Improving Health Outcomes in Type 2 Diabetes

EUROPEAN HEALTHCARE INNOVATION LEADERSHIP NETWORK
TYPE 2 DIABETES WORKING GROUP

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Improving Health Outcomes in Type 2 Diabetes: Recommendations of the Type 2 Diabetes Working Group

Overview

Initiated by the European Healthcare Innovation Leadership Network ("the Network") and convened by Tapestry Networks, the Type 2 Diabetes Working Group brings together world-class thought leaders and decision-makers from the ranks of medical experts, regulators, health technology assessors (HTA), payers and advisers, patient representatives and industry. (Appendix A lists Network members, while Appendix B shows the roster of the Working Group.) Working Group participants are committed to addressing unmet medical needs in type 2 diabetes. Working together over the course of 2009, the Working Group established a Shared Value Framework for drug development in this area and developed approaches for more effective collaboration among all stakeholders to encourage and enable innovation. A Shared Value Framework is an approach that multiple stakeholders can use to improve the clarity, transparency and alignment of how the value of new medicines can be determined and rewarded, with the goal of improving health outcomes. This document summarises the Working Group's recommendations.

The need for innovation to improve health outcomes in type 2 diabetes

Type 2 diabetes mellitus is a complex and progressive metabolic disorder linked to obesity and sedentary lifestyles and characterised by the presence of hyperglycaemia (elevated blood sugar).[1] The disease is progressive in nature, as glucose control deteriorates over time and requires increasingly aggressive treatment.[2] The primary concern in treatment is not so much acute hyperglycaemia itself but long-term complications from chronically elevated blood sugar.

The incidence of type 2 diabetes constitutes a world-wide epidemic. The International Diabetes Federation estimates that 285 million adults are afflicted with diabetes world-wide, a figure expected to grow to 438 million by 2030.[3] Type 2 diabetes accounts for approximately 90% of this total. Around 3.2 million deaths every year – six deaths every minute – are attributable to complications of diabetes.[4]

Unmet needs in type 2 diabetes

Working Group participants agreed that *"we need more robust therapies"* that produce better health outcomes for type 2 diabetes patients, including:

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[1] The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus, 2002 at p. 2.

[2] *Id.*

[3] International Diabetes Federation, *The Diabetes Atlas* Fourth Edition, 2009. Available at www.diabetesatlas.org/book/export/html/36.

[4] *See* World Health Organisation, Diabetes Facts at http://www.who.int/dietphysicalactivity/publications/facts/diabetes/en/.

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- **Arresting disease progression.** The progressive nature of type 2 diabetes requires an expansion in the scope of treatment with glucose-lowering agents every three to four years.[5] As a result, "eventually, even in spite of current combination therapy and/or insulin treatment, an important group of the patients is not well controlled."[6]
- **Reducing cardiovascular complications.** The rate of cardiovascular mortality among diabetes patients is double that of the general population. While there is solid evidence to suggest that long-term control of blood glucose reduces or avoids the risk of microvascular complications (such as blindness, neuropathy and nephropathy), the ability of present treatments to reduce cardiovascular risk remains uncertain at best.
- **Reducing the side effects of treatment.** The side effects of existing treatments, including the risk of cardiovascular (CV) harm, hypoglycaemia (excessive reduction of blood sugar) and weight gain need to be reduced to improve health outcomes and patient concordance.

Challenges to progress in enhancing health outcomes in type 2 diabetes

Despite the epidemic of diabetes and the host of unmet needs, the basis for demonstrating the value of new diabetes medications remains poorly defined. Participants believe that a fundamental challenge to improving treatments for type 2 diabetes is the absence of consensus on what constitutes value in a type 2 diabetes medicine – particularly from the perspective of payers and HTAs – and how that value should be demonstrated.

The complexity of diabetes as a disease affecting multiple organ systems, with outcomes that take many years to manifest, further complicates the situation. And while there has been incremental progress in understanding the benefits of multi-factor interventions (*i.e.,* control of blood sugar, blood pressure and lipids), there remains no validated short-term surrogate for some key long-term outcomes, in particular CV risk. This limits the ability of regulators and payers to evaluate the protective action of a new diabetes medicine at launch.

