

# AN INTRODUCTION TO KEY CONCEPTS IN HEALTH ECONOMICS FOR HEMOPHILIA ORGANIZATIONS

**Brian O'Mahony**

Chief Executive, Irish Hæmophilia Society

**Declan Noone**

Irish Hæmophilia Society

**Keith Tolley**

Tolley Health Economics

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**World Federation of Hemophilia**

1425 René Lévesque Boulevard West, Suite 1010

Montréal, Québec H3G 1T7

CANADA

Tel. : (514) 875-7944

Fax : (514) 875-8916

E-mail: [wfh@wfh.org](mailto:wfh@wfh.org)

Internet: [www.wfh.org](http://www.wfh.org)

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Brian O'Mahony, Declan Noone, and Keith Tolley

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## Introduction

People with hemophilia require lifelong treatment with clotting factor in order to manage frequent bleeding episodes and reduce the risk of joint damage (as well as other potential organ damage) requiring surgery and/or resulting in restricted mobility. The prevention of bleeds with factor concentrate has become standard practice for the treatment of hemophilia.

To date there have been few restrictions on funding and access to new treatments for hemophilia in developed countries. However, a climate change is occurring: as new expensive products come to market, healthcare payers wonder whether costs can be controlled without major detriment to patients. As a result, the areas of **health technology assessment**\* (HTA) and evidence-based medicine are increasing efforts to collect data on patient health outcomes and quality of life in hemophilia, and starting to assess the **cost-effectiveness** of different treatments with the aim to control costs into the future. In the U.S.A., **comparative effectiveness research** (CER) may have an impact on the provision of care in the future.

It is challenging to apply health economics to hemophilia due to the relative rarity of the disease, limits to data available (although this is changing as the need for outcomes evidence increases), and the fact that it affects children and their families as well as adults. Hemophilia patient organizations need to develop at least a basic understanding of the economics of hemophilia care and the methodology and terminology associated with health technology assessment. HTAs in hemophilia will only occur in some countries, but hemophilia patient organizations around the world need to be prepared to deal with economic data and arguments. A separate guide will be available later this year that covers the methodology and economic concepts in more detail (Tolley, K. "Health Economics and Haemophilia: A Guide to Methods," forthcoming).

The aim of this monograph is to:

- develop an understanding of the economics of hemophilia treatment;
- develop an understanding of the health technology assessment (HTA) process and its terminology and a basic understanding of the concept of comparative effectiveness research (CER);
- teach hemophilia organizations how to advocate on issues relating to the economics of hemophilia care;
- identify areas where hemophilia organizations can make contributions to the HTA process;
- identify the challenges in applying the HTA process to hemophilia.

This guide may also be useful for patients and patient organizations living in countries where HTA processes are not well developed. With the current global economic crisis projected to continue into the future, national hemophilia patient organizations and clinicians need to develop a greater appreciation of the economics of hemophilia care. The unrestricted availability of replacement therapy that has become the norm in many countries may be more difficult to sustain without the proactive collection of **evidence-based data** by clinicians and experiential data by patient organizations. In our separate and joint advocacy and lobbying activities in the coming years, economics will be an increasingly important criterion. We must have the ability to collect, collate, and interpret the relevant data and understand the economic concepts we will be challenged with in our efforts to improve or maintain therapy. The sort of experience-based information that patients and patient organizations contribute to HTA processes can also be useful in raising public awareness about the impact of treatment for hemophilia and the need for effective prevention and treatment. This data can help make the case for better treatment in a variety of settings including media campaigns, lobbying, or in individual consultations with doctors.

\*Words in **bold** are defined in the glossary on page 19

Most European and many other countries now have HTA agencies (listed in Appendix 2). HTAs will increasingly be used not only to evaluate new technologies or therapies but also to decide how to allocate limited **resources** for the treatment of many conditions using existing therapies. Health authorities to date have generally carried out HTAs where the therapy is used by many people in a country (such as statins to lower cholesterol or medications for diabetes) and therefore represents a significant economic burden. Though hemophilia is a relatively rare disorder, the cost of treatment for those with severe hemophilia is relatively high, so it is now starting to appear on the radar screen of HTA agencies as well. In Sweden, for example, a HTA on hemophilia is currently underway. This is not entirely surprising, as factor VIII concentrate is the third most expensive therapeutic product in Sweden (the first being a therapy for rheumatoid arthritis and the second test strips for diabetes; personal communication, Swedish Haemophilia Society). If we look specifically at Sweden as an example, HTAs have been completed in the following areas: migraine, diseases caused by excess stomach acid, asthma, chronic obstructive pulmonary disease and coughs, hypertension, depression, and lipid disorders. There are also ongoing assessments on therapies for diabetes, rheumatism, incontinence and prostate disorder, painkillers, and anti-inflammatory medications. Given these precedents, it is not a major surprise that the HTA authority in Sweden is now examining hemophilia. In Belgium, factor VIII ranked eighth in the list of the twenty-five most expensive therapies.

In this monograph, several of the concepts are illustrated using the example of prophylaxis in hemophilia. This example has not been chosen at random. Prophylaxis for children with severe hemophilia is recognized as the optimum standard of care by, among others, the European Association for Haemophilia and Allied Disorders [1], the Medical and Scientific Council of the National Hemophilia Foundation in the U.S.A., the United Kingdom Haemophilia Doctors Organisation, and the Canadian Association of Hemophilia Treaters. A widely quoted randomized clinical trial in 2007 – the Joint Outcome Study [2] – also supports this therapy. However, prophylaxis is relatively expensive compared to on-demand therapy and health funding agencies are therefore beginning to examine its cost-effectiveness. In particular, the continuation of prophylactic therapy into adulthood will be scrutinized. Though the clinical benefit has been

acknowledged, the merits of prophylaxis are vulnerable from a financial point of view.

## Health Technology Assessments

### Goals and purposes of HTAs

The term HTA can refer to any aspect of health care from prevention programmes, to devices, to drugs and procedures. The aim of a HTA is to examine the short and long-term consequences of using a healthcare technology, taking into consideration the medical, social, economic, and ethical issues related to its use. The process is meant to apply a systematic, transparent, and unbiased approach when evaluating health technologies.

HTAs are used differently across Europe. In some countries such as England and Wales, they are used to guide decisions about whether treatments and other technologies should be available on the National Health Service (the publicly-funded healthcare system), based on a judgement of whether they provide **value for money**. In other countries the focus may be less on value for money and more on evidence of **effectiveness**.

A HTA can provide information to support decisions about priorities in health care (i.e. how the total healthcare budget should be allocated) or decisions about whether new treatments should be introduced. For example:

- health authorities thinking of putting in place screening programmes;
- healthcare payers deciding which technologies (e.g. operations, drugs) should be paid for;
- healthcare organizations deciding whether to exclude or implement new treatments;
- healthcare companies deciding whether the benefits of producing new products will justify the cost. (A future relevant example may be long-acting factor concentrates.)

### HTAs and advocacy

Does this mean that decisions on the provision of care should be taken away from clinicians and that the role of patients and patient organizations should be excluded? Should health economists be the ones to decide which treatments are provided based solely on measured economic criteria?

The answer to both questions is a resounding no. There are many layers in decision-making and

different rationales for therapy. An economic assessment is but one of these.

The rationale for ensuring effective treatments has many components:

- Hemophilia is a rare genetic condition for which effective therapy is available. Treatment can transform the **quality of life** and indeed ensure the very survival of the individual. In the absence of good therapy, the child with hemophilia faces inevitable bleeding, joint damage, and perhaps early death. If he survives into adulthood, he faces arthropathy, pain, loss of mobility, and the inability to contribute fully to society.
- Adequate therapy allows the individual to treat bleeding early or ideally avoid bleeding entirely with prophylactic therapy. This helps to prevent joint damage in most individuals and allows them to get an education, work, and raise and support a family. The individual can contribute fully to society. There are many genetic or serious medical conditions where such a positive outcome is not even remotely possible, even with available therapies.
- In the past, provision of unsafe treatment products led to the infection of thousands of people with hemophilia with HIV, hepatitis B, and hepatitis C. Thousands have died. This catastrophe has resulted in an enormous human cost. It has also resulted in a very high financial cost for treatment, hospitalization, compensation, and inquiries. We should not allow health economists or governments to forget the high cost of providing unsafe or sub-standard treatment.
- Any individual can be born with a condition that is rare or expensive to treat. In a fair and equitable society, individuals and families should not be punished because of this. A Swedish survey [3] clearly demonstrated that taxpayers who understood hemophilia and the benefits of therapy were willing to pay more than the actual cost of both prophylaxis and on-demand therapy for those with hemophilia. This solidarity should be an important aspect of any reasonable society.
- Health economists obviously make judgments solely on economic grounds. Their job is to determine whether the benefits of a therapy or procedure justify the costs. Using the available evidence-based data, processes such as HTAs allow them to make predictions and calculations and, ultimately, decisions on the cost-effectiveness of treatment. However, it

should be remembered that the methodologies they use to do this are themselves very subjective. Techniques described later (including time trade off, standard gamble, or visual analogue scale) are generally based on the subjective opinion of those who are asked the questions (see “Measurement of Health Utilities” on page 11).

