *“When regulators and payers are in the same room, feeding off each other’s responses, that adds value to our interpretation of their responses.”* Another team member commented, *“We could see where the risks exist in the different perspectives – how large or small a gap is between stakeholders – and it helped to decide on trade-offs among the demands of the stakeholders.”*

- Other company participants emphasised the impact of the consultation on improving internal alignment regarding a development programme: *“The consultation helped develop accord with senior leaders concerning the viability of the product.”*

Benefits to advice-givers: mutual education and the development of more relevant evidence for assessments

For non-industry participants, the consultations provided opportunities to influence development programmes to yield evidence of relevance to their assessment needs, concrete insight into emerging health policy questions as well as opportunities to engage with their peers from other institutions on complex drug development questions.

Improved assessment through input into what evidence is generated

Participants agreed that the multi-stakeholder consultations provided benefits to assessors by clarifying the types of evidence that each stakeholder group finds valuable. An HTA participant commented that even though *“it has yet to be shown what happens when we get the application from the companies, I’m sure that we will make faster and better assessment of their applications.”* A payer concurred, adding, *“When the drug comes to our own tables, we will have a better understanding of the discussion that led up to it.”* A different HTA participant noted that candid, early conversations make it more likely that she will have access to the data she needs for assessment, stating that the *“openness of the forum makes it less likely that [my agency] will be frustrated when we see designs of studies with inappropriate comparators and it is too late for us to do anything about it.”*

Insight into policy implications of emerging technologies and health threats

Several participants agreed that the most appropriate application of the multi-country, multi-stakeholder forum is *“to shape the final complete value proposition of a new medicine.”* As an HTA leader pointed out, *“that includes having discussion on the very broad level, on the health policy level.”* A senior drug developer commented that *“some issues fall through the cracks between regulatory, HTA and total healthcare policy and that is where the value of the multi-stakeholder forum is.”* In this context the consultations provided a concrete forum for healthcare leaders to engage emerging and established questions of health policy within their remit: *“Some of the challenges that emerged from the [latter three] pilots are as much of a challenge back into the healthcare system as they are for the manufacturer. These are challenges that we are all dealing with and we don’t have ready answers.”*

Increased stakeholder interaction and mutual education

While some participants were more satisfied with the degree of stakeholder interaction than others, most agreed that the forum offered a significant opportunity to learn about other stakeholder groups’ values and requirements. An HTA participant in a later consultation observed, *“I expected more exchange of information between [non-industry] stakeholders, but I think every stakeholder took home something to change.”* Specifically, at one consultation, a regulator observed, *“Regulators realised that they must find a compromise between statistical*

rigour and clinical constraints, [and] experts helped the multiple regulators taking part in the consultation to align their views amongst themselves.”

HTA and payer participants stated that interactions with clinicians and regulators were particularly helpful. Clinical experts added great value to the consultation, especially when *“thinking can evolve during a meeting and you want to check with a clinician to make sure the advice is feasible and relevant [based on] what actually happens in practice.”* An HTA representative who focused on antibiotics emphasised interactions with regulators: *“The heterogeneity and fragmentation of HTA systems is frightening with this subject, [but] HTAs can signal to regulators what are the areas of unmet needs and urgencies.”* For their part, payers were able to act on the *“need to build up a common language with other stakeholders so they understand what payers require.”*

Patients and patient advocates added an additional educational element to the consultations. A patient commented, *“Involving patients at an early stage can bring clarity for other stakeholders on particular issues. People say, ‘We know patients will think this or that’ ... for example, patients will be very emotional, they want access to everything and will think only about their own situation. But when you ask the patients themselves, they will come up with a completely different view and make critical comments about the quality of research, the extent of benefits and the value to patients.”* An HTA participant agreed that the patient perspective added value to the consultation: *“What we need here is the individual patient perspective, without influence of other stakeholders.”*

