

# Meeting Summary

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK  
TYPE 2 DIABETES WORKING GROUP

15 JUNE 2009

## Type 2 Diabetes Working Group – 20 May meeting summary

### Overview

Initiated by the European Healthcare Innovation Leadership Network, the Type 2 Diabetes Working Group brings together world-class thought leaders and decision-makers from the ranks of medical experts, regulators, payers and advisors, patient representatives and industry. Working together over the course of 2009, Working Group members are committed to elucidating a value framework for new diabetes medicines and developing approaches to overcome barriers to innovation in addressing unmet needs in this therapeutic area through more effective collaboration among all stakeholders. The Working Group held its first meeting in Paris on 20 May 2009. This document summarises that day's discussion and the potential areas for collaboration that emerge from it.

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## Attendance and outcomes

Participants welcomed the meeting as “an incredible opportunity to engage with various stakeholders” and “a unique opportunity to learn,” noting that “more and more in the future there will be a need to have, around the same table, the patients, the academics, but [even] more the health technology institutions and the regulators.” The meeting comprised a mixture of plenary discussion, focused work in breakout groups as well as individual consideration of questions posed to the group. Tapestry Networks used polling to gauge participant views and obtain group priority rankings of emerging initiatives.

**Table 1**

### Meeting attendance by stakeholder group

<b>Medical subject matter experts</b>	<b>Payers, regulators, health economists and advisors</b>
Amanda Adler, Institute of Metabolic Science, Cambridge, UK	Eric Abadie, Chairman, EMEA CHMP, Europe
Jean-François Bergmann, Hôpital Lariboisière Paris, France	Andrew Briggs, University of Glasgow, UK
Bernard Charbonnel, University of Nantes, France	Peter Kolominsky-Rabas, Univ. Erlangen-Nuremberg, Germany
Ele Ferrannini, University of Pisa School of Medicine, Italy	Félix Lobo-Aleu, Universidad Carlos III, Spain
Philip Home, Newcastle University, UK	Noël Renaudin, CEPS, France
Mohan Kumar, NHS North Western Deanery, UK	Michael Schlander, Institute for Innovation and Valuation in Health Care, Germany
Andrew Morris, University of Dundee, UK	Angelika Szalayová, Health Policy Institute, Slovak Republic
Christian Berne, Akademiska, Sweden	Sjaak Verduijn, CZ Insurance, The Netherlands
John Buse, University of North Carolina School of Medicine, US	Hans-Georg Eichler, EMEA, UK
Vivian Fonseca, Tulane University Health Sciences Center, US	<b>Patient representatives</b>
Eberhard Standl, Munich Diabetes Research Institute, Germany	Maarten Ploeg, Dutch Diabetes Association, The Netherlands
<b>Industry representatives</b>	
Martin Fitchet, Johnson & Johnson	
Gunnar Olsson, AstraZeneca	
Carlo Russo, GlaxoSmithKline	

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The meeting yielded the following outcomes:

- A disparate group of highly respected thought leaders met as a group for the first time and began a process of collaboration to address the most pressing problems of type 2 diabetes drug development;
- The Working Group ranked areas of greatest unmet medical need in the disease and identified the opportunities for improved patient outcomes that they present;
- Participants put forth proposals for value indicators and measures for demonstrating progress in addressing unmet needs;
- The Working Group identified barriers to progress and approaches to overcoming these barriers;
- Participants ranked initiatives for priority action by the Working Group; and
- Participants committed to carrying these actions forward over the course of the year.

## Identifying opportunities for improved patient outcomes

### Selecting three components of therapeutic value

Network members and Working Group participants agree that value in medicines derives from addressing unmet medical needs. In conversations with participants prior to the meeting, Tapestry Networks identified the following main areas of unmet medical need in the treatment of type 2 diabetes:

- Controlling blood sugar more effectively, longer
- Preventing microvascular complications
- Preventing macrovascular complications
- Achieving positive effect on bodyweight
- Arresting disease progression
- Avoiding adverse effects of treatment

