Perceptions and recommendations of physicians/KOLs on value added medicines

European Medical Advisory Board on Value Added Medicines

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KEY OUTCOMES OF THE ADVISORY BOARD

Key outcomes of the advisory board

- Attributes such as improvement in quality of life (QoL), in convenience/ease of use, adherence or patients' preference were considered important and would be considered in physicians' prescribing decision-making process. However, participants also recognised that not all prescriptions are free across the EU, and not all drugs are available in all markets.
    - When asked about a product with the same efficacy but a better impact on QoL, all agreed that they would prescribe the product with the better QoL. However, if a product offered better QoL but lower efficacy, the participants agreed that it might depend on the severity of disease, and on the patient.
    - Patients' preferences are key. Patients want to be able to make decisions based on the balance of risk and benefit, and may value the benefit and risk differently than the doctor – they may be ready to trade high risk for high benefit. Furthermore, the balance of risks and benefit may vary between patients due to individual patient factors such as comorbidity, drug intolerance and age – requiring individualised decisions. This explains why guidelines and formularies may need to advise a range of acceptable prescribing options rather than one single treatment policy.
    - Adherence is considered a crucial issue, with a social and personal impact. Adherence may be helped by medication change, and by a behavioural science approach. The importance of this role of value added medicines was demonstrated in a 2017 systematic review of the economic impact of medication non-adherence. This estimated the annual adjusted disease-specific economic cost of non-adherence per person to range from $949 to $44 190 (in 2015 US$) [BMJ Open 2018;8:e016982. doi: 10.1136/bmjopen-2017-016982]
        - Payers will pay a premium if they considered the increased adherence worthy. How to measure the value of adherence was considered an issue, as there is a gap in adequate data that demonstrates this additional value.
        - A 'drug plus' offering, such as a drug and device, or drug and service that improves convenience/ease of use, can have a big impact on adherence, for example offering simple dosing or reducing the time-criticality of dosing. This improvement option increases value to the treatment.
    - All of the participants agreed that there were advantages to combining two or more existing medicines. They saw combinations as pragmatic, simple, cheaper and easier for patients. Real world studies show the added benefit of value added medicines and could be used to demonstrate benefit to authorities.
    - Physicians value reformulation, for example from IV to oral, or from drugs requiring intensive dosing schedules to more convenient ones.
    - Adding new devices to treatment can add value in many ways - from breakthrough lifesaving advances, to improvements in QoL or quality of healthcare - but may equally have benefit simply by being more user-friendly. For all these reasons – encouragement of continued device innovation was considered important even after a product is launched.

- Regarding evidence to demonstrate the value of value added medicines, it was agreed that there is a need for quality data for value added medicines. However, clinical trials can take eight or ten years to conclude, and a faster answer is needed for value added medicines that is tailored for the benefit that value added medicines can bring. For other types of pharmaceutical innovation, Medicine Regulators and Health Technology Assessment organisations have created "accelerated approval" pathways; this process needs to be widened to include an 'accelerated assessment' for value added medicines when the innovation is in value.
    - The group agreed that tailored approaches need to be developed to incentivise this type of innovation by using e.g. appropriate real world evidence
- Generally, only attributes such as efficacy and safety are considered in treatment evidence-based guidelines. The group agreed on the importance to introduce value added attributes such as convenience or QoL into next generation guidelines. One approach proposed is to use real world data and other studies to develop next generation guidelines:
    - There is a need for value added medicines in rhinitis that deliver fast-acting treatments to allow patients to control their symptoms optimally and reduce costs. An effective treatment for a non-responding moderate disease will have a great impact on patients. The example presented in rhinitis with the evaluation of value added medicines in a real world context and re-drafting guidelines based on real-world evidence could be applicable to other disease areas. These guidelines would help the medical and patient community.
- Physicians welcome digital innovation in treatments but recognise the generation of evidence in the field as a challenge. Regarding prescription, some physicians are early adopters, and selecting an enthusiastic core group of these would support studies. The doctors could work with patients on a new digital device in an area of unmet need, with the device then going for real world testing with a more sceptical audience.

