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In the fast-developing world of health technologies, especially under the pressure of COVID-19 but already before, there is a need for HTA to be both predictable and flexible

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Niklas Hedberg outlines the role of EUnetHTA as both a network and project built up of national HTAs in Europe, the potential for a continent-wide mandate on health technology assessment, the integration of RWE into decision making processes, and how EUnetHTA has adapted to cell and gene therapies.

Can you begin by introducing yourself and your national and international roles?

I am the chief pharmacist at the Swedish Dental and Pharmaceutical Benefits Agency (TLV), Sweden's pricing and reimbursement agency, where I have worked for almost 20 years. My work at the TLV has encompassed various roles, from assessor to head of department, chief pharmacist with mainly national duties, and now lately with a lot of international duties.

Sweden became a member of the EUnetHTA executive board in 2016, a process in which I was our lead partner, and then when there was a re-organization of the EUnetHTA governance structure in 2018, I was elected chair of the executive board.

What is EUnetHTA and its role today?

EUnetHTA is both a network and a project, built up of Health Technology Assessment Bodies (HTAs) from across Europe. The network has answered a number of calls from the European Commission (EC) and now counts 83 partners, some of whom have been members since 2006.

Currently, EUnetHTA Joint Action 3 (2016-2021), which aims to define and implement a sustainable model for scientific and technical cooperation on HTA in Europe, is coming to an end. This is the third such Joint Action; it is quite unusual for the EC to run three Joint Actions on the same topic.

Three years ago, the EC produced the first proposal on the future model for HTA. After the political decision-making that is still ongoing in the Council of the European Union after a number of different presidencies, it seems that during the end of the German presidency (July-December 2020) and the beginning of the Portuguese presidency (January-June 2021), an agreement will be struck and a decision made about which HTA regulation Europe will adopt in the future.

That means that the project base and the joint action base might eventually come to an end. But hopefully the network will remain, where we have a pool of participating agencies, communication and information exchange, interaction, and mutual learning.

What will the current HTA setup be replaced by? Will there be a mandated law about HTA assessment across Europe?

It is not possible to entirely say because discussions among member states in the Ministerial Council are still ongoing, but it will not be a fixed entity like the European Medicines Agency (EMA); it will not be a new EU agency. It will probably be a Secretariat, under the Commission, but we will have to wait and see. However, we can say that there will be more explicit regulation on how the network partners from different Member States act and work.

Drug safety is, for example, a joint issue. However, affordability is a member state mandate, which makes it complicated to navigate in this world. There is an ongoing dialogue about what the commission can dictate and what the member states still have the mandate to decide themselves.

Having walked this thin line between joint clinical assessments and national appraisals, what are the lessons you have learned that could be taken into consideration in the future?

You are right to say that there is a thin line between producing high quality reports that can easily and readily be implemented without making them pre-empt national decisions. The national decision making must still be national, but the report should be ready and easy to implement. Without this, the value of the joint work becomes questionable.

In the fast-developing world of health technologies, especially under the pressure of COVID-19 but already before, there is a need for HTA to be both predictable and flexible. Unexpected things happen all the time.

Many of the discussions that HTA bodies are involved in now are both interesting and challenging, but the general idea of a joint work on HTA is not under debate. Almost all partners are agreeing that we should increase our efforts on joint work.

How well equipped are HTA bodies in Europe to analyse and take into consideration new forms of data such as real-world evidence (RWE) in their decision-making processes?

A few years ago, my general impression was that payers had started to question the value of outcome-based managed entry agreements. This was something that had been talked about for five or ten years previously and was widely thought to be the future. These agreements are tremendously resource-intensive, involving sitting down and agreeing to only pay for the actual outcomes of products. They require agreement on the relevant outcomes and the collection of further evidence on these outcomes. However, a general concern was emerging where the payers were worried that whatever data situation finally emerged after the time period agreed, they would have to continue paying. The issue is that there is not enough agreement, nor sufficient infrastructure, to make sure that payers and HTA bodies can always have the data they want.

Sometimes the data is not available or accessible. It may not have been collected at all or it was collected but HTA bodies weren’t allowed to use it for their purposes. Without new data, if the older data set that is available for a particular drug seems to meet the agreed outcomes, the company will posit that the most reasonable thing to do is to stick to the original agreement, and followingly, to keep paying. If new data emerges that supports the original assumptions on outcomes, then the payers must still keep paying.

The third alternative is that new data that has become available through follow up will contradict pivotal study results and the assumptions made from the beginning. In this situation, companies have regularly said that the methods used to obtain the follow up data are not good enough and

the payers impression is that in the rare cases when this has happened, they have still kept paying.

On the other side of the coin, the companies say that no matter what agreement is made, they are caught in cycle of regular price cuts in every country across Europe. So what ever happens with new data, the price can only go down and never up

The key issue seems to be a lack of trust in the system used to gather data and adopt it for decision making. Together we must take up the responsibility to work on methodological development, and to agree that results will be used, both when it is good for business and when it is bad.

On the European level, this work normally comes too close to the pricing and procurement that is a national mandate so EUnetHTA has had other main focuses.

EUnetHTA has a work package on evidence generation where the HTA bodies have provided an opportunity for early dialogues to the pharma developers. There is also a work stream for post-launch evidence data generation and in this work EUnetHTA has rolled out a number of pilots for evidence generation and has developed a quality tool for evaluating quality and relevance for quality registers.