While participants were comfortable addressing each of these areas independently in pre-meeting discussions, an attempted prioritisation of these unmet needs drew protests at the meeting. The difficulty arose from the causal relationship among several of the unmet needs as defined, as a result of which they are not independent of one another. As a medical expert opined, *“when you put together surrogates and endpoints like that, then talking about priorities is slightly nutty, because some of these are mechanisms to the other and that creates difficulties for me.”* As an example, he continued, *“if you are thinking about controlling microvascular complications ... what are the things that contribute to that? One of those comes out as ... blood glucose control,*

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*which is the top line.*” As another example of the causal link between unmet needs as defined, an industry participant suggested adding a category of unmet need around “reducing macrovascular risk factors” (i.e. impact on blood pressure, HDL and LDL cholesterol and body mass index), as a way of potentially bifurcating *“what you need to demonstrate pre-approval and what you need to demonstrate post-approval.”*

With the addition of this category, and the acknowledgment that the structuring of unmet needs will receive further attention, participants prioritised the following three areas for initial focus:

Rank	Points	Unmet medical need
1	21	Controlling blood sugar more effectively, longer
2	20	Arresting disease progression
3	13	Reducing macrovascular complications
4	11	Reducing microvascular complications
5	11	Achieving positive effect on bodyweight
6	10	Controlling cardiovascular risk factors
7	7	Avoiding adverse effects of treatment

The Working Group considered the top three priority topics (shaded) in breakout groups that sought to elucidate unmet needs and opportunities for improvement along each.

## **The convergence of blood glucose control and arresting disease progression into an unmet need for maintaining glucose metabolism**

As participants engaged these topics, it became apparent that “controlling blood sugar” and “arresting disease progression” presented a substantial overlap in terms of the opportunities they present, the disease processes involved and the way in which value along these objectives can be demonstrated. As a government participant summed it up, *“controlling blood sugar more effectively and longer ... would in fact be closely similar to the slowing of disease progression,”* while *“slowing of disease progression ... is controlling blood sugar more effectively and for longer.”* We therefore treat these two areas of unmet need and opportunity for improved patient outcomes together under the heading “maintaining glucose metabolism,” while pointing out where the two groups that addressed this area diverged.

## **Opportunities for improved patient outcomes through improved glucose metabolism: longer life with reduced complications**

Breakout groups considering the unmet need of maintaining glucose metabolism (both as “controlling blood sugar more effectively, longer” and “arresting disease progression”) identified longer life with reduced complications and adverse side effects of treatment as opportunities for improved patient outcomes. For the former group, the *“obvious”* outcome of controlling blood sugar more effectively was *“avoid[ing] disease progression.”* For the latter group, arresting

disease progression presents a “vast” opportunity. However, for progress to occur, they noted that “we have to disavow ourselves of this paradigm ... that type 2 diabetes is an inexorable disease” and treat earlier (as opposed to “treating to failure”), more aggressively and utilising both drug and non-drug (lifestyle, surgical) therapies. Doing so may consist of a variety of interventions, including “more systemic control using existing tools,” “understanding the mechanisms of hypoglycaemia,” treating “earlier and more aggressively,” giving ample consideration to non-drug therapies, and “helping out patients with compliance.”

## Demonstrating value in maintaining glucose metabolism

The indicators of value suggested by groups addressing the maintenance of glucose metabolism showed both overlaps and differences, as summarised below:

**Table 2**  
Demonstrating value in maintaining glucose metabolism

Indicators of value in maintaining glucose metabolism, by unmet need		
Value indicator	Controlling blood sugar more effectively, longer	Arresting disease progression
Progression of HbA1c over time	■	■
Coefficient of treatment failure / time to treatment intensification	■	■
Improvement in CV risk factors	■	■
Lack of adverse effects and tolerability	■	
Absence of weight gain	■	
Improved beta cell function		■
Management of insulin resistance		■

### Controlling blood glucose

Considering ways to demonstrate therapeutic value relative to controlling blood glucose, the breakout group suggested “measure[ing] how the HbA1c develops over time as well as keeping the correct medication to particular patients at acceptable levels.” They acknowledged that such an approach would require “a follow-up in the order of 3 to 5 years,” which is “a much longer exposure of patients than we normally see in today’s trials.” The group identified “lack of adverse events and tolerability,” as well as absence of weight gain, as additional “very important” aspects of glycaemic control, while noting that “if you prove additional effects on other CV factors, it could add to the value.”