The next steps

- Write a publication with the definition of value added medicines and that identifies value added medicines' opportunities, how to overcome the challenges to the further evolution of established medicines, and identify the resources needed to go further.
    - Rhinitis publication from Prof. Dr. Jean Bousquet was suggested as a model of a non-communicative disease, where the evidence post-launch was used to update the next generation clinical guidelines. This is because the patient value from better disease control is so great in comparison with the perceived impact of the disease – which is often seen as "trivial".
    - Apply the principle of Prof. Dr. Jean Bousquet "next generation clinical guidelines" to other therapeutic areas: inclusion of real world evidence and/or patient preferences' studies and/or other pragmatic tailored evidence that takes into consideration the attributes of value added medicines
- Focus on just two or three examples of value added medicines that work and can be tested. These could be assessed, including a meta-analysis of both randomised and real-world data. These examples could then be taken to the Medicines regulators, such as the EMA and US-FDA,

as well as HTA groups, to stimulate discussion about how best to encourage and advance this field of research and development.

  - Such dialogue needs to be stimulated at many levels including Patient organisations, Health System Payers and Healthcare Professional Societies (e.g. medical societies) – who may be willing to be involved when they realise the potential for the wider benefits of this approach.

- Crucial to the endeavour of delivering value added advances to existing treatments is widening understanding of this concept to the greater group of stakeholders in healthcare, namely medical societies (via publications and workshops for instance).

INTRODUCTION AND OBJECTIVES

Introduction and objectives

The objective of the European Medical Advisory Board was sharing knowledge on the following main topics:

1. Understanding the value added medicines landscape (e.g. expert physician perceptions and interpretation on value added medicines, current treatments and unmet needs, generation of evidence, future trends…)
2. Identify potential educational gaps & needs in the healthcare community with regards to value added medicines

Following introductions, the panel began with a discussion of the healthcare systems in Europe. This opened with the point that not all prescriptions are free across the EU, and not all drugs are available in all markets.

In the UK, the health technology assessment (HTA) body NICE (National Institute for Health and Care Excellence) makes the decisions on the drugs that can be prescribed, and then the Drug and Therapeutics Committee at the healthcare trust formalises the decision.

While doctors are able to write prescription for drugs approved in their counties, and while prescribing outside of the norm can be justified for individual cases, physicians may face limits to their prescribing.

In Italy, the government may cut salaries of doctors who prescribe 'irrationally', using data such as the Regional Administrative Database of Lombardy to find outliers at a local level can be used to bring prescribers 'back to the centre'.

Providing access and improving patient care

Cost-consciousness plays an important role in supporting access, which will in turn improve patient care. Other important parts of patient care include:

- keeping care pathways short
- maintaining a patient-centred approach
- responding to the needs of the patients
- supporting shared decision-making
- ensuring the right dose to the right patient at the right time
- providing preventive medicine

PRESCRIBING PATTERNS

Prescribing patterns

In your perspective, what are the key triggers when physicians are prescribing a medicine? Which factors do physicians take into consideration?

Drug characteristics
- Effectiveness
- Safety
- Ease of administration/convenience

Access
- Availability of the drugs
- Cost/affordability to patient or system
- Health system
- How the drug is reimbursed
- Whether the hospital gets drug income

Patient focus
- Patient profile
- Interactions with existing medications
- Cultural acceptability
- Patient's needs
- Patient education levels

Doctor's perspective
- Knowledge of the drugs
- Availability of drugs
- The physician type
- The number of patients they see
- Location/environment

Do physicians take into consideration in their decision-making process to prescribe:

- Improvement in quality of life?
- Patients' preference?
- Improvement in convenience/ease of use?
- Improvement in adherence?
- What kind of evidence doctors need?

Improvement in quality of life (QoL)

QoL is important to patients, and depends on the condition and on the individual patient. Any views on QoL should take into account family members, for example in Alzheimer's disease.

Doctors may not view QoL in the same way as patients, and need to understand that what they see as important may not be the same as the patient perspective.

When asked about a product with the same efficacy but a better impact on QoL, all agreed that they would prescribe the product with the better QoL. However, if a product offered better QoL but lower efficacy, the panel agreed that it might depend on the severity of disease, and on the patient.