Participants were also able to take the lessons learned from the consultation back to their institutions. A payer participant commented, *“Deliberating inside my agency [about the consultation] has been really important ... We want to be sure that as a national authority we will be able to give a specific answer to each one of the questions.”* An HTA representative said, *“I think we’re going to come out better at a national level as an agency with this process as a preparation for the future.”*

Multiple factors contributed to the effectiveness of the pilot consultations

Participants identified multiple factors contributing to the success of the pilots. A consultation process requires active project management to ensure that the pilot runs smoothly for all parties and that the development team has crystallized the key issues for the consultation. Further, each consultation must engage an appropriate group of stakeholders, in terms of size and expertise. All participants and their respective institutions must be supported by adequate resourcing so that they can fully engage with the issues raised in the consultation. At the consultation itself, all stakeholders need to have equal standing and equal access to information; toward that end, regulatory and HTA co-chairs must actively lead the consultation and elicit comments.

Effective organisational structure

An HTA participant noted the importance of *“project management”* in running a pilot in early advice, emphasising that *“the organisational side of things is very important – early*

scheduling so that everyone shows up at the right time, executing contracts, making sure the companies know what they're doing – it's not just about giving advice." For these pilots, Tapestry Networks, as a neutral third party, developed an effective organisational structure and oversaw its implementation. This role consisted of the following:

- Co-designing the pilot process with participating healthcare institutions
- Working with pharmaceutical innovators to identify appropriate assets, frame strategic questions and develop briefing documents
- Recruiting institutional representatives, experts and patient advocates
- Briefing all participants and ensuring that a transparent and equitable scheme for resourcing was available
- Leading clarification calls and producing a summary of feedback
- Understanding and communicating the skills required for effective co-chairing of consultations
- Co-developing an agenda for the consultation meeting with the development team and co-chairs
- Managing logistics and scheduling for each consultation meeting
- Debriefing participants and developing an informal consultation summary
- Continuously improving the pilot process based on participant feedback

Reflecting on the pilots, one payer commented that he could *"participate more openly in these meetings [because] they are run by a third-party neutral ... Other agencies and patients participating lent credibility as well ... It is much more difficult if a company contacts me directly."*

Diverse and knowledgeable participation

Each pilot consultation brought together a combination of actual, sitting decision-makers and independent experts with expertise relevant to the consultation topics. Participants found that experts recruited by a third-party intermediary without a stake in the outcome lent further credibility to the pilot process because they were unbiased by ties to the stakeholder groups present.

Participants noted that there was a trade-off between the number of stakeholders represented in the consultation and the depth that each could contribute to the discussion, given limitations on time. There was thus a need to balance depth and breadth so that the company received valuable input for its development programme, given that *"the more institutions [that are present], the less depth you can have."*

Further, participants who added the most value to consultations, according to their peers, were those who were active, willing to take risks when facing uncertainty and open to other

perspectives. One industry participant suggested, *“Everyone should feel a mandate to contribute [because] if we do not get all stakeholders’ views, the value of the multi-stakeholder meeting goes down.”* A regulator noted that the informality of the forum should *“encourage more openness and detailed responses to the company.”*

While patients are not typically involved in early-advice processes, these pilots served as an experiment in including the patient voice. Some stakeholders expressed discomfort with the patient presence: *“We understand that regulators and payers must make difficult decisions that may deny treatment to patients, and we want to have a frank discussion around [those decisions], without the emotional aspect that a patient brings.”* However, other stakeholders found it valuable to hear contributions of affected patients alongside budget-constrained payers who may limit access to medicines.

Participants emphasised the value of an independent patient voice, with a payer commenting that he could *“speak openly in this consultation,”* in part because *“the patient presence shields [me] from criticism of co-operating too much with industry.”* An HTA participant added, *“It’s very fruitful to hear from patient organisations.”*

Participants noted the importance of *“preparing patients so that they can understand [technical details] and participate fully”* and suggested that generally *“one patient voice is too few”* for a consultation.