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The group considered “*area under the HbA1c curve*” as a measure of sustained glucose control over time, but acknowledged that this approach fails to capture the shape of the curve and therefore does not reflect the trajectory of HbA1c levels over time. A medical expert noted that “*if you carried out the glucose area under the curve in ADOPT<sup>1</sup> you would miss the fact that the sulfonylureas are the most powerful [medicines], but would also be the earliest ones to lose control. Whereas, both metformin and rosiglitazone came down to a higher nadir at which they were stable.*” He recommended combining area under the curve with a “*coefficient of failure*” indicator, which measures the need for “*rescue medication*” in the event that the drug under study loses its effectiveness. He concluded that “*if one combined the area under the curve, which gives you the total exposure, which is an excellent measure, with the coefficient of failure, it gives you the time course of durability.*”

The group did not resolve the question of “*would it be possible today to register something that comes out as a first line parallel to metformin, or ... because of safety considerations and other considerations, you are always starting as an add-on and at best as a second line drug.*” Group members also expressed different views as to the increment of value that should be required for reimbursement.

## Arresting disease progression

A government participant set the bar by warning that while “*controlling blood sugar more effectively and longer is obviously a very interesting objective for all of us, and especially for the patient,*” demonstrating value in “*controlling disease progression or reducing, or slowing disease progression, is extremely difficult.*” Nonetheless, the disease progression breakout group considered value in terms of therapeutic endpoints for which a drug could get an indication. These included:

- Glucose control
- Improved beta cell function
- Management of insulin resistance and
- Reducing CV risk

The group considered “*time to intensification of treatment as a possible measure*” of controlling disease progression. In this regard, they noted the importance of “*continuation or stopping rules.*” In terms of indicators, the group found “*quite a strong concordance between those value components and the associated measures of outcome that were put in the straw man value framework,*” suggesting that that framework is a good starting point for further development.

Rather than defining a hard requirement for a minimal increment of value worthy of reward, the group concluded that reimbursement level should be keyed to value increment, such that

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<sup>1</sup> G Viberti, SE Kahn, DA Greene, WH Herman, B Zinman, RR Holman, SM Haffner, D Levy, JM Lachin, RA Berry, MA Heise, NP Jones, MI Freed. **An international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes: A Diabetes Outcome Progression Trial (ADOPT).** Diabetes Care October 2002 vol. 25 no. 10 1737-1743.

*“smaller levels and smaller prices are consistent and higher levels and higher prices might be consistent, but not mixing those up.”*

## Overcoming challenges and barriers to progress

### Controlling blood glucose

The control of blood glucose group identified the length of studies required to assess the durability of control as a barrier to progress in this area, noting that *“the challenges are really the timing and the cost, and how to cost-effectively run these very large and lengthy trials.”* Their proposed approach to this barrier – and one also recommended by the disease progression group – was a form of phased evidence development, involving *“a traditional filing ... as an interim, and then continue[d] [evidence development] with the studies uninterrupted in order to really generate the very long follow-up, so that in the end you would know where your drug is placed.”* This approach would entail *“starting a trial for registration but then continuing it for three to five years to really look at the long-term effect of glycaemic control.”*

In seeking cost-effective mechanisms for post-launch evidence generation, the group identified the principle that *“some components of studies are very important, specifically in the randomisation initially, so that you know you have that under very good control.”* In highlighting the importance of maintaining rigorous standards for data generation, a medical expert remarked that *“just because we are widening the fields of play we are not sacrificing the rules of play.”* The group raised the possibility of using disease registries for post-launch data collection, but did not reach consensus as to the adequacy of this mechanism for meeting the principles they identified.