- HTAs provide a guide for health authorities on the relative cost-effectiveness of a medical intervention or treatment. The authorities may accept and base their decision on this, but that is not necessarily the case. In Sweden for example, an assessment on therapy for a genetic disease called phenylketonuria (which, if not carefully regulated in infancy, can cause mental retardation) was favourable and the cost was lower than the generally accepted Swedish cut-off cost for therapy. Despite this, the HTA finding was not implemented and the therapy has not been approved. In Ireland, a HTA on the provision of HPV vaccination for girls to prevent cervical cancer showed a relatively low cost, but the vaccination programme was not initiated (this decision has now been revisited).

If hemophilia care is subjected to a HTA, an unfavourable finding is not necessarily going to be implemented. The normal methods of advocacy and government lobbying would continue to apply. However, it would obviously be better if the HTA outcome was favourable. The likelihood of this is enhanced if clinicians and the national hemophilia patient organization understand the process and participate from the earliest possible stage. That is the rationale for this guide.

## Patient and Patient Organization Contribution to HTAs

This section examines why patient experience is important. It suggests a framework for patient organizations to contribute to the HTA process by collecting and interpreting experiential (i.e. based on experience) and experimental evidence and data. It should also be noted that even if the HTA process has a negative result, this evidence can be used to appeal the findings. A HTA is *not* a decision; it only informs the decision-making process.

### Why patient experience is important

Although HTAs are used to control costs spent on health care, the results of the HTA generally do not

affect the politician or decision-maker directly. The real effects are felt by the patients, caregivers, and in a wider sense the public in general. Therefore, it is essential that the patient perspective is considered in the HTA process.

HTA agencies collect all the available scientific data they believe is needed to make a decision, but the reality of the illness on a day-to-day basis can be overlooked. The only way for the real impact of living with a condition like hemophilia to be understood is for the patients and patient organizations themselves to provide evidence. For example:

- Evidence-based, scientific data may describe treatment regimes in terms of the annual number of bleeds with on-demand therapy versus prophylaxis. However, this information is meaningless unless the person examining it knows what a bleed actually is, what it feels like, and what its impact can be. Describe how much it hurts when a joint bleed is left untreated. Describe the inevitable long-term effects of repeated bleeds into joints or muscles. Point out the very real possibility of life- or limb-threatening bleeds. Point out the real consequences for everyday life (e.g. you cannot go to work/school, or you have to get your wife/partner to help you get dressed).
- Record the amount of time missed from work/school over a year. Note if you are planning to take time out for medical reasons, such as an operation due to joint damage, and time for hospital appointments. Also note the times you have had problems during the weekend and have had to rest and miss activities with the family.
- Describe the impact a treatment has on daily life (e.g. "it allows my child to sleep over at a friend's house and not be afraid").

*The effect of both the illness and the treatment on all aspects of life is one of the reasons that evidence from patients and the public is so important. The patient and the patient organization should focus on explaining their needs rather than advocating for a specific product or treatment.*

### **Patient involvement**

Patient involvement should be evident in all stages of the HTA process. However the mechanism for this involvement will differ between HTA agencies. Some HTA agencies will proactively seek the views of the relevant national patient organization early in the process. Others will not seek this, but will be open to input from the patient organization. It is important

that you determine how your organization can get involved with the HTA agency in your country before a HTA begins on any aspect of hemophilia care. Do not wait until it is too late. Find out from your HTA agency which priority areas they will be examining in the coming year or years. If they are intending to examine any aspect of hemophilia care, get involved early. Contact the agency and ensure they know that you wish to make a submission. Put this request in writing. If they refuse to hear your submission, the proof that you have requested and were denied the opportunity to do so will be a strong advocacy tool in any future campaign against a negative result. Ideally, get involved at an early enough stage to allow your organization to positively influence the specific areas that will be examined. If you can influence the questions, you are more likely to influence the outcome. The sooner there is patient involvement in the process, the better. Getting involved late in the process and answering the HTA agency's questions is not as effective as being involved from the start and helping them decide which questions to ask in the first place. The outcome of a HTA may be negative or positive, but you can only influence the decisions taken if you are involved in the process. If the HTA result is negative, it will be much easier to lobby the government and point out the flaws in the decision if you have first-hand knowledge of how the decision was made.

As this process is relatively new and more and more countries are using these methods, it is important to take a proactive approach.

- Start now by learning about the methods used in other countries to do a HTA. Appoint someone within the patient organization who has an interest and encourage them to develop their knowledge.
- Find out about your national HTA agency and what HTAs they have planned.
- Every country has a different approach to conducting a HTA and uses different methods. Learn about the approach and the background to the methods they are using.
- If you are asked to be involved in the process, get involved if you have the resources. If resources are unavailable, look to other organizations that have been through the experience. Use the same people and build up knowledge now. This is a complicated process with specific terminology. Token representation will not be useful.
- If the HTA process does not ask for patient involvement, contact the agency carrying out the



assessment and offer your help. People like you who might be directly affected by the assessment have an important perspective to provide. You should explain the experience you have (with the clinical situation and/or the technology) and the relevance of what you are able to contribute. If necessary, lobby for involvement.

- Do NOT wait to be contacted by the HTA agency if you are aware that a HTA on hemophilia will take place in your country. Contact them and politely but firmly insist that the views of the national hemophilia patient organization must be considered by the HTA panel or you will view the process as fundamentally flawed.

### Providing patient evidence

Different HTA agencies will accept patient evidence in different ways. Most have a panel of experts that a patient and/or the patient organization will meet with to discuss the important aspects of patient needs. There are two main ways in which patient evidence can be used to contribute to a HTA. The first is through the patients (and/or caregivers) talking directly about their own lives and how the illness affects them on a day-to-day basis. This can humanize the condition for the HTA panel. Those who are chosen to speak should be able to make their message clear to academic and other professional experts. Present the two or three key messages you want to deliver at the beginning and then elaborate with concrete examples. Return to reinforce the key messages at the end of your allotted time. This type of presentation should be factual, anecdotal with real case examples, and non-emotional.

Patient evidence might include:

- the impact of a bleed, either short or long-term;
- a description of symptoms;
- symptoms that are difficult to live with;
- the limitations hemophilia imposes on daily life, ability to work, social life, enjoyment of family and friends;
- the impact on a person's mental health;
- activities that people living with hemophilia find difficult;
- whether the illness prevents people from fulfilling their chosen role in life;
- the degree of pain due to bleeding episodes and joint damage; how the pain interferes with daily activities, whether pain medication needs to be taken regularly;
- the aspect of the illness that patients find most difficult.

The second way in which patient evidence can be accepted by the HTA agency is through the patient organization/ hemophilia society. The patient organization should start gathering evidence through qualitative research, which describes views and opinions. Patient organizations may also collect statistical data or quantitative research. The patient organization can group trends and present an overall picture that a single individual cannot convey. Considering the cost of hemophilia treatment, this information is not only valuable in preparation for a HTA, but it is also extremely useful when advocating to governments on any aspect of hemophilia care in which economic considerations may play a role.

Patient organizations should survey members, caregivers, and healthcare providers regularly about such issues as:

*For a HTA on a proposed new therapy:*

- What patients and carers expect from a new treatment.
- What benefits the treatment brings.
  - How the benefits compare with those of existing treatments.