Adequate resourcing and preparation

Multi-stakeholder consultations are resource intensive and require preparation to address the diverse issues raised by the development team. The pilot process required at minimum a commitment to read and reflect on the briefing book, participate in a one-hour clarification teleconference, potentially to *“consult with experts”* to prepare sufficiently detailed responses to the company’s questions, attend the four-hour consultation and participate in a one-hour debriefing teleconference. By way of comparison, however, according to an HTA participant, the multi-stakeholder pilots *“required less time than advice at the national level.”*

Each institution followed its own mandate for giving advice. Thus, the EMA contributed significant time and resources, through its traditional Scientific Advice Working Party process, to produce a written response to the company. AIFA (the Italian Medicines Agency) also contributed written responses for consultations that it attended. Many HTA institutions, however, either do not provide written advice in their own processes or did not do so in these consultations.

The pharmaceutical companies that contributed the pipeline drugs *“invested quite significantly”* in these consultations. Each company *“brought together a team across R&D, regulatory, HTA and payer [functional units] at an unusually early stage in the development process, which led to greater understanding of each other’s challenges and solutions.”* Although *“man hours were a challenge,”* the general conclusion was that *“the pilots are a worthwhile investment [and] there will likely be a tendency for earlier engagement between development and market access units [in the future].”*

Equal representation and active co-chairing at the consultation meeting

To maintain an open dialogue, all parties in the consultations participated with equal standing. Participants have suggested that this characteristic differentiates the pilots from other advice forums. One industry participant reflected, *“I have plenty of experience attending [other advice] meetings. They are very formal, the atmosphere is more inquisitorial and the industry [participants] may feel sometimes to be on the defensive. This was not what we experienced in the pilots. We felt relaxed, and that genuinely people were really engaged and interested in understanding others’ points of view.”*

Each consultation was co-chaired by a regulatory participant and an HTA participant, to encourage contributions and perspectives from all stakeholders. Over the course of consultations, the different chairs became more active in soliciting responses from participants to enrich the multi-stakeholder discussion.

The consultations provided lessons in best practices for chairing: chairs should strive to *“be proactive”* in engaging all parties and be able to *“produce lively engagement.”* It is the role of the chair to *“probe and challenge”* all stakeholders to participate and to *“steer the meeting by following a structured plan”* in order to *“maximise use of time.”* Consultation worked best when *“chairs more actively steered around the table so that as many people as possible gave answers to as many questions as possible ... Calling on people also offered non-English speakers positive pressure to speak.”*

The pilot consultations highlighted commonalities and differences among stakeholders

In the opinion of several participants, the pilot consultations provided a rare opportunity to compare how regulators, HTAs and payers addressed the questions raised by development teams. While not supporting a systematic comparison, the consultations did provide some valuable anecdotal insight into the different ways these stakeholders approach the question of value in new medicines and how that value should be demonstrated.

Commonalities among stakeholder perspectives

The pilots highlighted commonalities among stakeholder perspectives on the value of new drugs and the evidence needed to demonstrate that value. One HTA participant commented, *“I don’t think the differences [between stakeholder groups] are as great as everyone anticipated before the consultations ... Often you can satisfy the needs of the HTA in a trial without changing what is being done for the regulators.”* Participants noted similarities in stakeholder perspectives regarding proof-of-concept studies, choice of comparators, validation of endpoints and generation of outcomes data.

Proper sizing of the proof-of-concept study

Pilot participants emphasised across consultations that a proof-of-concept study should be of a size and scope required to persuasively settle the questions it is designed to answer. In one consultation a regulator advised the company, *“You’ve put too much into this proof-of-concept*

study. You have tried to show that the medicine will work in some types of patients but not the others; that it will be better than [a comparator]; that the two doses will discriminate. I think it's a little bit too ambitious.” To lay a firm foundation for a development programme, a payer suggested “taking an approach of longer and bigger studies at the beginning.”