New regulatory requirements issued by the U.S. Food and Drug Administration to demonstrate the CV safety of new medicines[7] are leading to longer and larger clinical trials. While all participants acknowledge the importance of screening new medicines for CV safety, some expressed concern that this increased cost and complexity will lead developers to *"deprioritise diabetes because they can't afford to get their drug to market and to the patient."*

Indicators and measures for assessing value

The Working Group agreed a set of indicators and measures for the assessment of value in type 2 diabetes medicines as a key element of a Shared Value Framework for the disease (*See* Appendix

[5] The European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus, 2002 p. 2.

[6] *Id.*

[7] United States Department of Health and Human Services, Food and Drug Administration (FDA), Center for Drug Evaluation and Research, Background Introductory Memorandum – The role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus at p. 15 *et. seq.*

C). This framework provides a common language for identifying and assessing the characteristics of a medicine that are relevant to its value in treating the disease.

Applying the value framework: differentiation based on individual value indicators

"It is not enough to provide evidence that the medicine is working, but that it is different from medicines that are already reimbursed" – HTA-payer participant.

The starting and ending points of existing therapy for type 2 diabetes are metformin and insulin. One offers an inexpensive and relatively well-tolerated oral treatment, while the other delivers unsurpassed glucose lowering. Participants agreed that new medicines are well-served to show distinction in areas such as durability of control, improved adverse effects profile, effectiveness in patients who fail on other therapies, and the capability to replace combination therapies.

Applying the value framework: differentiation based on composites of value

Working Group participants noted that reimbursement authorities have begun using composite assessments of medicinal value to differentiate and focus the value proposition of new medicines. This approach creates an opportunity to match medicines with certain profiles to a stratified subpopulation of patients for whom those profiles are most appropriate. Most participants viewed this trend as an important evolution in the treatment of type 2 diabetes. Some participants believe this approach is a necessary alternative to having a large number of undifferentiated medicines with *"nothing to guide the practitioner on which choice he takes ... other than industry marketing."* A more strongly-worded payer view is that a subgroup focus is increasingly *"the only way that new drugs can get access to the market."*

The Working Group identified two fundamental clinical and commercial success factors for matching medicines to patient subpopulations based on composite value assessments:

- **Meaningful boundaries for stratification.** The Working Group recommends that the stratification of patient populations for targeted treatments be based on meaningful clinical distinctions to avoid creating arbitrary cutoffs that exclude patients who would truly benefit from a medicine. One approach suggested as promising is to provide medicines broadly, coupled with "stopping rules" for ending treatment if desired clinical outcomes are not achieved.
- **Parity between the size of the development programme and the size of the targeted market.** Working Group participants noted that more focused treatment populations should correspond to a targeted development program. However, regulatory concern about off-label usage in a broader patient population makes acceptance of a targeted development path difficult. A potential solution is for developers to streamline and focus the programme of Phase 3 trials to enhance the viability of targeted drug development. The opportunity for such streamlining is but one of the expected benefits of early stakeholder consultation, which is the second major component of the Shared Value Framework.

Early stakeholder consultation

The Working Group concluded that a consensus view of indicators and measures for describing the value of a medicine, while necessary, is alone not enough to resolve the substantial ambiguity inherent to drug development and focus the industry on developing medicines that society truly values. Participants believe that *"transparency and openness of [the drug development] process"* is required and strongly recommend additional early multistakeholder consultation to create a receptive environment for patient access to innovative and beneficial medicines. Such expanded consultation is needed to guide all stakeholders' resourcing and prioritisation decisions and to streamline and focus the development process.

While all phases of development would yield benefits, Phase 2 may be the most appropriate time for these discussions. Such timing would be late enough to allow discussion to be anchored in early clinical trial results while being sufficiently early for drug developers to tailor the larger clinical trial and value demonstration programme for a medicine to the needs of other stakeholders.