*For a HTA on existing therapy:*

- How it helps affected people fulfil their chosen role in life.
- How important the benefits are to the patient.
- The outcomes from treatment they value the most.
- How the benefits impact on patients' daily life.
- What unwanted effects the treatment causes, such as risk of inhibitors.
  - How the unwanted effects compare with those of other treatments.
  - How the unwanted effects are balanced against the potential benefit.
- What would happen to patients if there was limited or no access to the treatment.
- How patients and carers value the treatment.
- How easily the treatment fits into patients' daily life.
- What the impact of treatment is on a person's psychosocial wellbeing.
- What the financial impact of the treatment is in terms of:
  - cost of travel to hospital;
  - loss of earnings;
  - cost of paying a carer;
  - financial impact on the individual and family (for example, if a child is denied access to

- optimal treatment, a parent may have to stop working to look after them).
- What impact treatment has on the caregiver:
  - taking time off work to care for the patient;
  - paying for a carer for the patient;
  - paying for childcare because the patient cannot look after the child/children;
  - financial hardship because they reduce their working hours;
  - watching the patient/child suffer.

Once the appropriate information is collected, all the documentation that the patient organization will provide should be put together in a comprehensive report for the HTA agency. This will be added to the evidence-based data the agency will have gathered from journals and other publications and with the assistance of the clinicians and the pharmaceutical companies who provide the therapy. The report from the patient organization needs to be planned clearly and concisely. The report should contain items such as:

- a) Why the contribution of the patient is valid:
    - the experience of the individual and the organization submitting the evidence;
    - who the organization represents;
    - the services the organization provides;
    - focus group results and surveys undertaken, statistical analysis from your own country and then outside the country.
  - b) Commentary on existing data:
    - clinical trials: positives and negatives;
    - comparison of methods;
    - a perspective on the well-known evidence-based data.
  - c) Experience of the illness:
    - symptoms: a description of a bleed, quotes on the pain;
    - effects on daily living: arthritis, pain, work, etc.
    - short and long-term impact on length and quality of life: HIV, hepatitis C, vCJD risk;
    - psychological and sociological effects of the illness;
    - deformities due to bleeds.
  - d) Impact of the treatment:
    - benefits of the treatment: prophylaxis, home treatment;
    - impact on everyday life: school/work, pain, exercise;
- psychological and sociological effects of the treatment and of not having the treatment;
  - comparisons of countries with more/less access to treatment;
  - financial impact of lack of treatment.

### Working in partnership

In a HTA process, patients are not the only group that have a legitimate interest in the results of the assessment. Insurance companies, scientific societies, clinicians, hospitals, and industry will all have their own interests, and some of those interests will be shared with the patients. Ideally, the key hemophilia clinicians in the country will cooperate with the patient organization and submit an agreed report to satisfy the requirements for evidence-based data. The hemophilia patient organization should liaise closely with the clinicians. The organization should be aware of the evidence-based data that is being submitted and should familiarize themselves with the key arguments and data. The organization should cooperate with the clinicians in studies, surveys, or data collection designed to strengthen the case being made. They should also share with the clinicians the experiential data they plan to submit. The highest possible degree of cooperation and coordination between the clinicians and the patient organization will help optimize the probability of a positive outcome from the HTA process.

The patient organization should also use the extensive network of the World Federation of Hemophilia (WFH), the European Hemophilia Consortium (EHC), and other relevant international organizations to provide them with additional data, resources, or argumentation. Contact other hemophilia societies who have gone through this process, as well as other organizations in your country that have gone through the HTA process. These organizations can be an invaluable source of feedback and advice on how to approach the process and the HTA panel in your own country.

### Key Concepts in Health Economics and Cost-Effectiveness

**Health economics** is concerned with the utilization of limited resources (monetary, human, etc.) to cover all the treatments and interventions that improve the health of a society. For example, the amount of money is limited by a budget, but the amount of a nurse's time is limited by the working hours in a day.

More nurses could be employed, but the demand for healthcare will always outweigh the supply of such resources. Therefore, this leads to a *selection process by which some treatments and patient groups receive resources and others do not. This is called rationing of healthcare resource use.*

Rationing (or resource allocation) can be determined on the basis of criteria such as age or ability to pay, or on the first-come, first-served principle. Health economics and **cost-effectiveness analysis** help make rationing decisions primarily according to “efficiency” criteria. The principle of **efficiency** is not about minimizing costs but about allocating the resources available to produce the maximum benefit. This is not used to discriminate between individuals but to maximize overall welfare in a society. To achieve this aim, *health economists use cost-effectiveness analysis to identify which treatments produce the greatest population benefits for the resources available.*

Cost-effectiveness analysis is used to determine value: the value of the resources (both paid and unpaid) used to provide treatment and care, and the value of the health benefits to a population of patients as a result of this treatment. The time that a nurse or doctor spends treating a patient with hemophilia can be simply valued according to the market salary paid for that time. However, the time spent by a child with hemophilia and the family member transporting that child for treatment is not paid, but has a value (for example, value of time lost from school or work). A treatment, such as home treatment, that can reduce these costs by allowing the doctor or nurse to perform other tasks and/or reducing patient/family absenteeism from school/work has a value that can offset the additional costs associated with the treatment. Likewise, the benefit in health-related quality of life associated with the control of bleeding episodes has a value to the person with hemophilia and to others, including family members. *It is the purpose of cost-effectiveness analysis to quantify the value of these costs and benefits.* The key issue and controversy concerns what should be included within the value framework for the **economic evaluation**. This is considered in greater detail later in this monograph.

One final key concept to introduce is **equity** (justness and fairness). A treatment that is not cost-effective may still be selected if society places an extra value on its benefits because of who (or how many) experiences the health improvement. For example, a

society may consider it fair for children or the elderly to have greater access to treatments and associated health benefits than other segments of the population. Also, in many countries, an additional value is placed on the benefits from **orphan or ultra-orphan drugs** for rare conditions. Patient organizations working in hemophilia have a lot of experience with ensuring just and fair access to effective treatments and can help make sure that equity factors are considered within any assessment of the cost-effectiveness of hemophilia treatments.

### Introduction to HTA terminology

As mentioned previously, HTAs have very specific terminology. An important aspect of learning about HTAs is understanding this terminology and using it effectively in everything from planning experiential data collection, to reviewing published papers, to presenting information to the HTA panel.

#### *Outcomes, utilities, and QALYs*

An **outcome** is the impact or result of a test or treatment on the health of a patient. Outcomes can be expressed in clinical terms (e.g. number of patients who fully recover from an illness, number of hospital admissions, number of bleeds avoided), in life years (e.g. the number of years of life a person gains from treatment), or, most commonly, in **quality-adjusted life years (QALYs)**, which combine the impact of treatment on both expected length of life and quality of life.

A **utility** generally refers to the value individuals attach to different outcomes (usually health). A utility can also mean a patient’s preferred outcome. Utilities are expressed on a scale of 0-1, with zero being equivalent to death (or worst possible **health state**) and one being perfect health. Table 1 illustrates this concept using the example of headache/migraine.

Utility scores can be used in the calculation of QALYs to compare the length of time spent in different health states. As mentioned above, the QALY measure combines survival outcomes with a utility for the health-related quality of life (HRQOL) associated with remaining **life expectancy**. QALYs are often measured in terms of a person’s ability to perform activities of daily living and their freedom from pain and mental disturbance. They are measured by patients, or observers with knowledge in the area, who rate these various states in relation to the specific disease.

**Table 1: An illustrative graphic of the 0–1 scale with examples of possible health states (using the headache/migraine related example) corresponding to each score.**

Utility	Health state
1	<b>PERFECT HEALTH</b>
0.9	Normal health
0.8	Headache once a week
0.7	Migraine once a week
0.6	3 migraines per week
0.5	Daily migraines
0.4	Regular severe migraines
0.3	Regular severe migraines and other pain
0.2	Regular pain (including severe migraines)
0.1	Constant migraines and pain
0	<b>DEATH</b>

More specifically, QALYs are calculated by multiplying the number of years of life a person would gain as a result of a treatment by the utility score associated with the health state they would be living in for those additional years. Basically this means that a year of active, normal life gained as the result of a treatment is rated higher than a year of living with reduced quality of life (such as being in extreme pain or being in hospital).