### Arresting disease progression

This group identified the difficulty in showing incremental value relative to the standard of care as a barrier to drug development in this area. They remarked: *“Proprietary prices and the effectiveness of the ‘cheap and cheerful’ metformin [as a comparator for] showing additional benefit”* are the main challenges of showing value at launch. *“There was a feeling that it would be very difficult to show anything other than a small additional benefit to metformin and therefore justifying high prices would be difficult.”*

The arresting disease progression group also proposed a form of phased evidence development. In this regard, they reported,

*“a feeling that getting the licensing authorisation might well happen on the basis of some of these [surrogate] markers, or that you could get licensing authorisation for glucose reduction, but that post-launch you would need to show that the expected annual increase in HbA1c was where most people would agree it ought to be ... post-marketing you would also have to demonstrate the link, which would only have been hypothesised at launch, between the surrogate measure and the hard endpoints.”*

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The breakout group also proposed an effort to harmonise *“the evidentiary input going in”* to the HTA process for drug evaluation. As a payer–advisor reported for the group, *“there was certainly a lot of discussion about the need to get pan-European agreement to facilitate the ease of bringing products to market, and linked to that, discussions between industry and reimbursement agencies in a similar way to industry and licensing authorities. In particular, the process must be streamlined so that the outcomes agreed by the regulator are accepted by the reimbursement authorities when reimbursement claims are being made.”* A payer–advisor added: *“that dialogue already exists with the regulator, and it is about getting the same sort of dialogue going with the reimbursement authorities and in a sense trying to encourage them to come into line with the regulator and accepting the same outcomes.”* As a result of such a process,

*“the outputs of the different reimbursement authorities might not be the same, but the evidentiary input going in could well be very similar. For example, in the UK NICE like to see QALYS but that is not the case in Germany, where IQWiG explicitly does not want to see QALYS. In a sense, it is all about getting the hard endpoints, agreeing the hard endpoints, and then those authorities that want QALYS could build them with those endpoints.”*

A government participant commented that making the link between the various national HTA authorities *“would be a far reaching objective”* that may not be within the Group’s purview. He continued: *“On the other hand, as far as the medical added value is concerned, we have the European guidelines pertaining to registration. I think it could be possible to get a broad agreement between the regulators and those who are acting beyond regulation on the way to demonstrating the medical added value of a new medicine.”* As examples, he mentioned *“the population ... the endpoints ... the clinical relevance of the difference between the test and the placebo, [and] the choice of the active control[.]”* While he suggested that *“this action should be pursued at the political level,”* he said that, *“at the very least, [we] have the opportunity to sit around the same table and try to talk about that would be an improvement, because it has never been done before.”*

The disease progression group also recommended *“more use of some form of arrangement [among stakeholders] for developing the evidence. The point was made that this would need to be done early in the process and there would have to be some kind of risk sharing, such that if the claim is not met then the price would have to come down[.]”* Such an arrangement of *“conditional reimbursement”* would represent *“a two-way street that will give [the drug developer] extra leeway in making some claims without hard endpoints. Then you have to follow up and show those hard endpoints.”* A payer–advisor added support for this approach of conditional reimbursement, noting that *“only then for this group of medicines are we able to get enough hard evidence or intermediate evidence to get a good view of the potential of the medicine.”*

## Opportunities for improved patient outcomes through preventing cardiovascular complications: reduced mortality and morbidity with improved quality of life

The breakout group charged with considering the unmet need to prevent cardiovascular complications reported *“avoiding death and major morbidities”* and *“improving quality of life”* as the main opportunities for improving patient outcomes. Participants noted that, despite the array of available treatments, type 2 diabetes patients *“still have a substantial excess of macrovascular events compared to the general population”* and indicated that *“preventing, rather than controlling”* these complications is their *“number one”* objective. They also acknowledged the overlap with cardiovascular safety as a question of side effects: *“We all accept the need to establish CV safety as well, although we are talking about CV efficacy here, so that tends to rather overlap.”*

### Demonstrating value in preventing cardiovascular complications

The group considered *“the standard spectrum from surrogate, intermediate to hard endpoints.”* In so doing, participants noted that among *“the key challenges”* is how reimbursement requirements are *“much more opaque”* than those for registration. They acknowledged the need *“to help with value arguments and drive reimbursement.”* The group considered the following indicators of value, with those for which the causal link to outcomes was not well established marked by a “?”.