Questions to be addressed by early consultation

With a focus on Phase 2, the Working Group concluded that the most pressing topics for discussion and agreement during early consultations are the following:

- **Target profile and evaluation criteria.** The Working Group believes that early consultations should support a discussion – and validation – of whether the drug developer has the right profile for what would be a valuable medicine. This should allow the parties to clarify *"what criteria the reimbursement authority is going to use to define whether or not it is willing to pay for the product."*
- **Potential indications.** Participants believe that consensus on the appropriate indication to target would be a critical benefit of early consultation, because it would determine the course of the development plan for the medicine, as well as the size and nature of its potential market, including a potential targeted subpopulation.
- **Positioning in the treatment hierarchy and appropriate comparators.** HTA and payer participants made clear that a new medicine needs to demonstrate added value relative to the existing standard of care. Clarifying the standard of care and appropriate comparators for assessing a new medicine can be a significant benefit of early consultation.
- **Endpoints of interest and ways to demonstrate value.** *"Good input from regulators and payers prior to Phase 3"* is needed for industry to develop medicines that require long-term outcome data to demonstrate value.
- **Safety and side effects.** With the ever-increasing attention being paid by regulators and payers to drug safety, early consultation as to a drug's mechanism of action can orient the developer's testing plan as to demonstrating safety or – just as importantly – provide an early signal to terminate development due to safety concerns.

Principles and criteria for use of post-launch mechanisms

Participants agreed that *"the idea that everything is completed when marketing authorisation is awarded is an idea of the past,"* while recognising that the post-launch area *"remains very under-developed."*

An application of the post-launch environment of particular interest to some participants is to provide the basis for risk shares. Such arrangements allow market access at a set initial reimbursement price that is reviewed within a pre-agreed time based on evidence collected by the developer after launch of the medicine. Participants noted that a successful risk share requires clear specification and accurate evaluation of the outcomes that will define the medicine's success or failure. In addition, they agreed that *"it is only fair"* for a risk-sharing arrangement to include provisions for reimbursement levels to rise – not just decrease or be maintained, as is the current practice – upon the appropriate post-launch evidentiary showing. These aspects of risk shares are well suited to testing and development through pilots recommended by the Working Group.

The path forward: pilots to test the Working Group's recommendations

Participants strongly support piloting the Working Group's recommendations in 2010. The pilots will apply the Shared Value Framework for type 2 diabetes to actual medicines in development, through a set of early stage multi-stakeholder consultations. An emerging design for pilot consultations is provided in Appendix D.

In considering the design of pilots, participants sought to develop a process that is transparent and inclusive. Summarised below is their resulting initial design guidance:

- **Ensure institutional support for public-sector participation.** Participants recommended obtaining official sanction from organisations to enable decision-makers to participate in the pilots, and encouraged those organisations to promote participation in a manner that allows flexibility and openness to pursue innovative processes and thinking. This could be achieved by setting clear expectations and governance principles and appropriately preparing pilot participants similar to the Working Group briefing processes. A related point is the need to engage the appropriate individuals and organisations; in a payer's words, *"to seek out people who are able to think outside of their organisation and who are interested in thinking beyond their own role."*
- **Prototype pilots across, not simply within, Member States.** Participants recommended prototyping an early consultation process with actual medicines across a manageable subset of Member States. While acknowledging that this approach is *"quite ambitious,"* several participants considered it a step toward alignment on the inputs used by the various Member States to evaluate new drugs according to their own different methodologies.
- **Balance the benefits of collaboration with the retention of role independence.** The tension between independence and collaboration between stakeholders is of

particular importance, since a lack of collaboration would function as a *"gating factor for the success of new forms of interaction."* Participants acknowledged the need to *"nudge the balance toward greater collaboration"* while ensuring that public sector participants continue to act within the responsibilities set by their official roles.

- **Ensure process transparency while protecting confidentiality of content.** Participants agreed that the objectives, structure, participants and process details of the pilots should be fully transparent. They also acknowledged the need to protect outcomes related to a specific compound in order to protect the confidentiality of medicines in an early stage of development.
- **Agree to non-binding outcomes.** Due to the innovative nature of the pilots, participants recommended that advice provided in the consultations should be non-binding and should not displace existing channels for regulatory and reimbursement approval.
- **Share lessons and general clinical guidelines derived from the pilots.** Working Group participants agreed that *"pilots need to be approached in the spirit of learning,"* with an opportunity and obligation to provide generalisable guidelines on non-competitive clinical questions after the pilots.