Patient preference

As part of the prescribing process, doctors look at what patients prefer, and discuss the benefits and side effects. As diseases are better controlled, other needs emerge.

Patients want to be able to make decisions based on the balance of risk and benefit, and make value the benefit and risk differently to the doctor. Here, the severity of disease and stratification is important – for example, patients are more likely to accept SEs in MS than rhinitis.

Natalizumab (Tysabri) was withdrawn four months after approval because of the risk of progressive multifocal leukoencephalopathy. However, patients were ready to trade high risk for high benefit, and the drug is approved for use in severe patients. Certain HIV drugs have been withdrawn due to risk, but patients still have a preference for these.

As needs are met, other needs are exposed, and it's important to ask patients what they need on an ongoing basis. As an example, better control of sickness in cancer treatment could reduce costs of other drugs in cancer. People with HIV or cancer are now more likely to survive, so may have new needs long-term.

Patients want to be able to make decisions based on the balance of risk and benefit, and may value the benefit and risk differently than the doctor – they may be ready to trade high risk for high benefit. Furthermore, the balance of risks and benefit may vary between patients due to individual patient factors such as comorbidity, drug intolerance and age – requiring individualised decisions. This explains why guidelines and formularies may need to advise a range of acceptable prescribing options rather than one single treatment policy.

Improvement in adherence

Doctors need to take time to discuss the importance of adherence, and the reduction in benefit that comes with non-adherence. The discussions, however, may be limited by the amount of time the doctor is able to spend with the patient. The importance of this role of "value added medicines" was demonstrated in a 2017 systematic review of the economic impact of medication non-adherence. This estimated the annual adjusted disease-specific economic cost of non-adherence per person to range from $949 to $44 190 (in 2015 US$).[1]

Physicians may need to change medications to increase adherence. Adherence also requires a behavioural science approach, and doctors need to take time to discuss the importance of adherence, and the reduction in benefit that comes with non-adherence. The discussions, however, may be limited by the amount of time the doctor is able to spend with the patient.

How to measure the value of adherence came up as a discussion point, as there is a gap in data the added value of convenience.

[1] [BMJ Open 2018;8:e016982. doi: 10.1136/bmjopen-2017-016982]

Adherence is considered a crucial issue, with a social and personal impact. Adherence may be helped by medication change, and by a behavioural science approach. The importance of this role of "value added medicines" was demonstrated in a 2017 systematic review of the economic impact of medication non-adherence. This estimated the annual adjusted disease-specific economic cost of non-adherence per person to range from $949 to $44 190 (in 2015 US$) [BMJ Open 2018;8:e016982. doi: 10.1136/bmjopen-2017-016982]

Payers will pay a premium if it is worth it, for example increased adherence. How to measure the value of adherence is an issue, as there is a gap in data that demonstrates the added value of convenience.

Improvement in convenience/ease of use

A 'drug plus' offering, such as a drug and device, or drug and service that improves convenience/ease of use, can have a big impact on adherence, for example offering simple dosing or reducing the time-criticality of dosing. This improvement option increases value to the treatment.

Improvement in value

Defining value is a critical step in this process. Value can be defined differently by different stakeholders – for example when seem from patient's as against the Payer's perspective.

Clinical Value may be straightforward to define – as improved length of life, improved quality of life or both. In contrast defining "Economic Value" can be more problematic. To be of most use, economic value needs to assess the wider benefits to patients, families and society rather than simply reflect the payer perspective. This is important when a more expensive medicine with better disease control saves future treatment costs, or when spending on medicines saves costs elsewhere in the health system – such as the need for nursing staff or avoidance of surgery, that may be provided from different financial budgets.

Types of evidence

As well as clinical studies and other evidence, physicians look to clinical experience and what the patient says. While politicians like HTAs, doctors need to see clinical value and impact on the patient management of the disease.

The value of new innovative and high-cost drugs, and their impact on access, is generally measured with information that is incorporated in their clinical development and approval process. Regarding value added medicines, there is a need to tailor the data that demonstrates the new benefits.