Importance of the treatment pathway in choosing comparators

Regulators and reimbursers alike advised development teams to focus on the drug's proposed position in the treatment pathway when choosing a comparator. One HTA participant suggested that *“focusing on the clinical pathway and thinking about where you want to place your product”* was more important than making comparisons according to effectiveness in reaching a particular endpoint. A regulator added, *“Regulators would agree that the most important consideration for developers is the position in the therapeutic pathway of your product.”*

Validation of surrogate endpoints and the importance of starting outcomes studies early

Participants agreed that surrogate endpoints derive their value from their ability to predict outcomes accurately and noted the intrinsic difficulty in providing evidence toward validation. A regulator in an early consultation recognised that *“if we are talking about surrogates then we need to validate them, and it is probably a difficult task.”* An HTA representative added, *“From our perspective, the degree to which a surrogate is useful is the extent to which it predicts those final outcomes that we are interested in ... The more data you have and the longer period for which you have data, the less uncertainty in the extrapolations.”*

HTAs and regulators both encouraged development teams to integrate outcome studies early in the development programme. An HTA representative advised *“thinking about HTA as well as regulatory evidence earlier [in a development programme] to make it more likely that trials are done the right way.”* A regulator agreed, recommending that *“you should start your outcome study very early – that's not mutually exclusive with showing that you have a sustained effect on the [endpoints].”* A regulator summarised the participants' recommendation: *“within the same development plan, to come to the marketing authorisation with a sustained effect on the biomarkers ... and as soon as possible after the marketing authorisation, to come out with [the] outcome study that you will have started early in the plan.”*

Patient outcomes data

While stakeholders at the pilots played different roles in requesting and assessing outcomes data, they shared similar views on its importance in providing patients with safe and effective medicines. During one consultation, a regulator clarified that the EMA is limited in what it may request from companies in terms of outcomes data, but also mentioned that new pharmacovigilance legislation may give the EMA *“an opportunity to ask for efficacy and safety studies within the risk management plan.”*

An HTA representative highlighted the importance of regulatory leadership in collaborating with companies to generate long-term outcomes data: *“Those times when we have come the furthest*

in the discussions with the companies is when the EMA in the first place has said something about a need for follow-up.” A regulator added, “I think that the learning in [my country] is that commitments and restrictions should be put in place by EMA so that it is easier for reimbursers to make certain requests to developers in the future.” Turning to the payers in the room, the regulator continued, “Another possibility for the regulators may be to discuss with the payers which type of effectiveness studies should be incorporated in the risk management plan.”

Differences among stakeholders in approaches and requirements

While diverse stakeholders shared some common perspectives regarding the drug development process, HTAs and payers demonstrated distinct evidentiary needs from their regulatory colleagues for assessing new drugs across the six pilots. These differences include preferences for trial comparisons, attitudes toward integrating real-world practice and requirements for links to patient and economic outcomes.²

Trial comparisons

When assessing trial design, regulators sometimes require only placebo-controlled trials to demonstrate safety and efficacy, whereas HTAs and payers often require comparisons to other available treatments to demonstrate cost-effectiveness and added benefit. For example, in one consultation, regulators accepted a placebo-controlled trial, questioning only the small percentage incremental benefit suggested by the company, while an HTA representative advised the company, *“If you want to improve [demonstration of this added benefit of your drug], look at the comparators doing the same or trying to do the same.”* This reimbursement request for head-to-head comparisons became a theme across consultations.

Future clinical practice

HTAs and payers demonstrated more interest than their regulatory colleagues in ensuring that clinical trials reflect current and anticipated conditions of clinical practice. In one consultation, an HTA representative advised the company to *“consider how you think [the drug] is actually going to be used in practice, what its comparators will be, what variations there might be around different jurisdictions, and whether your approach will allow you to cope with those variations.”* Thus, companies that take into account real-world clinical practice in their trials are more likely to produce evidence requested by reimbursers as well as regulators.