Using Table 1 as an example, a person who experiences migraines three times a week would have a utility score of 0.6. If they were to live another 10 years in this state, this would in fact represent  $10 \times 0.6 = 6$  QALYs. Now suppose a treatment became available that could reduce the number of migraines this person experiences to, say, only one a week (utility = 0.8). Assuming the person were still to live for 10 years, this would correspond to eight QALYs ( $10 \times 0.8$ ), which means the treatment led to a gain of two QALYs.

### Evaluation of cost-effectiveness

There is no single approach to performing cost-effectiveness analysis. In fact, there are a number of variables. A good example is the first box in Figure 1, perspective. The perspective determines which

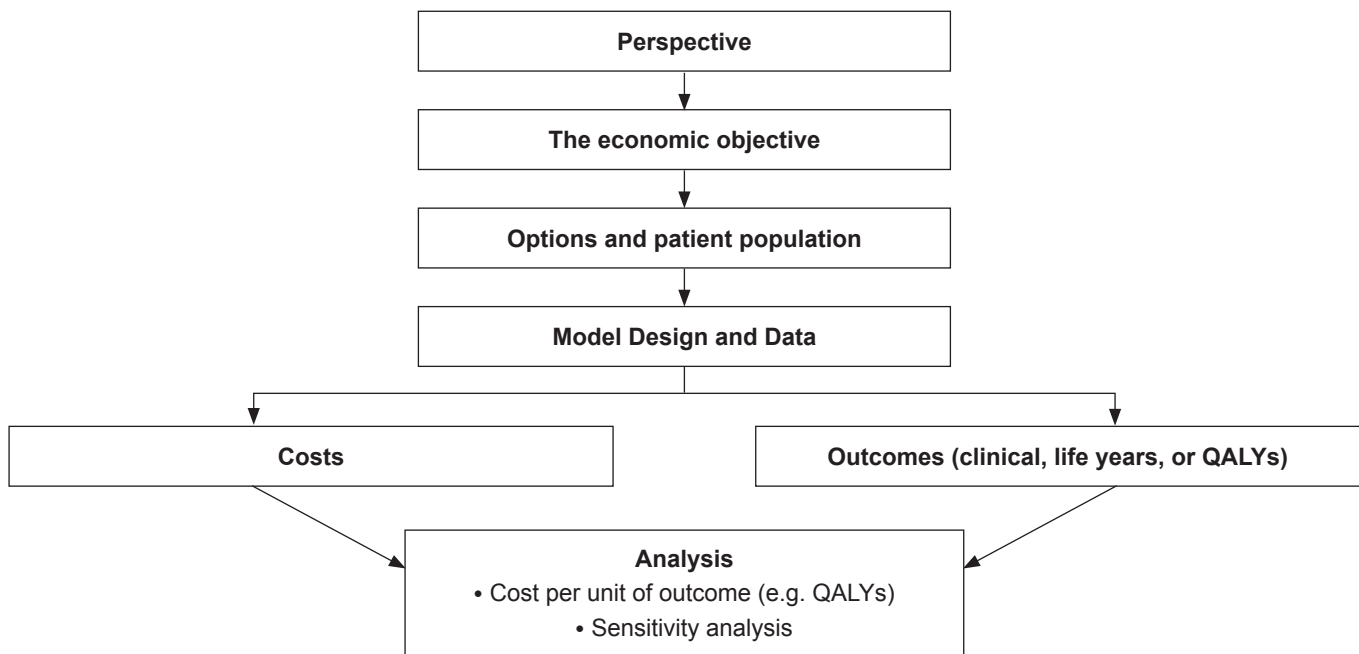
values (for costs and benefits) will be taken into account in the evaluation of cost-effectiveness. The most common perspectives adopted are the healthcare payer and the society perspectives. There are differences in the approach used by HTA agencies. For example:

- In the U.K., the National Institute for Health and Clinical Excellence (NICE; the HTA agency covering England and Wales) and the Scottish Medicines Consortium (SMC) measure health effects using the concept of QALYs. Both agencies assess costs from a healthcare payer perspective when evaluating the cost-effectiveness of pharmaceuticals. In this framework, the QALY measure focuses on the outcome for the patient and does not, for instance, additionally examine the benefits for other family members/carers (such as less time missed at work due to having to care for the individual). In recognition of the fact that end-of-life treatment is often more expensive (for example with advanced cancer), treatments that benefit patients at the end of life may often be recommended even if they have a relatively higher cost per QALY.
- In Sweden and the Netherlands, the HTA agencies (TLV and NVTAG/CVZ respectively) also adopt QALYs as the primary outcome measure, but unlike the U.K. and several other countries, the perspective of society, not the healthcare payer, is used for evaluating the cost-effectiveness of pharmaceuticals. Hence, costs and benefits to family members, carers, and to the economy (e.g. economic productivity) are taken into account.
- In Germany, use of cost-effectiveness analysis by the national HTA agency (IQWiG) to support reimbursement decision-making and guidance is still in the process of development but will not use the QALY. Instead, they will use clinical outcome measures (e.g. bleeds avoided, surgery avoided) to compare healthcare technologies within a specific disease area.

The rationale behind the use of the QALY is that it is a generic measure that can be used to compare the cost-effectiveness of treatments across diseases. Cost-effectiveness analyses in which the QALY is used are called **cost-utility analyses** (CUA).

Box A is an example of how a QALY is calculated and used to demonstrate cost-effectiveness.

**Figure 1: The basic cost-effectiveness framework**



How can we tell whether a treatment is cost-effective using the QALY approach? This depends on the value placed on each QALY gained in the country where the evaluation is being performed. In the U.K., NICE and SMC use a benchmark of €23,000-€34,000 per QALY gained. In Sweden, the benchmark used is closer to €50,000, although it can vary based on factors such as the severity of the disease. In general, these benchmarks have been arbitrarily set but can be argued to reflect the willingness to pay of health-care payers (in the U.K.) or society (in Sweden) for health benefits. The benchmark is higher in Sweden, which may be due to this greater focus on societal values. Although the QALY approach has been adopted as the main measure for cost-effectiveness, there are a few issues with the concept.

The point was made earlier in the monograph that these values are subjective. An examination of the data using clinical measures such as the number of bleeds avoided annually or increased ability to work or attend school because of the therapy provided should also be considered.

Key issues to consider in relation to QALYs, cost-effectiveness, and hemophilia are:

- Just how robust is the measurement of utilities and QALYs?

- Whose perspective is included when measuring costs and QALYs? Whose values count?
- What costs are included?
- How much uncertainty [in clinical effectiveness data] is acceptable?
- How are health benefits/QALYs that occur in the future valued?

**Box A: Calculating the QALY and cost-effectiveness**

A hemophilia patient who has several bleeds per month may have a utility score of 0.5 (on the scale of 0-1), which is quite a poor quality of life. If they live for the next 10 years with this quality of life, the QALYs they get are five (10 x 0.5). A treatment that could prevent bleeds could increase the quality of life score to close to normal (say 0.9). So, then they would get nine QALYs (a gain of four QALYs).

To calculate cost-effectiveness, we work out the additional net costs of treatment and divide them by the additional benefits — the QALYs gained. So if over a 10 year period the extra net costs of treatment are €60,000 per patient (for four extra QALYs gained), then the cost per QALY gained would be €15,000.

The last two points are explored further in the next section (see points 1 and 3).

### Challenges for HTAs in hemophilia

In the course of a HTA, the main challenges that patient organizations and health professionals working in hemophilia could be involved in addressing are:

1. **The limits to the clinical and outcomes data available.** For example, in relation to prophylaxis, there is just one published randomized study comparing prophylaxis with on-demand factor VIII therapy [2]. This study was conducted in young boys aged under 30 months who were followed up to the age of six years: 93% of boys in the prophylaxis group had normal joints compared to 55% of the on-demand treatment group. This study had good duration of follow-up but was limited in patient numbers (n=65 in total). Additional clinical evidence and studies are needed to provide essential data to improve the robustness of cost-effectiveness analyses. Trials designed with health economic objectives in mind (i.e. to collect quality of life and resource use/cost data) would be valuable.
 