On the national level in Sweden, TLV has worked with RWE for a number of years and we have started to utilise new or untraditional kinds of evidence. As a society I would say that we are all a bit behind in the methodological groundwork when it comes to real world data (RWD). Therefore, TLV has also started the work to proactively contribute to the development of new methods.

How has the conversation with patients and patient groups evolved in Europe and do you see these groups as having matured to a sufficient level to contribute meaningfully to debates?

The dialogue between HTA bodies in general including EUnetHTA and patient groups have definitely matured, and we are much better off now than a few years ago. There are many examples of really fruitful discussions and developments with patient involvement. Of course, there are also examples where we did not succeed and acted too late but in general, we have quite a good position.

The important thing to remember is that this is a journey that never comes to an end. There will never be a point where we can point to there being “enough” patient involvement or engagement.

Everyone needs to be humble and remain interested to learn, discuss, and do more. However, we have made significant progress and earned respect and acknowledgement for our actions.

When confronted with paradigm-shifting cell and gene therapies, what questions has EUnetHTA had to ask itself and its peers?

We have had to relate to new kinds of evidence which are structured in new ways. For example, there has been a need to handle umbrella, basket, and single-arm trials as grounds for medical approval; meaning that the clinical trial paradigm has been turned upside down.

Over the past five to ten years, we are, on national and regional level, increasingly being asked to grant reimbursement for products where the data is based on Phase I studies, even though, traditionally these studies only included healthy volunteers. This is especially true of new products in oncology, orphan drugs and precision medicine.

This is of course challenging but we must not forget the basic tools with which we start every assessment. In the national setting at TLV we had our first experiences with CAR-T about two years ago. Then we realised that many of the challenges we were facing were also those facing us in assessing traditional products. The difference is that these uncertainties were multiplied by a larger number for cell and gene therapies.

After that, since medical approval had already been granted, we had to focus on follow-up data and evidence generation and how we were able to make wise decisions now that are still meaningful for the downstream decision maker. We must maintain the triangle of relevance, predictability, and flexibility.

If the HTA always says that more research is needed and that the data is too weak to draw any conclusions, then downstream stakeholders like regions, individual clinics, and clinicians will have to meet the patient and make decisions without us. Therefore, TLV has preferred to say that an assessment result is very uncertain and that it is of utmost importance to follow-up and generate further data. Clinicians should know that they have a responsibility, if they want to use an expensive new drug, to make sure that we can follow up the results.

One of the sponsors' arguments is that because cell and gene therapies are often only used as a last resort, efficacy would be improved if patients were treated with these

products at an earlier stage. Might this be a valid argument that would help to produce more robust data?

Yes and no. That's exactly the formulation we need to use. RWD must be used to create more robust evidence. It cannot be used to produce the first evidence. There must be some kind of traditional data to support the argument that a drug will be more effective or more cost-effective if used as a first line treatment.

How do you foresee the evolution of these therapies impacting your work and how are you planning to square the affordability circle?

I need to look into the pipeline more and update my horizon scanning a bit, but we will probably be having this same discussion for the upcoming three to five years. There will be an ever-increasing number of products and an increasing number of patients, but ultimately, they will still serve only fairly small patient groups.

In the longer run of the next eight to ten years there needs to be a shift, as even the wealthier nations are challenged on affordability. I cannot see how, in general, we will be able to afford all these interventions with the prices that they come with today.

That is a tremendously difficult discussion. Right now, we can still afford the discussion that perhaps we haven't put all the value components into the equation. Perhaps we need to rethink how we do the analysis. But in the long run, for equitable care, more and more people are starting to talk about national responsibility for these therapies rather than the responsibility lying with individual hospitals.

I am not going to judge whether that is a positive or negative development, but the national money also needs to come from somewhere. National budgets will also have their limits. I am seriously worried about the affordability of precision medicines if we don't start talking about a shift to something more sustainable for developers, patients, assessors, and payers

To what extent does EUnetHTA interact with cell and gene therapy developers themselves and what arguments are they giving about pricing?

We do interact with sponsors, though we try to avoid pricing discussions on a EUnetHTA level as that is a national mandate. This again touches on the particular nature of EUnetHTA and the thin

line we walk between assessment and appraisal. Pricing discussions are always from appraisal and downstream. We do have interactions with the developers on an EUnetHTA level, but that is for early dialogues and joint relative assessments.

What would you like developers, regulators, and other stakeholders to keep in mind about cell and gene therapies moving forward?

We are trying to formulate that there are different and separate challenges. The first challenge is a just assessment of the value of a product. There are a number of difficulties there, including the assessment of new kinds of evidence or putting a value on a product that may be given in combination with another.

Then there needs to be a discussion and an agreement on how to evaluate cost effectiveness. Although not all countries work with cost effectiveness, there are questions around how calculations and analysis is done and what can be brought in from the value and costing discussions.

The third challenge is different payment models, whether they are made based on assumptions or results and how they are discussed.

Finally, there also needs to be a discussion about financing models; how is the money going to be paid, when, for what kinds of results, and where is it going to come from?

It is useful not to mix these discussions, but to realise and clearly state that these are different kinds of discussions. We must try to solve them all. Just going in very fiercely to the discussion about value and cost effectiveness does not solve the financing issue.

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