**Table 3**  
Demonstrating value in preventing cardiovascular complications

Indicators of value in preventing cardiovascular complications	
<b>Hard endpoints</b>	
Stroke	■
Myocardial infarction	■
Cardiovascular death	■
Acute coronary syndrome (ACS)	?
<b>Intermediate endpoints</b>	
- None recommended -	
<b>Surrogate endpoints</b>	
HbA1c	■
Blood pressure	■

Table 3

Demonstrating value in preventing cardiovascular complications (*continued*)

Indicators of value in preventing cardiovascular complications	
Surrogate endpoints	
HDL and LDL	?
Weight	?

### Hard endpoints

The group first took up *“the standard definition of hard endpoints and the adjudication of hard endpoints.”* Group members agreed on the *“standard three”* hard endpoints of stroke, myocardial infarction and cardiovascular death, while leaving the door open for the inclusion of acute coronary syndrome (ACS). The group noted *“a surprising amount of concern around the differences in definition of those hard endpoints.”* In addition, they raised the important question of how they could be combined, asking what *“composites [of these endpoints] should look like.”* The group therefore recommended as an action *“a request that a key group get together, perhaps the European Society of Cardiology or health technology assessors and patient groups, to agree the endpoint definitions in diabetes that would be needed to define cardiovascular risk, the absence of risk and – eventually – the presence of cardiovascular protection.”*

### Intermediate endpoints

The group did not endorse intermediate endpoints, noting that *“nobody was keen on these. Everyone around the table, medical experts and reimbursement experts, said that they see very little value in intermediate imaging endpoints, such as IBIS, as providing even intermediate evidence of value or driving value.”*

### Surrogate endpoints

The group reported that acceptability of the *“surrogates A1c and blood pressure were not questioned,”* while the relevance of HDL and *“even LDL ... has been brought under a significant amount of question.”* They asked whether a diabetes drug needs to reduce blood pressure or lipid levels, since *“we have very effective agents to do that anyway”* and noted that participants were *“really interested in the impact on glucose as the major surrogate of interest.”*

Participants also considered the impact of reducing body weight, noting that, while *“it is very beneficial in the treatment of diabetes ... it does not plug in well to any model of cardiovascular risk, [such as] OXFORD.”*<sup>2</sup> They noted that *“it is very difficult to understand what a reduction*

<sup>2</sup> PM Rothwell, A Coull, M Giles, S Howard, L Silver, L Bull, SA Gutnikov, P Edwards, D Mant, CM Sackley, A Farmer, PAG Sandercock, MS Dennis, CP Warlow, JM Bamford, P Anslow. **Changes in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire from 1981-2004: the Oxford Vascular Study.** Lancet 2004; 363: 1925-33.

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*in weight means in terms of long-term benefit, yet we all believe it is important in the treatment of the diabetic.” The group concluded that there is a need to incorporate body weight “in the future as part of a surrogate profile to encapsulate value.”*

While concurring on the validity of surrogates, “*what was questioned was how the surrogates would be used.*” The group addressed the applicability of surrogate data to reimbursement decisions, positing that, “*in many cases [when] you may have a lot more surrogate data as a sponsor that is not in the product labelling, would a reimbursement authority accept those data in terms of supporting the evidence of benefit of the product? ... Some colleagues around the table said no, and others, particularly from the UK, said that those may be accepted and put into appropriate models of cardiovascular risk.*”

Thus, an even more complex question than selecting which surrogate measures should be studied is how reimbursement authorities will use such data in valuing impact on cardiovascular outcomes. Speaking for the group, a participant noted that “*there is a significant difference in the way one health technology agency will model [those data, while] other perhaps non-HTA approaches will not accept those data but will need to wait for hard endpoints ... NICE, for example ... are very open to modelling cardiovascular risk through the OXFORD model to understand potential long-term benefits of a drug as an intermediate assessment of benefit. There were other representatives from other European countries who felt that was not tenable; it was hard endpoints or nothing.*”