There is a growing acceptance across Member States and stakeholder groups that real progress can be made to address the rising cost of medicines and the declining rate of innovation by overcoming barriers to collaboration and aligning on value. As one leading payer exclaimed, *"If you would have asked me 3 years ago if we could have arranged trilateral meetings between regulators, payers and industry, I would have said 'no way'. But now the time is ripe and all are eager to meet."*

The initiative to create Shared Value Frameworks for drug development, assessment and reimbursement thus far has engaged over 100 European healthcare leaders across eight Member States. Those involved share the view that the current model for bringing new medicines to market is unsustainable and that change will be required from all stakeholders. There is strong support for redefining how value in medicines can be more effectively demonstrated, assessed, captured and rewarded. Participants believe that the European Healthcare Innovation Leadership Network and its Working Groups are an important step on that journey.

Appendix A: European Healthcare Innovation Leadership Network members

Members

Member States

Czech Republic

- **Pavel Hroboň** | Former Deputy Minister |Ministry of Health

France

- **Eric Abadie** | Direction Générale | Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS)
- **Noël Renaudin** | President | Economic Committee for Health Products (CEPS)

Germany

- **Rainer Hess** | Impartial Chairman | Federal Joint Committee (G-BA)
- **Wolfgang Schmeinck** | Beauftragter des Vorstandes | BKK Landesverband Nordrhein-Westfalen

Netherlands

- **Mike Leers** | Advisor - Board of Commissioners| CZ Healthcare Insurance Group
- **Martin van Rijn |** CEO | PGGM

United Kingdom

- **Mike Farrar CBE** | Chief Executive | National Health Service – North West
- **Sir Michael Rawlins** | Chairman | National Institute for Health & Clinical Excellence (NICE)
- **Professor Sir Mike Richards CBE** | National Clinical Director for Cancer & End of Life Care| St Thomas' Hospital

Pharmaceutical Innovators

- **Eddie Gray |** President, Pharmaceuticals Europe | GlaxoSmithKline
- **David Norton |** Company Group Chairman - Global Pharmaceuticals | Johnson & Johnson
- **Ulf Säther |** Regional Vice President, Europe | AstraZeneca

Other Key Constituents

- **David Byrne** | Former EU Commissioner, Health and Consumer Protection
- **Thomas Lönngren** | Executive Director | European Medicines Agency (EMA)
- **Anders Olauson** | President | European Patients' Forum
- **Sophia Tickell** | Executive Director | SustainAbility & Director | Pharma Futures

Appendix B: Type 2 Diabetes Working Group participants

Participants

Medical subject matter experts

- **Amanda Adler,** Institute of Metabolic Science, Cambridge, UK
- **Jean-François Bergmann,** Hôpital Lariboisière Paris, France
- **Christian Berne,** Uppsala University, Sweden
- **Bernard Charbonnel,** University of Nantes, France
- **Ele Ferrannini,** University of Pisa School of Medicine, Italy
- **Vivian Fonseca,** Tulane University Medical Center, USA
- **Philip Home,** Newcastle University, UK
- **Harald Klein**, Ruhr-Universität Bochum, Germany
- **Mohan Kumar**, NHS North Western Deanery, UK
- **Andrew Morris,** University of Dundee, UK
- **Eberhard Standl**, Munich Diabetes Research Institute, Germany

Payers, regulators, health economists and advisors

- **Eric Abadie,** Committee for Medicinal Products for Human Use (CHMP), Europe
- **Andrew Briggs**, University of Glasgow, UK
- **Hans-Georg Eichler,** European Medicines Agency
- **Peter Kolominsky-Rabas**, University of Erlangen-Nuremberg, Germany
- **Félix Lobo-Aleu**, Universidad Carlos III, Spain
- **Noël Renaudin,** Economic Committee for Health Products (CEPS), France
- **Michael Schlander**, Institute for Innovation & Valuation in Health Care, Germany
- **Sjaak Verduijn,** CZ Insurance, The Netherlands