HTA bodies and decision makers can be reminded that hemophilia falls within the definition of a rare or **orphan disease** and as such there are limits to the ability to conduct large studies in this field. Also, specific groups such as those patients with inhibitors are even rarer. This should be taken into account by HTA bodies when considering the feasibility and uncertainty that is inherent in clinical and economic studies of orphan conditions. There is ongoing debate among health economists about the feasibility and validity of economic evaluation of orphan diseases.
2. **The lack of a standard approach to utility measurement for QALYs and limited availability of appropriate utility data relevant for hemophilia.** Further data is required on the quality of life, in particular utilities, associated with on-demand and prophylaxis treatment in children and adults with hemophilia A.
3. **The weighting of future benefits.** Therapy such as prophylaxis in hemophilia confers obvious immediate benefits to the individual but also very large future benefits. Most

economic evaluations discount the future benefits of current therapy too severely, especially for conditions such as hemophilia. The concept of discounting is based on the assumption that health benefits in the future have a lower value than current health benefits from treatment or a health intervention. For conditions such as hemophilia, therapy such as prophylaxis for children has a clear current value to the child in preventing bleeding episodes, but it also has a substantial future benefit as the damaging consequences of repeated bleeding, such as joint damage, will generally be avoided and quality of life will be improved. Health economic evaluations generally value these future quality of life benefits for hemophilia patients at a lower rate than current benefits, in the same way we might value future costs at a lower rate than current costs for other conditions.

The discount rate is the rate at which you discount the potential future benefits accruing from current therapy. An annual discount rate is applied to costs and QALYs. The selection of appropriate discount rates by HTA bodies for health economic evaluations seems to be fairly arbitrary and varies by country. In the U.K., NICE applies an annual discount rate of 3.5%. In the Netherlands, a lower rate of 1.5% is applied. Setting the annual discount rate too high inevitably leads to a higher estimate of the cost of therapy.

4. **The inclusion of the societal perspective.** It is important for economic analyses in hemophilia to adopt a society perspective with all key values captured. This may include the recognition that any child may be born with a lifelong, relatively expensive to treat medical condition, but the individual or family should not suffer unduly because of this.
5. **Incorporating equity considerations.** A strong case can be made for expanding or weighting the QALY to bring certain equity considerations associated with hemophilia care into account (e.g. children are affected, it is a genetic disorder, it is very rare).

In all the above areas (and others) there is room for patient organizations and health professionals working in hemophilia to raise the level of debate with

HTA bodies charged with estimating the cost-effectiveness of interventions for hemophilia patients.

## Measurement of Health Utilities

Utility measurement is the core of the QALY, but also the most controversial aspect. The basic method of utility measurement within a cost-effectiveness analysis consists of two main aspects:

- a) A clear and accurate description of the key attributes of the health states or outcomes that impact on health-related quality of life.
- b) Valuation of those health states/outcomes on the 0–1 utility scale.

There are two main approaches to the measurement of the utility: direct and generic measurements.

Direct measurement consists of a set of methods by which utilities for disease and/or treatment-specific health states and outcomes are directly valued by patients or members of the public. In contrast, generic measurements consist of a variety of questionnaires that measure patient utility for general aspects of health, such as level of mobility, level of anxiety, or ability to perform usual activities. Within each category there are a number of different techniques available, none of which tend to produce the same results [4].

### Direct measurement techniques

The main direct measurement techniques used in HTAs are the standard gamble (SG), time trade-off (TTO), and rating scale (also called the visual analogue scale or VAS). A short explanation of each of these techniques is provided in Table 2. Each technique has advantages and disadvantages. SG and TTO are better measures of preference, but VAS has the advantage of simplicity. Each of these measures is completed by either patients with the disease or health state of interest, carers/parents, or members of the public.

There are some challenges with these methods, such as accurate description of the health states. It is difficult to draw up descriptions that capture the key quality of life and other affects for the health states that would not be considered biased (i.e. exaggerating the impact) by HTA agencies and decision-makers.

### Generic utility questionnaires

These are questionnaires that capture patient responses to questions relating to general aspects of health, such as level of mobility, level of anxiety, or ability to perform usual activities. Overall, the instrument that is most popular with HTA agencies is the EQ-5D (also known as the EuroQol), but other instruments used include the Health Utilities Index (HUI) and SF 6D [5]. A short description and

**Table 2: Direct measurement techniques for utilities**

Valuation method	Description
Standard gamble (SG)	Respondents are asked to specify the likelihood of accepting a gamble resulting in either perfect health (for life) or death, rather than experiencing a health state (e.g. five bleeds per three months) for certain for life. For example, they might accept the gamble if there were a 60% probability of perfect health, so the utility for the bleed health state would be 0.6 (60% divided by 100%).
Time trade-off (TTO)	Respondents are asked to specify the amount of time of perfect health they would give up to avoid a longer time with the health state in question (e.g. five bleeds per three months). For example, assuming a scenario of 10 years in the health state (i.e. experiencing five bleeds per three months, followed by death), the individual might be willing to give up four of those years to be in perfect health (followed by death). The utility for the health state would be 0.6 (10–4=6 years divided by 10 years).
Rating scale (VAS)	Respondents are simply asked to place a mark for the health state on a visual analogue scale from 0–100, with 0 = death and 100=perfect health. A utility of 0.6 for the five bleeds per three month health state means the respondent placed the mark at 60 on the scale (rescaled so that 60=0.6).

comparison of these instruments is provided in Table 3. Each technique has strengths and weaknesses for use with different disease areas. For example, the EQ 5D may be more useful for severe conditions, whereas HUI may be better for sensory disabilities (e.g. impaired vision).

Generic utility questionnaires are even more subjective given the fact that the rating tables are based on the subjective opinions of people not affected by the condition. For example, if a person with hemophilia completes an EQ-5D questionnaire, the utility value this gives you is based on a time trade-off exercise that has been conducted among members of the public with limited or no specific knowledge about hemophilia. Further details on the methods of utility measurement can be found in the monograph *What are health utilities?* [6].

### Cost-Effectiveness Analysis in Hemophilia

In Europe, debates on the issue of HTAs and their use for drug access decisions are increasing in frequency. Some of the questions in relation to hemophilia that could be asked by HTA agencies over the next five years are:

1. Is it cost-effective to provide prophylactic use of

factor VIII or factor IX for severe hemophilia or is on-demand a more cost-effective therapy?

2. Is provision of prophylactic therapy for adults with severe hemophilia cost-effective?
3. Is recombinant clotting product cost-effective compared to plasma-derived products?
4. Is prophylaxis for patients with inhibitors cost-effective?
5. Will new recombinant factor VIII products, which have an extended **efficacy**, offer good value for money compared to existing recombinant products such that they should be reimbursed?

The first and second questions are most likely to be examined earlier, especially in relation to treatment of adults with primary prophylaxis. Therefore it is worth examining these in some detail (see “The prophylaxis example”, below).

Question three is arguably the least likely to be addressed first in the developed world, given the history of HIV and hepatitis, but it may come in time. Question four covers an area of growing cost and payer interest: the cost-effectiveness of different products for the treatment of joint bleeds in hemophilia patients with inhibitors to factor VIII. The last question has not been relevant to date, but as new products come to market offering increased benefits

**Table 3: Comparison of three popular generic utility instruments**

EQ-5D	SF 6D	HUI
<ul style="list-style-type: none"> <li>• 5 health domains (<i>mobility, self care, usual activities, pain/discomfort, anxiety depression</i>)</li> <li>• Utilities based on TTO methods</li> <li>• Valued by general population (in several countries)</li> <li>• Only adult version currently validated</li> <li>• Has a greater range of scores than SF 6D</li> <li>• May lack sensitivity due to fewer domains, especially in less severe health problems</li> <li>• Quick questionnaire to complete</li> <li>• Ceiling effects found (large percentage of respondents report no problem)</li> </ul>	<ul style="list-style-type: none"> <li>• 6 health domains (<i>physical functioning, role limitation, social functioning, pain, mental health, vitality</i>)</li> <li>• Derived from the validated generic quality of life questionnaire SF36</li> <li>• Based on SG methods</li> <li>• Valued by general population (in U.K.)</li> <li>• Only adult version currently validated</li> <li>• Floor effects found (large proportion of respondents report low scores)</li> </ul>	<ul style="list-style-type: none"> <li>• 7-8 health domains (HUI3) (<i>speech, vision, ambulation, dexterity, emotion, cognition, pain</i>)</li> <li>• Based on SG methods</li> <li>• Valued by general population (in Canada)</li> <li>• Includes a version available for use in children (HUI2)</li> <li>• Has stronger emphasis on sensory elements than other instruments</li> </ul>



(such as less frequent infusion) at a potentially higher cost per unit, they will have to be shown to be cost-effective. These products may well be subjected to an innovative HTA process specifically designed for new or novel therapies.