A medical expert characterised this dichotomy as one of “*hard endpoints – just counting bodies – and risk factors,*” and said: “*I think the former is going to be a hurdle that nobody can overcome, because if anything has to go on top of existing standard of care, which includes ACE inhibitors, statins and aspirin, who is going to be doing that?*”

## Distinguishing between cardiovascular safety and cardio-protective effects

A government participant clarified the difference between an assessment of cardiovascular safety and an extension of indication to cardiovascular protection. As to the former, he said that “*the regulators would like to see a drug which is safe and effective in the indication treatment of type 2 diabetes based on the reduction in A1c, and based on, I would say, a safe dossier in terms of cardiovascular.*” He conceded that “*we are not sure today that the drugs which are currently marketed in Europe and elsewhere are safe from the point of view of the cardiovascular system,*” hence the FDA – and forthcoming EMEA – requirements for enhanced cardiovascular safety testing.

As to demonstrating reduced incidence of cardiovascular complications, he predicted that “*the payer will be interested in a medicine that shows undoubtedly that there is ... a reduction in the incidence of cardiovascular complications.*” He noted that the patient populations enrolled in efficacy studies are poorly suited to the demonstration of cardio-protective effects. He said: “*If you choose the type of patients who are currently in the dossier who are [typically] young diabetics with a duration of diabetes of less than five years, you will not find anything.*” He concluded that a higher-risk patient population is key to showing effects: “*If by chance we had*

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*the opportunity to see a type of patient that has been recruited, for instance, diabetics at higher risk of cardiovascular complication or having already suffered cardiovascular complication, it would be probably easier to show either a deleterious effect of the medicine or an improvement in the reduction of the incidence of cardiovascular complication.”*

## Overcoming challenges and barriers to progress

The primary action proposed by the group was to “*get the relevant stakeholders together and agree composite endpoints, their definition and adjudication to demonstrate (1) the exclusion of cardiovascular risk; and (2) the benefit of cardiovascular protection*” Like their fellow participants, members of this breakout group agreed that “*it would be wonderful to have pan-European alignment on reimbursement criteria for value around cardiovascular risk, whether that be modelling or endpoints.*” However, some group members raised concern that doing so may be “*just politically impossible.*” However, an industry participant clarified that this was “*a proposed action that was not shot down but questioned.*”

## Setting the Working Group agenda

### Taking stock of challenges and barriers to achieving improvement opportunities

The above discussion should serve to illustrate that several of the barriers and solutions for overcoming them that the breakout groups and plenary discussions identified overlap among the different unmet medical needs. We provide a summary below:

**Table 4**  
**Potential solutions to address challenges and barriers to progress**

Challenge or barrier	Potential solution
<b>High cost of evidence development</b> <ul style="list-style-type: none"><li>Need for long-term post-launch studies to demonstrate value</li><li>Need for cardiovascular outcome studies</li></ul>	<ul style="list-style-type: none"><li>Elucidate tiered evidence development / staged value demonstration framework</li><li>Align views on use of surrogates</li><li>Validate surrogate endpoints using epidemiological data</li><li>Expand use of IT and electronic patient records for data collection</li><li>Explore use of registries and other non-RCTs for post-launch data</li><li>Seek pan-European harmonisation regarding the data inputs to reimbursement decisions</li></ul>

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Table 4

Potential solutions to address challenges and barriers to progress (*continued*)

Challenge or barrier	Potential solution
<b>Difficulty in showing incremental benefit versus metformin (“the metformin dilemma”)</b>	<ul style="list-style-type: none"> <li>Test new drugs not only against metformin but also in combination with metformin</li> <li>Explore use of registries and other non-RCTs for post-launch data</li> </ul>
<b>Absence of well-defined endpoints</b> <ul style="list-style-type: none"> <li>For demonstrating value in arresting disease progression</li> <li>For identifying cardiovascular events</li> <li>For quality of life impacts</li> </ul>	<ul style="list-style-type: none"> <li>Agree appropriate outcomes and endpoints, along with measures, indicators and increments of value</li> <li>Convene specialist panels to define CV events to include and exclude</li> <li>Agree appropriate measures for quality of life impacts</li> </ul>
<b>Opaque and conflicting reimbursement requirements</b>	<ul style="list-style-type: none"> <li>Elucidate shared framework of value</li> <li>Seek pan-European harmonisation as to the data inputs to reimbursement decisions</li> </ul>