Patient and economic outcomes

Even though regulators note the importance of links from endpoints to outcomes, HTAs and payers are more likely than regulators to require links to long-term outcomes in targeted patient populations for their assessments. While regulators may be satisfied by a demonstration of statistical improvement in an endpoint for purposes of safety and efficacy evaluation, a reimbursers

² Similar findings are presented in ME Backhouse, M Wonder, E Hornby, A Kilburg, M Drummond and FK Mayer, “Early Dialogue between the Developers of New Technologies and Pricing and Reimbursement Agencies: A Pilot Study,” *Value Health* 14, no 4 (June 2011), pp 608–15.

is more likely to suggest *“measuring the quality of life at the points when the patients are in the different health states.”*

Further, regulators may request safety data from a broader population, whereas reimbursement authorities prefer that patient outcomes be demonstrated in patient populations that are likely to benefit most from the drug tested. An HTA participant suggested targeting a specific patient population, noting the tendency of some reimbursers *“to restrict reimbursement to smaller populations than the indication initially given at the EMA.”*

HTAs and payers additionally place more emphasis on links from trial data to economic outcomes than their regulatory colleagues. For example, an HTA participant in one consultation stated, *“From a reimbursement perspective, the evidence for a therapeutic benefit leading to decreased costs of hospitalizations is important for us ... You need to create some link.”* A payer observed, *“Regulators seemed less stringent, because HTAs and payers want studies big enough and long enough with sufficient patients to demonstrate outcomes.”* By creating links to longer-term patient and economic outcomes, companies are more likely to gain reimbursement.

The pilot consultations evolved from proof of concept into a more candid and open forum for addressing strategic questions

As the series of pilots progressed, participants noted the development of greater openness and a common language among participating stakeholders. This shift in mindset opened the door to a willingness to address more open-ended, strategic issues relevant across medicines, and for non-industry participants to propose new strategies to the companies, rather than simply reacting to company positions. For their part, company development teams learned to develop briefing books that more effectively frame their strategic questions and provide the necessary data to support the discussion. Tapestry served as a bridge across the pilots, debriefing consultations and sharing findings with participants.

Increased open-mindedness and comfort through interaction among stakeholders

Particularly in early pilot consultations, participant communications focused upon differences in the stakeholder groups' approaches to drug development in general and to the pilot process in particular. However, repeated interaction over the six pilots alleviated some of these tensions, and one regulator *“noticed a big improvement in communication and outcomes as participants [got] to know each other.”*

Narrowing differences in the various stakeholders' approaches to the consultations

Consultation participants – representing various stakeholder groups engaging with challenging drug development questions together for the first time – noted differences in assessment styles and approaches. Regulators at times expressed a preference for greater detail in the responses of their HTA and payer colleagues, suggesting that *“participants need to uncover themselves and not be so shy.”* One regulator wondered whether the disinclination of his reimbursement colleagues to produce written responses indicated a lack of transparency in methodology, and a

different regulator added, *“A structured written response from HTAs would help tremendously in getting the different groups to understand one another.”*

For their part, reimbursers felt that they already understood *“what regulators want because reimbursers routinely build on results of the EMA,”* and because of their position in the drug development pathway, *“regulators have more to learn from other stakeholders than other stakeholders have to learn from the EMA.”* While other stakeholders recognised that regulators must follow *“rules and procedures,”* they suggested that regulators could be more flexible and wondered *“to what extent regulators’ hands are tied by legislation.”*

Payers emphasised that, unlike the other stakeholders, they must *“look at the impact [of a new drug] on the whole system, not just considering each product as it comes along in isolation,”* and they expressed hope that their participation in the pilots would help *“upstream stakeholders to understand payer resources and requirements.”*

Improving consultation outcomes over repeated interactions

As participants occupying different roles, perspectives and geographic homes grew accustomed to addressing together the questions raised about a particular development programme, they created an atmosphere of open-mindedness and a *“sense of shared responsibility.”* A regulator commented, *“Participants got to know each other with conference calls and [over the course of multiple consultations] ... It showed that everybody was able to discuss more in depth, and the discussions became better and the outcomes more useful for the companies.”* An HTA representative agreed: *“I think there has been some growth in mutual understanding over time ... There was actually more confidence on the part of the participants to contribute because we understood one another a bit better.”*