There is a need for quality data for value added medicines. However, clinical trials can take eight or ten years to conclude, and a faster answer is needed for value added medicines that is tailored for the benefit that value added medicines can bring. For other types of pharmaceutical innovation, Medicine Regulators and Health Technology Assessment organisations have created "accelerated approval" pathways; this process needs to be widened to include an 'accelerated assessment' for value added medicines when the innovation is in value.

Regarding each of the topics mentioned in question 2, who starts the discussion: physicians, patients or other (e.g. caregiver, another healthcare professional, etc.)?

- Improvement in quality of life
- Patients' preference
- Improvement in convenience/ease of use
- Improvement in adherence

Conversations about new drugs may be started by patients, for example saying, 'I want a good quality of life'. The physicians then follow up the enquiry. According to one physician, in Portugal, 48% of diagnostic tests and 27% of drugs are first requested by primary care patients.

Physicians also have a role; where the provision of a new drug requires approval before reimbursement, for example in the UK, an enthusiastic physician will take the request, along with evidence, to their therapeutic or formulary committee. If there is little cost impact, then the answer is likely to be a yes. If the drug has a higher cost, then data on both clinical effectiveness and cost effectiveness will need to be provided before approval by Clinical Commissioning Groups.

Health systems also need to develop ways that manufacturers can directly request reviews for value added medicines. Conventional Health Technology Assessment often responds to the approval of novel medicines or new labelled indications – while improvements from subsequent value added development can be ignored or delayed from timely assessment.

There were disagreements over the balance between patient and societal impact. One view was that patients will view societal benefit as more important than their own benefit, another was that patients want what is better for them over what is better for society, and so doctors need to respond to the needs of the patients.

Guidelines, which are evidence based, look at attributes like safety and efficacy. Would it be possible to introduce attributes such as convenience or QoL into next generation guidelines? One approach proposed is to use real world data and other studies to develop next generation guidelines.

Are the topics below reflected in any prescribing guidelines?

- Improvement in quality of life
- Patients' preference
- Improvement in convenience/ease of use
- Improvement in adherence

Prof Dr Bousquet used value added medicines in rhinitis as a patient-centred model to improve adherence. Adherence is low in the management of rhinitis, and 50% of patients are self-medicated. The issue is not health literacy but behavioural science, and there is a need to change practice using change management.

There is a need for a VAM in rhinitis that is fast-acting treatment to allow patients to control their symptoms optimally and reduce costs. An effective treatment for a non-responding moderate disease will have a great impact on patients.

Patients often self-medicate and use OTC medications, and do not always follow the physician's prescription. This is also true of physicians with rhinitis, who don't take their own advice. This shows that the issue is not health literacy but behavioural science, and there is a need to change practice using change management.

Prof Dr Bousquet is adapting existing guidelines and then testing them against real word evidence to see if these need to change. Prof. Dr. Bousquet used real world data from the MASK-air mHealth strategy, which asks patients four simple questions each day. This data and data from papers was then used to adapt the ARIA guidelines and e-CDSS.

There is a need for value added medicines in rhinitis that deliver fast-acting treatments to allow patients to control their symptoms optimally and reduce costs. An effective treatment for a non-responding moderate disease will have a great impact on patients. The example presented in rhinitis with the evaluation of value added medicines in a real world context and drafting guidelines could be applicable to other disease areas. These guidelines would help the medical and patient community.

Do physicians value reformulation of medicines? If yes, in which context?

All panel agreed that physicians valued reformulation, one panel member added that information and education are also important.

Reformulating a drug from a number of daily doses to a single daily dose provides equivalent efficacy with better compliance. This can be hard to prove in a clinical trial, as patients 'have' to be compliant in trials, but can be captured in observational studies. Physicians value reformulation of medicines.

Physicians value reformulation, for example from IV to oral, or from drugs requiring intensive dosing schedules to more convenient ones.