## Actions to overcome barriers to progress: setting the agenda of the working group

The purpose of the first meeting of the Type 2 Diabetes Working Group was primarily to set the Group’s agenda for the year. The discussion summarised above served to illuminate the areas of opportunity in which the Working Group may have the highest impact, consider the evidence required to show benefit along those areas and seek ways to overcome the potential barriers to progress. All of these serve to address the problem that, in the words of a medical expert, “*our current model of developing drugs for diabetes is fairly sick.*” As such, the prioritised actions are best viewed as elements of a cohesive new paradigm of drug development, rather than individual initiatives. Moreover, as participants consider how to flesh out the initiatives that the Group identified for priority action, it may be helpful to keep in mind the full slate of potential approaches to overcoming barriers to progress presented in Table 4 above.

During the course of the meeting, the Working Group engaged in two prioritisations of potential actions that emerged from the day’s discussion. Combining the results of the two, and accommodating for the fact that some of the initiatives voted on separately were in fact “*very similar*” yields the following list of high priority initiatives:

- Develop mechanisms for staged evidence demonstration
- Develop and pilot guidelines for risk-sharing and conditional reimbursement

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- Elucidate a model of value along with regulatory and reimbursement requirements for key value components
- Validate and reach alignment on surrogates for hard outcomes

Our goal is to help these initiatives take shape over the coming weeks. Below we offer an added layer of specificity to the Group's discussion, with the understanding that the next phase of interactions with participants will seek to syndicate and round out this agenda.

## Developing mechanisms for staged evidence demonstration

Several Working Group participants expressed support for the development of staged evidence demonstration frameworks, as, in the words of an industry participant, *“a mechanism of understanding how to build effective programmes.”* He described the process as follows: *“you have the surrogates going your way and then you take the next thing and then we are into what you need to demonstrate pre-approval and what you need to demonstrate post-approval.”* Breakout groups comprised of multiple stakeholders also supported this approach, as discussed above.

An initiative to develop a mechanism for staged evidence demonstration could consist of the following elements:

- Harmonise expectations among industry, regulators, HTA and payers as to the sequence and content of evidence development
- Identify touchpoints for consultation with regulators, HTA and payers along the development process
- Develop guidelines for post-launch evidence development

This initiative is linked to suggestions for earlier consultation with regulators and payers, since one implies the other, as well as to conditional reimbursement, since evidence developed post-launch could be used by payers to adjust the reimbursement price.

## Developing and piloting guidelines for risk-sharing and conditional reimbursement

This initiative also featured strongly among participants' priorities, though it received less discussion during the meeting than the other priority actions. When participants did address this initiative, opinions diverged as to how conditional reimbursement can be implemented, or whether it can be implemented at all. The question for participants is how the availability of a drug can be curtailed in practice – once it has been made available to patients – in the event that the drug's effectiveness is lower than anticipated (and therefore the “condition” for reimbursement is not satisfied). Participants suggested four alternative models for how a mechanism for conditional reimbursement could handle such a situation:

- ***Removing reimbursement if the condition is not satisfied with the acceptance of the political cost of doing so.*** A payer-advisor voiced support for withdrawal of

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reimbursement of a drug that turns out not to meet the agreed-upon condition, while acknowledging the potential *“political hazards associated with such proposals.”*

- **Failure of the condition can result in a lowering of the reimbursement price.** A payer-adviser suggested that failure to satisfy the agreed-upon condition need not curtail the availability of the drug in question, but rather reduce its reimbursement price. He posited that *“the condition is on the price. If the condition is fulfilled, the price stays at a high level. If the condition is not fulfilled, the price goes down.”*
- **Failure to meet the condition can result in denial of reimbursement to future patients while maintaining it for those already relying on the drug.** A medical expert pointed out an alternative model implemented in some Member States in which *“we stop new individual treatments”* with a drug that turns out not to satisfy the agreed-upon condition for reimbursement, without *“insist[ing] that individuals already being treated have the treatment withdrawn.”*
- **Patients cannot be denied treatments they already take; therefore pulling reimbursement on a drug already in use is not feasible.** Along this vein, a medical expert participant asserted that *“conditional reimbursement...is practically impossible when thousands of patients receive the treatment and are reimbursed for it. If new information reveals a very big safety problem then you have to cancel the drug. But if the drug is on the market, you cannot say to the patient, ‘now you will continue treatment but you will have to pay for it yourself.’”*