### The prophylaxis example

Prophylaxis is the optimal therapy for children with severe hemophilia. This has been recognized from the results of the Joint Outcome Study [2], which demonstrated that prophylaxis in children was associated with an 83% reduction in joint damage. Prophylaxis has been widely used in Sweden for many years as the preferred therapy for both children and adults. Prophylaxis prevents many of the debilitating joint and muscle bleeds associated with on-demand therapy. It may also play a role in reducing the risk of intracranial bleeding and in reducing the risk of inhibitor development [7]. It clearly enhances quality of life [8].

Prophylaxis as optimal therapy for severe hemophilia is one of the principles of hemophilia care supported by the European Association for Haemophilia and Allied Disorders (EAHAD) [1]. These principles in turn have been endorsed by both the WFH and the EHC. The European Division for the Quality of Medicines (EDQM) also stated that prophylaxis in adults should also be considered (personal communication, Prof. P. Giangrande, B. O'Mahony). Prophylaxis is widely used as the optimum therapy in many countries. In a survey of 19 European countries in 2009, ten countries made prophylaxis available to all children with severe hemophilia and a further four countries made prophylaxis available to 50-75% of children [9]. The countries where prophylaxis was not available to children were those with substandard access to treatment and a low gross domestic product per capita.

The majority of the published health economic studies have focused on comparing the costs and clinical outcomes (bleeds and surgery/hospitalization avoided) associated with the use of primary prophylaxis with factor VIII concentrate for severe hemophilia A and on-demand treatment. These studies date back to the mid 90s, but it wasn't until 2002 that the first cost-utility analysis of primary prophylaxis with QALYs as the outcome measure was published [10]. The general conclusion from the studies is that primary prophylaxis is clinically superior (in terms of reducing bleeds and reducing need for surgery) and produces better health-related

**Table 4: Cost per QALY estimates of FVIII prophylaxis in hemophilia A**

Study	Cost per QALY estimate (€)
Miners, 2009	41,000
Miners, 2002	50,000
Roosendaal, 2007	230,000
Risebrough, 2008	320,000
Lippert, 2005	1.24 – 2.21 million

quality of life outcomes compared to on-demand treatment of severe hemophilia A, but this comes at (significant) additional cost.

The cost-utility studies in prophylaxis have used similar health economic modelling approaches, but come up with remarkably different results. There have been at least five such studies published [10-14] showing QALY estimates of factor VIII prophylaxis in hemophilia A (Table 4).

It is worth examining the different QALY cost estimates for prophylaxis with these studies and the reasons why the cost per QALY varies to such a large extent. Some of the reasons may include:

- the duration of the study;
- the assumed number of bleeding episodes annually with on-demand therapy;
- the assumed cost per unit of factor concentrate;
- the discount rate applied to the future benefits of current therapy.

Typically, HTA agencies heavily discount the future benefits of current therapy. As discussed, prophylaxis in hemophilia has current benefits for the individual, but also very real and significant future benefits. These should not be discounted by the process. A child being treated with prophylaxis will derive great benefit during his adult life, as he should be able to avoid joint and muscle damage, get a good education, employment, and live a normal lifespan with a near-normal quality of life.

Clearly, it would be difficult to make a strong case for prophylaxis in adults if the **incremental cost**

**(ICER) per QALY** can be in excess of €2 million, as in the Lippert study [11]. There are a number of possible reasons why this figure is so high. This paper examined a short time period of only one year, which is insufficient to take into account long-term outcomes. The difference in the quality of life measured with on-demand therapy (0.7427) compared to prophylaxis (0.7754) was also extremely small (Table 5). This small difference means that the additional cost appears remarkably high.

To demonstrate how we arrive at the incremental cost per QALY using the Lippert study as an example:

- A utility value (QALY) of a person under 30 in Germany with on-demand treatment (HIV negative) is 0.7427 and costs €85,451.
- A utility value (QALY) of a person under 30 in Germany on prophylaxis (HIV negative) is 0.7754 and costs €157,972.
- The difference in cost is €72,521, for 0.0327 of a QALY (0.7754-0.7427). The incremental cost of a full QALY (€72,521 divided by 0.0327) is therefore **€2,217,768**.

If however, using the same data, we look at the cost per bleed avoided:

- A person under 30 with on-demand treatment has an average of 16.8 bleeds a year at a cost of €85,451.
- A person under 30 on prophylaxis has an average of 5.9 bleeds a year at a cost of €157,972.
- The difference in cost is €72,521, but by using prophylaxis, the individual avoids 10.9 bleeding episodes per year. The cost per bleeding episode avoided is **€6,653**.

This is a much lower and more readily understandable figure. The impact of a single bleed can be devastating if it is, for example, a central nervous system or other life-threatening bleed. It can be life-altering if it is limb-threatening. At the very least, it will cause acute pain, loss of short-term function, and possibly add to the long-term joint or muscle damage, which may limit the individual's ability to fully participate in society. This is without considering the disruption and anxiety caused to the individual, their family or carer, and the impact on their education and employment.

In Canada, the Risebrough study [12] showed a cost per QALY for primary prophylaxis versus on-demand treatment for children aged up to 6 years of over \$500,000 CAD (€320,000). In this study, prophylaxis was associated with a utility (QALY) value of 0.95 and on-demand with a surprisingly high value of 0.875.

The 2009 update study [13] by Miners et al., (updating an economic analysis published in 2002) shows a base case cost per QALY gained for lifelong primary prophylaxis of £37,000 (€41,000), an improvement from the initial 2002 estimate of £46,500 (€51,000) [10]. This is still above the usual **cost-effectiveness threshold** approved by NICE in the U.K. of £30,000, but not excessively so. This study discounts the future benefits of current prophylactic therapy to a lesser extent. In addition, the utility (QALY value) associated with prophylaxis in a 30-year-old (0.87) showed a greater difference when compared with on-demand therapy (0.66) than was seen in the Lippert study [11]. This larger difference translates into a much lower incremental cost per QALY of €41,000.

**Table 5: Utility estimates for prophylaxis and on-demand treatment from three published studies**

Study	Utility for on-demand health state (mean)	Utility for prophylaxis health state (mean)	Incremental cost per QALY gained prophylaxis vs. on-demand (in €)
Miners et al., 2009 (U.K.)	0.66	0.87	41,000
Risebrough et al., 2008 (Canada)	0.87	0.95	320,000
Lippert et al.	0.7427	0.7754	1,240,000–2,210,000

The difference in the utility values between prophylaxis and on-demand therapy seen with the Miners study seem to the authors to be more realistic, and they certainly correspond to a far greater extent with the results of the study of young adults conducted in Sweden, Ireland, the U.K., and France [15]. This study found an average utility value on prophylaxis of 0.93 when compared to 0.73-0.76 for on-demand therapy. The treatment costs were not examined in this case, so the ICER per QALY could not be calculated. However we would expect it to be much closer to the figure seen in the Miners study than what was found in the Risebrough or Lippert studies.

There is reason for hope (given also other arguments relating to equity and other special circumstances of hemophilia care) that primary prophylaxis would not be instantly dismissed as cost-ineffective by HTA bodies such as NICE. However, if future health economic analyses were to produce results similar to those in the Canadian or Lippert studies, there would be less cause for optimism. It is likely that HTA agencies will use similar approaches to the economic modelling used in the U.K. [10] and Canadian [12] studies.

Recently, as mentioned above, the Irish Haemophilia Society, in conjunction with the Swedish, U.K., and French societies, collected experiential data comparing prophylaxis, on-demand, or combined treatment in 20–35 year-old males with severe hemophilia [15]. Medical and psychological data were collected from 58 males (average age 27.5 ± 4.7 years) in a phone survey. As part of this survey, an EQ-5D questionnaire was filled out. This survey had five broad questions and the utility values were then read from a chart. Values ranged from 0 (death) to 1 (perfect health). The survey demonstrated that people with severe hemophilia in Sweden in this age group spent a significantly higher percentage of their life on prophylaxis, reported lower presence of target joints, less major bleeds, and significantly lower mobility problems. Respondents from Sweden had an average utility of 0.93, which is a better quality of life compared to respondents from Ireland (0.76), the U.K. (0.73), or France (0.73). Respondents on prophylaxis reported fewer bleeds per year (mean = 3) compared to on-demand treatment (mean = 26) or on-demand treatment with intermittent periods on prophylaxis (mean = 20). They also reported lower presence of target joints and significantly lower mobility problems based on the EQ-5D. On-demand treatment was associated

with more days missed at work (mean = 33 days) compared to those on prophylaxis (mean = 3 days) or on combined treatment (mean = 11 days). Sixteen people reported having no target joints, fifteen of whom lived in Sweden. Prophylaxis started at an early age and continuing into adulthood resulted in less bleeding, less damage to joints, and less time missed at work. Prophylaxis increased mobility and the ability to do everyday activities and improved the health-related quality of life of people with severe hemophilia.