However, participants recognised that breaking out of deeply rooted mindsets is *“not something you can achieve over one consultation; it is something you have to practice over time. You must want to understand other parties’ needs to create a shift in mindset.”* One industry participant summarised, *“The discussions in the consultation, and in similar meetings elsewhere, will help improve these processes over time, in different ways, in different countries as the systems evolve.”*

Increased willingness to address strategic issues and to propose novel solutions

Consultation participants accustomed to their traditional roles of giving advice based only on available data and proposals from the company displayed an increasing willingness to consider more open-ended, strategic questions and to jointly identify novel solutions. At an early consultation, an industry representative observed, *“[Regulators and HTAs] do not engage in hypothetical discussions ... [For early advice] we need to change that mentality of ‘show me the data before I am willing to respond.’”* An HTA participant agreed: *“Reimbursers have to learn to think about added value in advance, not just when the data is already there ... [In these consultations] we are forced to discuss what we don’t know and give as much as possible in this [early] stage of development.”*

The evolution of strategic thinking in the pilots was evident after the sixth consultation (focused on a novel antibiotic combination for treating multi-resistant infections), when a regulator declared that the consultation was “a success” because “the discussion went beyond products and into a global problem.” An industry participant agreed, saying that the “forum was good for tackling specific issues around products and also broader strategic questions – there should be a mix.” Thus not only were stakeholders willing to engage in more open-ended conversations, but they also showed appetite to consider issues broader than the specific products in question. Even with this evolution, however, one stakeholder observed, “People could have been more open, but it is difficult to position yourself when you represent a public authority ... You don’t want to commit too early.”

The increasing openness of pilot participants to engage with difficult questions jointly with their peers allowed them to suggest their own solutions to the company’s questions. A patient advocate in a later pilot observed that it was “encouraging that people felt able to be frank and not simply articulate their organisation’s policy.” An HTA representative noted, “There are few places where regulators, HTAs and payers can interact with and understand each other ... The perspective on drug development is more powerful if it comes straight from other agencies, and the sentiment is more so when stakeholders look to each other for solutions.”

Improved briefing book presentation of pipeline drugs and consultation questions

Over the six multi-stakeholder consultations, companies, with Tapestry’s support, developed an improved capability to generate briefing books that frame strategic questions and provide necessary data to support a multi-stakeholder discussion. Following early pilots in which briefing documents were relatively light on data, participants requested that future briefing documents contain “more information on why questions are important to the company, how the company came to the questions it asked, and how the company wants to develop the drug in the context of the treatment pathway.” Stakeholders further requested that the document provide a “balance between data and assumptions” and “a position upon which to comment.”

Tapestry integrated this feedback and worked with development teams in later consultations to develop more effective briefing documents. Companies were advised to phrase questions in an open-ended manner to generate a broader range of responses and to limit and prioritise those questions through discussions during clarification calls and with co-chairs prior to the meeting. One stakeholder noted, “Over the several consultations, we saw an improvement in the content of the briefing documents.”

An HTA expert commented, “What became better is not only that ... there were questions for all participants, but there were also questions which were addressed only to the HTAs and payers, for example. This procedure turned out to be very useful for both types of questions.” A patient appreciated that later consultations “directed questions to patients in particular.” Companies also made improvements by offering concise appendices and full-text copies of key supporting references for interested stakeholders, rather than addressing technical details not directly relevant to the questions in the body of the document. These developments led to a

more rewarding experience for all stakeholders throughout the process, and also to better discussion and advice during the consultation.

The pilot consultations identified the types of development challenges for which multi-country, multi-stakeholder advice is most appropriate

A multi-country, multi-stakeholder consultation is one of several forums from which a company may seek advice on its programme. These consultations are intended to complement, not supersede, existing advice processes. Several participants noted that over six consultations the pilots evolved *“from addressing questions very similar to the traditional scientific advice process to those that are very much about steering the entire clinical development path.”* This experience suggests that the most appropriate application of the multi-country, multi-stakeholder forum is for addressing the *“health system value”* of a new technology and *“how to build the total value proposition package around the product.”* An HTA leader noted that, *“as a consequence, you have to get into complex questions of how health systems around Europe are dealing with the policy issues”* that the new technologies raise.