A good example of the value of reformulation is that a systematic review of randomised trials of short-acting vs long-acting formulations of filgrastim show equivalent outcomes; yet in repeated real-world studies the long-acting formulation is better – resulting in less hospitalisations for patients undergoing cancer chemotherapy. The randomised trials were performed with trial nursing support to ensure adherence with the 7-14 daily subcutaneous injections required for short acting filgrastim administration, against the single injection needed for the long-acting "value added" formulation [Adv Ther. 2018 Nov;35(11):1816-1829. doi: 10.1007/s12325-018-0798-6. Epub 2018 Oct 8.].

Do physicians see advantages to combine two or more existing medicines? If yes, in which context?

All of the participants of the panel agreed that there were advantages to combining two or more existing medicines. They saw combinations as pragmatic, simple, cheaper and easier for patients.

Real world studies show the added benefit of value added medicines and could be used to demonstrate benefit to authorities. Value should either be "clinical value", with the metric of improved disease outcomes and/or "societal value" and/or "economic value" with similar outcomes delivered at lower overall cost/overall savings.

Do physicians see advantages in adding a certain medical device or an additional service to medication? If yes, in which context?

Asthma inhalers were cited as examples of the advantages of combining drugs and devices, as around three quarters of asthma drugs are combinations.

Each asthma drug has a new device. Critical to assessment is to ask is there much difference between these, or are the new devices simply marketing tools? To better understand their value, new devices need to be tested against older ones, with patient-focused endpoints such as exacerbations, rather than endpoints like FEV1. There is a need for a device that makes a real difference, is user-friendly, and where the cost of the initial device is not too high or is balanced by cost-savings elsewhere – such as the reduced need for physician review or hospitalisation.

Devices can also be linked to apps, to provide real-time dosing data. This is known as a drug in a "companion system", and is accepted by HTA authorities such as NICE.

Adding new devices to treatment can add value in many ways - from breakthrough lifesaving advances, to improvements in QoL or quality of healthcare - but may equally have benefit simply by being more user-friendly. For all these reasons – encouragement of continued device innovation is important even after a product is launched.

VALUE ADDED MEDICINES

Value added medicines

What are value added medicines?

Value added medicines are medicines based on known molecules that address healthcare needs and deliver relevant improvements for patients, healthcare professionals and/or payers.

The added value may be achieved through finding a new indication (drug repositioning), finding a better formulation or dosage (drug reformulation), or developing a combined drug regimen, adding a new device or providing a new service (drug combination). Relevant improvements include: a better efficacy, safety and/or tolerability profile; a better way of administration and/or ease of use; and new therapeutic uses (indication/population).

Are physicians using value added medicines in their clinical practice?

Yes, examples of value added medicines in use included:

- **Omalizumab – originally provided as a dry powder for reconstitution, and now available in prefilled syringe**
- **Sildenafil – initially developed for hypertension and angina, now approved for erectile dysfunction, and may have potential in other indications. However, there could be a risk of abuse if reimbursed outside of sexual dysfunction.**
- **Once-daily/weekly/monthly reformulations of short-acting drugs.**

What would be the evidence acceptable to physicians to demonstrate the additional benefits of value added medicines?

- What would be alternative ways to demonstrate the added value of these medicines to physicians?

Physicians want information on drugs that responds to their needs:

- Safety, efficacy and side effects
- How to use the drugs
- What interactions there may be
- The impact of drugs on different subgroups of patients
- Information that includes interpretation of the data
- Real practice cases and real world evidence.

This information should come from:

- Societies, drug agencies, and the industry.
- The views of colleagues, their boss, patients, and peers.

Doctors need support, such as information, and electronic devices that analyse patient data and provide rapid analysis and feedback. Research and Evolution in the gathering of Patient Reported Outcomes (PROs) needs to be encouraged not just as treatments are first approved – but also later in the cycle of drug development and evolution.

Trial data can be useful for value added medicines, but this is difficult for manufacturers because of the challenge of getting return on investment by the authorities. Regulatory standard trials for novel therapies are time-consuming, expensive and divert potentially willing patients from entering other trials that might also have a potential for future benefit. Overcoming this barrier should encourage development of more value added medicines. For this reason, more tailored approaches need to be developed to incentivise this type of innovation from appropriate real world evidence.