This type of experiential information is vital for societies to collect. This is the type of information that should be put in a report or submission from the patient organization and then discussed with the HTA panel.

## Comparative Effectiveness Research (CER)

The cost of health care in the U.S.A. has, for many years, been a topic that has energized legislators and policy makers. The Congressional Budget office in 2007 stated that “only a *limited amount of evidence is available* about which treatments work best for which patients and whether the added benefits of more-effective but more-expensive services are sufficient to warrant their added costs – yet current practice tends to adopt more-expensive treatments *even in the absence of rigorous assessments* of their impacts” [16].

HTA is not widely used in the U.S.A., where an alternative system called comparative effectiveness research (CER) is used. CER is the direct comparison of existing healthcare interventions to determine which work best for which patients and which pose the greatest benefits and risks. The core question of comparative effectiveness research is which treatment works best, for whom, and under what circumstances. Unlike HTAs, CER focuses on the effectiveness of interventions and not on the cost-effectiveness.

The Institute of Medicine (IOM) committee has defined CER as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve

health care at both the individual and population levels." CER involves the conduct of systematic and structured reviews of the existing evidence for the efficacy, clinical benefits and/or safety of drugs, diagnostic tests, other healthcare technologies, different service plans and structures, or the generation of new evidence on comparative effectiveness of interventions or services.

CER is an important component of President Obama's healthcare reforms, and was signed into law as part of the American Recovery and Reinvestment Act (ARRA) in February, 2009. A total of \$1.1 billion of government funds have been allocated for CER, to "inform healthcare decisions by providing evidence on the effectiveness, benefits, and harms of different treatment options" [17]. A new council, the Federal Co-ordinating Council for Comparative Effectiveness Research, has been set up to coordinate research and guide investments in comparative effectiveness research funded by the Recovery Act.

The new U.S. Health reform bill (Section 6301) establishes a private, nonprofit entity (the Patient-Centered Outcomes Research Institute) governed by a public-private sector board appointed by the Comptroller General to identify priorities provide for the conduct of comparative outcomes research. It requires the IOM to ensure that subpopulations are appropriately accounted for in research designs. It prohibits any findings to be construed as mandates on practice guidelines or coverage decisions and contains patient safeguards to protect against discriminatory coverage decisions by the department of Health and Human Services (HHS) based on age, disability, terminal illness, or an individual's quality of life preference. The act provides funding for the IOM and authorizes and provides funding for the Agency for Health Research and Quality to disseminate its research findings (as well as other government-funded research), to train researchers in comparative research methods, and to build data capacity for comparative effectiveness research.

Depending on the results of the research recommendations, changes to individual patient treatment plans could be made. In 2009, the U.S. Institute of Medicine identified 100 priority study topics for CER relating to a range of diseases, service delivery options, and disability and health inequalities [18]. More than half the topics related to service delivery. Prominent disease areas included cardiovascular disease, geriatrics, mental health, and pediatrics.

Interestingly for hemophilia, the IOM recommended CER be conducted on rare diseases that disproportionately affect certain subgroups of the population. Absent from CER is any notion of using health economics to assess the cost-effectiveness of different interventions. In a healthcare policy sense, cost-effectiveness remains a largely taboo term in the U.S.

The first research grants for CER are starting to be awarded. For example, the U.S. Society of Nuclear Medicine (SNM) has been awarded US \$48,000 to hold a conference to develop research on the comparative effectiveness of positron emission tomography relative to other molecular imaging techniques, primarily for the diagnosis and management of cancer [19]. As yet, specific hemophilia research has not been funded for CER, but as a rare and expensive treatment area, it could well attract attention.

The sort of research advocated using CER would not be considered novel in Europe. HTA involving systematic reviews of clinical effectiveness to inform policy decisions has been standard in many European countries for several years. However, as it is government-led research, it represents a cultural shift for the U.S. Critics argue that CER findings could lead to direct rationing, government intrusion into the doctor-patient relationship, and could halt progress in '**personalized medicine**' that is growing in popularity in the U.S. [20, 21]. There is a concern that the main rationale for CER is to contain cost, rather than to improve service and access to treatment. If it is just about costs and coverage restriction, then hemophilia treatments could suffer under CER implementation. If it does what it is meant to do, then it could help improvement in healthcare quality and outcomes, including those for hemophilia patients.

Anyone is allowed to make suggestions for research topics for CER, so there are opportunities for hemophilia societies to take direct action and suggest research that would be most useful for patients.

## Conclusions

HTA is likely to become an increasingly important influence in decisions about what is provided in health care, whether it be screening for diseases or treatments for serious illnesses. In Europe, there is already considerable discussion about greater collaboration between HTA agencies. It is important that a HTA take the needs of the people who will be

most affected by its recommendations into account: patients, their caregivers, and the public.


As a key component of HTAs, the QALY concept can be criticized in terms of the limits to what it captures as a measure of benefit. Although QALYs are a measure of value of health and health-related quality of life, they may not capture all the key outcomes for specific patients such as those with hemophilia. The great variety of techniques and generic instruments available for utility measurement is a concern as the results they produce vary and there is no clear way of justifying which is the most valid method to use in each circumstance.

For the time being, QALYs are here to stay and are being used by HTA agencies around the globe to appraise the cost-effectiveness of new health technologies. Hemophilia treatment and care is expected to be subjected to this scrutiny in several countries, and decisions on resource allocation and reimbursement will likely follow. So while arguments can be raised against QALYs, patient organizations and health professionals should work with the QALY paradigm for the time being while understanding its methods, limitations, and opportunities within health economic analyses in hemophilia.

Going forward, it would be useful if patient organizations were to join forces with sympathetic health economists and clinicians to design studies to fill the key data limitations (especially around utilities), and to lobby HTA agencies on the importance of taking a broad perspective on costs and outcomes (including values of the parent/carer as well as the patient and society).

While participating in a HTA can be time-consuming and challenging, it is a real opportunity to influence the delivery of health care. Patient and public input can help determine whether a new treatment is made available.

The challenges faced by the hemophilia community because of economic constraints will increase in the future [22]. All the key stakeholders – patient organizations, clinicians, and industry – must respond and should, when appropriate, cooperate. Pharmaceutical companies should ensure that competition between them does not result in damaging messages being delivered to HTA agencies, which could deprive people with hemophilia of the required therapy. Clinicians in each country should optimize their cooperation and coordinate the

submission of key clinical data. Clinicians should also ensure that they have a close working relationship with the national hemophilia patient organization. Collaboration on the collection of evidence-based and experiential data should be a key goal [23]. Patient organizations in each country should be fully aware of the economic realities and pressure points on their national healthcare budgets. They should work with clinicians and with other national patient organizations to collect the data required to vigorously defend or improve their access to care and treatment. They should be aware of and clearly understand the key evidence-based data that supports optimum treatment and equally understand the data that could be used to advocate for a reduced standard of care. They should proactively collect experiential data on an ongoing basis. Once a HTA is announced, it may be too late to collect data in time to influence the process. Patient organizations should seek to be involved and formally consulted as early in the HTA process as possible. Finally, and most importantly, they must not ignore these challenges with the expectation that they will never have to confront these issues at any level. A HTA in hemophilia in your country may not occur, but knowledge of the economics of hemophilia has never been more important. 

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## Appendix 1: Glossary of Terms

**Comparative effectiveness research:** The direct comparison of existing healthcare interventions to determine which work best for which patients and which pose the greatest benefits and risks.

**Cost-effectiveness:** The description applied to an intervention (treatment, diagnostic test, etc.) for which the costs are considered to be justified by the benefits provided.