We note that none of the above scenarios allows for the possibility of reimbursement levels *rising* based on post-launch evidence in a framework of conditional reimbursement. Developing and piloting guidelines for risk-sharing and conditional reimbursement could consist of the following elements:

- Explore the potential for risk sharing and conditional reimbursement in enhancing innovation in type 2 diabetes drug development
- Explore types and structure of potential agreements
- Agree principles for their use.

## Elucidating a model of value along with regulatory and reimbursement requirements for key value components

This initiative builds on the objective expressed by several participants. A payer-adviser summed up the need to *“elucidate the different perspectives on value, because value talk is abundant but at the same time it is a Tower of Babel – everybody has a different understanding of value.”*

From the payer perspective, this lack of convergence results in dossiers that *“do not answer the questions we are really interested in,”* while *“answering questions that we do not care about.”*

A fellow payer-adviser pointed out that *“the pricing of diabetes drugs is perhaps the most difficult thing we have to do, because it is difficult to recognise the added value of new drugs.”*

This difficulty is felt by industry as well. A participant responsible for diabetes drug development

explained that *“it is absolutely key for me to understand as broadly as possible the unmet need and the value that we would expect from a new therapy for diabetes.”*

Elucidating a joint model of value would also serve to harmonise *“the evidentiary input going in”* to the HTA process for drug evaluation, as called for by multiple breakout groups. It is thus no surprise that participants gave high priority to elucidating a model of value along with indicators and measures for how to demonstrate that value. This initiative could consist of the following elements:

- Agree on the clinical endpoints of relevance to therapeutic effects that the workgroup identified as associated with key unmet needs (such as arresting disease progression and preventing cardiovascular risk)
- Structure the value framework to reflect causal relationships among components. Early consideration of this approach based on participant comments suggests a revision of the high-level categories of unmet medical needs as follows:
  - Maintaining glucose metabolism
  - Preventing cardiovascular complications and
  - Avoiding side effects of treatment
- Agree set of indicators and measures for demonstrating therapeutic value of new medicines

We suggest that this initiative is not only a worthwhile undertaking in and of itself, but is a necessary element of an agreed framework for staged evidence demonstration, while being closely linked to the fourth initiative to which the Working Group attached a high priority: validating and seeking agreement on acceptable surrogates.

### Validating and seeking agreement on acceptable surrogates

Participant breakout groups addressing both the unmet needs of arresting disease progression and preventing cardiovascular complications expressed a need for greater alignment as to surrogate endpoints. The former indicated *“a need for support for surrogate endpoints but possibly more advanced modelling relating to surrogate endpoints, such that there might be a risk equation itself that would be an outcome.”* In turn, the latter group reported that *“we recognise there is some need to align everybody’s views, particularly in the area of surrogates and how they can be applied.”* We note that this initiative scored very highly in the first prioritisation undertaking by the Working Group, but dropped substantially in the second. We therefore include it for completeness but recognise that participants’ enthusiasm for this effort may by this time have waned.

Such an initiative could consist of the following elements:

- Define surrogates and their use then syndicate with relevant stakeholders
- Validate surrogates using epidemiological data

# Meeting Summary

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK  
TYPE 2 DIABETES WORKING GROUP

We invite participants to consider the extent to which the Working Group has an ability to drive progress in each of these areas. We also invite you to consider whether these initiatives should take a different form from that outlined above, and – most importantly – to which of these initiatives you would consider committing your efforts. Tapestry Networks will reach out to participants in the coming weeks to validate and refine this agenda and chart a path forward. We thank you for your commitment to progress in this area and look forward to your continued insight and energy.