On this basis, participants agreed that there are certain circumstances wherein a multi-country, multi-stakeholder consultation would be particularly valuable to all contributors:

- **Novel or transformational drugs.** Participants recommended that a company turn to multi-stakeholder advice when it seeks to develop a *“particularly novel or transformational medicine.”* An example of such a medicine is one that would *“change the paradigm of a traditional treatment pathway.”* Participants also suggested that such a forum could be appropriate when a drug may be used for a *“new or different indication.”*
- **Medicines and therapeutic areas that elicit different approaches among stakeholders.** Pilot participants noted that a multi-country, multi-stakeholder approach could be especially valuable *“where there are either technical or policy issues that different countries or institutions approach differently ... These are the most important areas on which to get convergence.”* The same need for convergence may support a multi-country, multi-stakeholder approach for advice regarding medicines to treat *“diseases that are less well understood.”* In a therapeutic area where the science is uncertain and assessment methodologies are not yet consistent, mutual education among stakeholders can promote alignment on acceptable approaches.
- **Development programmes seeking a multi-stakeholder strategy to obtain relevant data in clinical trials.** A multi-country, multi-stakeholder approach also has been suggested for more focused issues including *“identifying the relevant patient population”* and *“determining the clinical relevance or therapeutic value of endpoints that are going to be used in clinical trials before marketing authorisation.”* While these issues are not as wide-ranging as those outlined above, receiving perspectives from diverse stakeholders early in the development process would ensure that a company is able to provide the required evidence to each group of stakeholders so that the relevant patients may gain access to the new drug.

Opportunities for progress on the basis of the pilot consultations

The six pilot consultations have provided a proof of concept for the viability and value of multi-country, multi-stakeholder consultations in drug development and given rise to a cadre of institutional healthcare leaders with experience in this setting. Participants have expressed support for leveraging the experience of multi-country, multi-stakeholder consultations and applying it to more medicines even as healthcare institutions are experimenting with other configurations of stakeholders and geographies for early engagement in drug development. A payer participant summarised: *“The pilots were certainly a very significant step. We have learned a lot from this so we have now the duty to go forward, improve the process and define steps to keep [the multi-country, multi-stakeholder forum] going for the long haul.”*

One stakeholder noted that a permanent multi-stakeholder advice forum should be *“public”* and offer an *“accepted infrastructure to organise procedures, people and funding.”* This will require effective collaboration among healthcare institutions, patient representatives and clinical experts, built upon an infrastructure of institutional linkages. Necessary components of such an infrastructure are likely to include an agreed governance model, effective integration of operating practices, and appropriate resourcing. A secretariat, either free standing or located in an existing institution, would provide an invaluable co-ordination role.

In parallel with these developments, several of the consultations have raised significant issues that cut across specific pipeline drugs. These include a multi-stakeholder approach to the evaluation of Alzheimer’s disease treatments; the valuation and reward for companion diagnostics for personalised medicine in oncology; and a multi-stakeholder approach to enhancing innovation in antibiotics. Tapestry is building on the momentum generated by the pilot consultations to develop and launch initiatives in each of these areas.

Conclusion

When Tapestry launched the pilot consultation process at a meeting in July 2010, participating regulators and HTA and payer leaders looked around and noted that this was the first time that such a group had been in a room together. Over the six multi-country, multi-stakeholder consultations that followed, these leaders and others who joined them broke new ground in creating value for health systems, patients and drug developers through greater openness, transparency and a willingness to jointly engage with the challenges of drug development.