Patient representatives

- **Maarten Ploeg**, Dutch Diabetes Association, The Netherlands

Industry representatives

- **Martin Fitchet**, Johnson & Johnson
- **Gunnar Olsson**, AstraZeneca
- **Carlo Russo**, GlaxoSmithKline

Appendix C: Value indicators and measures for type 2 diabetes

Value component	Measure
Maintaining glucose metabolism	
Glycaemic control (surrogate endpoint)	
Glycaemic control	▪ HbA1c reduction (Δ %) ▪ % change in HbA1c level relative to baseline (%)
Durability of control	▪ Progression of HbA1c over time (while on particular medication) ▪ Coefficient of treatment failure ▪ Time to treatment intensification
Preservation of glucose metabolism	▪ Measures of improved beta cell function and / or reduced insulin resistance to be developed (e.g. c-peptide)
Avoidance of microvascular complications (intermediate and hard endpoints)	
Reduced diabetic retinopathy	▪ % of patients with microvascular eye problems ▪ Time to progression of retinopathy
Reduced diabetic nephropathy	▪ % of patients with microalbuminurea / proteinurea ▪ Time of progression to microalbuminurea / proteinurea ▪ Improvement of creatinine
Reduced diabetic neuropathy	▪ Measures of peripheral / autonomic / proximal / focal neuropathy
Preventing cardiovascular complications	
Control of cardiovascular risk factors (surrogate endpoints)	
Weight control	▪ Change in BMI ▪ Absolute change in body weight (kg) ▪ Change in waist circumference
Reduced diabetic dislipidaemia (improved lipids)	▪ Change in LDL cholesterol level (mg/dL) ▪ Change in blood triglyceride level (mg/dL) ▪ Change in HDL cholesterol level (mg/dL)

Value component	Measure

Value component	Measure
Reduced hypertension	▪ Change in systolic blood pressure (mm Hg) ▪ Change in diastolic blood pressure (mm Hg)
Avoidance of cardiovascular disease (hard endpoints)	
Reduced cardiovascular disease morbidity	▪ Age-adjusted non-fatal myocardial infarctions per patient year ▪ Age-adjusted rate of strokes per patient per year ▪ Age-adjusted urgent coronary revascularisations per patient per year
Reduced cardiovascular disease mortality	▪ Annualised age-adjusted death rate due to cardiovascular events (MI, stroke, acute coronary syndrome)
Reduced all-cause mortality	▪ Annualised age-adjusted death rate from all causes
Enhanced treatment safety and convenience	
Drug safety and side effects	
Avoidance of hypoglycaemia	▪ Major / minor hypoglycaemic episodes per patient per year
Avoidance of weight gain	▪ Absolute increase in body weight (kg) ▪ Increase relative to ideal body weight (kg)
Improved tolerability	▪ % discontinuing medicine due to side effects ▪ % reporting moderate to severe side effects
Cardiovascular safety	▪ CV mortality, myocardial infarction and stroke in phase 2 and 3 trials versus comparator
Reduced serious, chronic or irreversible side effects	▪ Incidence of adverse effects
Enhanced treatment convenience	
Delayed need for multiple therapies	▪ Time to progression from monotherapy
Delayed or avoided need for injections (insulin or other drugs)	▪ Time to progression or other injected therapies
Ease of comfort of administration	▪ Degree of patient compliance with treatment regimen

Health system benefits	
Reduced demand for healthcare resources	
Reduced overall health system costs	▪ Total expenditure per patient per year ▪ Medicines expenditure per patient per year
Fewer surgical procedures required	▪ DM-related surgical procedures per patient per year ▪ Same on inpatient / outpatient basis
Reduced hospitalisation costs	▪ Number of hospital admissions for DM and complications per patient per year ▪ DM-related impatient days per patient per year
Fewer visits to related specialities (chiropodist, nephrologist)	▪ Specialist visits per patient per year ▪ Ratio of visits to general practitioners versus specialists
Enhanced treatment alternatives	
Improved treatment alternatives for hard-to-treat subgroups	▪ Subgroup-specific efficacy and tolerability
New mechanisms of action	▪ First or among first medications with new mechanism of action

Appendix D: Emerging pilot design