How can the medical community work together with manufacturers to:

- improve existing medicines
- create more awareness on the benefits of value added medicines in the medical community?

Novel drug approvals or label extensions are based around prospective clinical trial data that is expensive and time-consuming to collect. Once drugs are launched, there is a need for patient registries of sufficient scale and inclusivity to be accessible so that researchers and developers can identify unmet needs, and ultimately prove, the value of further evolution of those treatments.

Some physicians are early adopters, and selecting an enthusiastic core group of these would support studies. The doctors could work with patients on a new device in an area of unmet need, with the device then going for real world testing with a more sceptical audience.

Companies and physicians need to have ethical relationships. Physicians don't and should not want financial incentives, like travel, to encourage their interest in value added treatment. Instead, when involved in treatment innovation their needs may be best served through enhanced educational and research support.

What are your thoughts on combining drugs with digital solutions?

The drug/digital approach would need evidence before adoption into routine practice. There would be challenges in studies, for example choosing the treatment policy to use as a comparator and in patient data protection issues.

In this context, it has been suggested that cluster trials may be useful. The advantages of cluster randomised controlled trials over individually randomised controlled trials include the ability to study interventions that cannot be directed toward selected individuals (for example – web based education) and the ability to control for "contamination" across individuals (for example, when one individual's changing behaviors may influence another individual to do so).

There is a danger that the rapid appearance of many "health Apps" is running ahead of their critical assessment. The device regulations in Europe are changing, and are moving closer to drug regulations. Because of this, studies will need to show a clear clinical superiority, or a significant benefit to the patient.

Health systems need to identify and reward research and development potential within their whole workforce. Physicians welcome digital innovation in treatments but recognised the generation of evidence as a challenge. Furthermore, some physicians are early adopters, and selecting an enthusiastic core group of these would support studies. The doctors could work with patients on a new device in an area of unmet need, with the device then going for real world testing with a more sceptical audience.

Evaluating value added medicines

Is real world data enough to change treatment strategy and convince HTA bodies? It may be necessary to go a step further, to create a hypothesis with real world evidence and test it in traditional clinical trials. Furthermore, promising trials need a source of funding.

Studies that look at good days/bad days integrate all the benefits from a patient's experience, so will feed into patient preference and QoL.

There is currently not a clear route to evaluating value added medicines, or to protecting their IP. There is an EMA guidance for biosimilars but not for repurposing drugs. It will take a lot of time to change the rules.

Testing hypothesis of real world evidence with digital data in clinical trials would go beyond state of the art RCTs, and could be used to reach conclusions that can become guidelines.

European Medical Advisory Board on VAMs – Future Recommendations

Write a publication with the definition of value added medicines and that identifies value added medicines' opportunities, how to overcome the challenges to the further evolution of established medicines, and identify the resources needed to go further.

- Rhinitis publication from Prof. Dr. Jean Bousquet was suggested as a model of a non-communicative disease, where the evidence post-launch was used to update the next generation clinical guidelines. This is because the patient value from better disease control is so great in comparison with the perceived impact of the disease – which is often seen as "trivial".
- Apply the principle of Prof. Dr. Jean Bousquet "next generation clinical guidelines" to other therapeutic areas: inclusion of real world evidence and/or patient preferences' studies and/or other pragmatic tailored evidence that takes into consideration the attributes of value added medicines

Focus on just two or three examples of value added medicines that work and can be tested. These could be assessed, including a meta-analysis of both randomised and real-world data. These examples could then be taken to the Medicines regulators, such as the EMA and US-FDA, as well as HTA groups, to stimulate discussion about how best to encourage and advance this field of research and development.

- Such dialogue needs to be stimulated at many levels including Patient organisations, Health System Payers and Healthcare Professional Societies (e.g. medical societies) – who may be willing to be involved when they realise the potential for the wider benefits of this approach.

Crucial to the endeavour of delivering value added advances to existing treatments is widening understanding of this concept to the greater group of stakeholders in healthcare, namely medical societies (via publications and workshops for instance).

Perceptions and recommendations of KOL physicians on value added medicines

European Medical Advisory Board on Value Added Medicines

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