The six pilots not only served as proof of concept that a diverse group of senior decision-makers can collaborate in assessing the value of a new drug, but also evolved into a forum inspiring a broader and more open-ended debate on critical issues relevant across medicines. A patient representative summarised, *“It was a great added value of this exercise that regulators, reimbursers and payers were in the same room and learned from each other to understand how all stakeholders approached the issues.”* Reflecting on the need for further multi-stakeholder collaboration in giving early advice, an HTA participant concluded, *“The system, with candid discussion and a good environment, can only last as long as we remain open and keep some confidence in each other.”*

Public-Private Networks

Principles and guidelines for use in the European Union

Public-Private Networks

- Tapestry Networks is an independent business that specialises in the creation of exclusive, leader-to-leader networks. Our networks set the agenda for economic, social and organisational change.
- The networks that we produce may include a cross-section of private sector leaders, non-profit experts and public officials uniquely equipped to advance a common set of interests. These public-private networks create a context for dialogues that define issues and develop multidisciplinary projects to advance shared interests.

Ethical and Legal Considerations

- There are four broad areas of the law that may apply to the management of public-private networks with which Tapestry Networks complies. They are election law, the body of laws governing gift giving, lobbying law and competition law.
- Equally important, our networks are guided by a set of ethical rules and considerations that protect both the interests of network members and the constituencies they represent.
- Tapestry Networks has adopted principles and guidelines for all public-private networks it produces which reflect these areas of the law and the ethical obligations and responsibilities of its sponsors and members.
- Tapestry Networks, its sponsors and members do not engage in directly or indirectly offering or promising any benefit to a public official or any other person or otherwise exercise any undue influence on such persons which may influence these persons in the exercise of their duties.

Election Law

- Members and networks are non-partisan in composition and disposition and do not engage in any election-related activities.
- While our networks engage in meaningful dialogues on important social, global and economic issues, Tapestry Networks does not actively seek to influence any election-related activity; in particular, Tapestry Networks does not contribute to the funding of any political party or representatives of any political party in the European Union.

Gift Giving Law

- Tapestry Networks, its sponsors and members adhere to the laws and rules governing gift giving, including but not limited to meals, travel and entertainment.
- Public officials and individuals working for a public entity or carrying out a publicly funded project participating in any network event pay all related meals, travel and entertainment costs.
- No gifts or indirect gratuities are given by Tapestry Networks, its sponsors or members.



Lobbying Law

- Our networks, as unique public-private entities, may discuss topics related to public policy and may determine to take action based on those discussions.
- In the course of these discussions and associated actions, network members may engage in activities that could be considered lobbying contacts with covered officials. In these cases, network members are subject to the requirements and regulations dictated by their positions and organisational affiliations.
- Tapestry Networks is not a registered lobbyist in any jurisdiction. We do not attempt to influence public policy or legislation on behalf of our clients, our networks, or our own corporate interests.
- Our networks make their papers, meeting summaries, and other deliverables freely available to the public upon request. All network conversations are protected by a modified version of the Chatham House Rule, whereby participants' names are a matter of public record but no comments are attributed to any individual.

Competition Law

- Tapestry Networks, its sponsors and members adhere to the relevant competition and antitrust laws.
- Tapestry Networks, its sponsors or members will not exchange or facilitate the exchange of commercially sensitive information, including but not limited to prices, terms of sale, costs, customers, suppliers, strategy plans, investments, marketing, or technology.
- Tapestry Networks, its sponsors or members will not agree on or take commercial actions.

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- Tapestry Networks, its sponsors and members adhere to the laws and rules governing the indirect or direct offering or promising of any benefits, incentives, premiums or gifts to any organisation or individual active in the medical or pharmaceutical sector.

Ethical Considerations

- Tapestry Networks provides a unique service that advances both the interests of our sponsors and contributes to broader social and economic advancement. Although not required by law, our networks also strive to uphold the highest ethical standards including:
 - A commitment to candid, non-partisan dialogue
 - A willingness to accept accountability and transparency of action
 - A shared sense of a greater good that transcends the interests of any particular organisation represented in the network