**Cost-effectiveness analysis:** A form of economic evaluation in which the results are expressed as a ratio of cost per unit of health outcome, the latter normally being expressed in “natural units” (e.g. mm Hg change in blood pressure, symptom free days, bleeds avoided).

**Cost-effectiveness threshold:** The ceiling ICER [see **incremental cost-effectiveness ratio** below] beyond which interventions are no longer considered cost-effective, reflecting the maximum value decision-makers attach to health benefits. This may be stated in terms of cost per QALY gained.

**Cost-utility analyses:** A form of cost-effectiveness analysis in which the results are expressed in terms of cost per QALY gained.

**Economic evaluation:** A comparative analysis of two or more alternatives in terms of their costs and benefits.

**Effectiveness:** The effect of a treatment as measured in the usual clinical environment.

**Efficacy:** The effect of treatment as measured in the controlled environment of a clinical trial.

**Efficiency:** The allocation of resources in such a way as to maximize the total amount of benefit.

**Equity:** The concept of fairness in economics.

**Evidence-based data:** Information gained from scientific investigation, including clinical trials and reviews of published studies.

**Health economics:** The application of the theories, tools, and concepts of economics to the topics of health and health care. Economics is concerned with the allocation of scarce resources, and health

economics is concerned with issues relating to the allocation of scarce resources to improve health. This includes both resource allocation within the economy to the healthcare system and within the healthcare system to different activities and individuals.

**Health state:** The description of a person’s quality of life.

**Health technology assessment:** A review of the evidence (usually a systematic review) on the impact of a healthcare intervention (or “technology”), often including economic evaluation evidence.

**Incremental cost-effectiveness ratio (ICER):** The difference in costs between one intervention and an alternative, divided by the difference in outcomes. An ICER is the technical term for measuring a unit of outcome, for example, a QALY or bleeds avoided.

**Life expectancy:** The average further number of years that a person at a specified age may expect to live.

**Orphan disease:** A rare medical condition.

**Orphan or ultra-orphan drugs** An orphan drug is a pharmaceutical agent that has been developed specifically to treat an orphan disease [see **Orphan disease** above]. The assignment of orphan status to a disease and to any drugs developed to treat it is a matter of public policy in many countries, and has resulted in medical breakthroughs that may not have otherwise been achieved due to the economics of drug research and development. Ultra orphan drugs are drugs which are developed for the treatment of very rare diseases.

**Outcome:** The impact or result of a test or treatment on the health of a patient.

**Personalized medicine:** The systematic use of information about an individual patient to select or optimize preventative and therapeutic care. Essentially, the right treatment for the right person at the right time.

**Quality-adjusted life year (QALY):** A measure of benefit of health care combining the impact on both expected length of life and quality of life.

**Quality of life (health related):** A person's subjective well-being, often encompassing physical, psychological, and social dimensions.

**Rationing:** The selection process by which resources (monetary, human, etc.) are distributed to cover all the treatments and interventions that improve the health of a society.

**Resources:** Inputs into the production of health care or goods and services in the economy generally. These would include staff time, hospitals, drugs; equipment etc. and patients' time undergoing treatment. A person's availability for, and capacity to, work may also be a relevant resource.

**Utility:** In economic evaluation, this term is typically used to mean a measure of the value individuals attach to different outcomes (usually health). These are often used in QALYs to weight periods of time in different health states.

**Value for money:** see **Cost-effectiveness** above.



## Appendix 2: List of HTA Agencies

### Argentina

*Institute for Clinical Effectiveness and Health Policy*

Tel: +54 11 4966 0082

E-mail: info@iecs.org.ar

### Australia

*Australian Safety and Efficacy Register of New Interventional Procedures — Surgical*

Tel: +61 8 8363 7513

E-mail: asernips@surgeons.org

*Adelaide Health Technology Assessment*

Tel: +61 8 8303 3575

E-mail: tracy.merlin@adelaide.edu.au

*Medical Services Advisory Committee*

Tel: +61 2 62896811

E-mail: msac.secretariat@health.gov.au

### Austria

*Ludwig Boltzman Institute of Health Technology Assessment, LBI@HTA (former ITA)*

Tel: +43(0)1-2368119-0

E-Mail: office@hta.lbg.ac.at

*Gesundheit Österreich GmbH, Austrian Health Institute*

Tel.: +43 1 515 61-0

E-mail: info@goeg.at

*Hauptverband der Österreichischen Sozialversicherungsträger*

Tel: +43 (1) 711 32

E-mail: posteingang.

allgemein@hvb.sozvers.at

### Belgium

*KCE — Belgian Health Care Knowledge Centre*

Tel: +32 2 287 33 88

or +32 2 287 33 97

E-mail: info@kce.fgov.be

### Brazil

*Tecnologia e Insumos Estratégicos, Departamento de Ciência e Tecnologia*

Tel: +55 61 3315 3197

E-mail: flavia.elias@saude.gov.br

### Canada

*Institute of Health Economics University of Alberta, Public*

Tel: +1 780 4484881

E-mail: ejonsson@ihe.ca

*Agence d'Évaluation des Technologies et des Modes d'Intervention en Santé*

Tel: +1 514 8732563

E-mail: Reiner.Banken@

aetmis.gouv.qc.ca

*Canadian Agency for Drugs and Technologies in Health*

Tel: +1 613 226 2553

E-mail: tammymc@cadth.ca

*Ontario Ministry of Health and Long Term Care*

Tel: +1 416 314 3999

E-mail: MASinfo.moh@ontario.ca

### Chile

*Department of Quality and Patient Safety of the Ministry Health of Chile — Health Technology Assessment Unit*

Tel: +56 2 574 0567

E-mail: pkraemer@minsal.cl

### Denmark

*CAST — Center for Anvendt Sundhedstjenesteforskning og Teknologivurdering, University of Southern Denmark, Center for Applied Research and Technology Assessment*

Tel: +45 6550 1000

E-mail: sdu@sdu.dk

*DSI — Danish Institute for Health Services Research*

Tel.: 35 29 84 00

E-mail: dsi@dsi.dk

*DACEHTA — Danish Centre for Evaluation and HTA*

Tel: +45 72 22 74 00

E-mail: sst@sst.dk

*HTA and Health Service Research, Center of Public Health*

Tel: 8728 4750

E-mail: mtv-stf@rm.dk

### England & Wales

*NICE — National Institute for Health and Clinical Excellence*

Tel: +44 (0)845 003 7780

E-mail: nice@nice.org.uk

*National Institute for Health Research HTA Programme*

Tel: 023 8059 5586

E-mail: hta@hta.ac.uk

### Estonia

*University of Tartu, Department of Public Health*

Tel: +372 737 5100

E-mail: info@ut.ee

### Finland

*FinOHTA — Finnish Office for HTA*

Tel. +358 9 3967 2297

E-mail: finohta@stakes.fi

### France

*HAS — Haute Autorité de santé / French National Authority for Health*

Tél. : 01 55 93 70 00

*CEDIT — Committee for Evaluation and Diffusion of Innovative Technologies, Direction de la Politique Médicale*

Tel: (33) 1 40 27 18 90

E-mail: info.cedit@sap.aphp.fr

### Germany

*DAHTA@DIMDI- German Agency for HTA at the German Institute for Medical Documentation and Information*

Tel: +49 221 4724-1

*IQWiG — Institute for Quality and Efficiency in Health Care*

Tel: +49 (0)221-35685-0

*German HTA Association*

Tel (0421) 218-3784

### Hungary

*HunHTA — Unit of Health Economics and Health Technology Assessment*

Tel: 0036-1-482-5147

E-mail: laszlo.gulacsi@uni-corvinus.hu

**Ireland**

HIQA — Health Information  
and Quality Authority  
Tel: +353 21 425 0610  
E-mail: info@hiqa.ie

**Israel**

Israel Center for Technology  
Assessment in Health Care  
Tel: +972 3 530 3278  
E-mail: ninaH@gertner.health.gov.il

**Italy**

ASR — Agenzia Sanitaria  
Regionale, Emilia Romagna  
E-mail: fsarti@regione.  
emilia-romagna.it

Università Cattolica del Sacro Cuore,  
Policlinico universitario “A. Gemelli”,  
Health Technology Assessment  
Unit and Laboratory of Health  
Economics (Institute of Hygiene)  
Tel: +39 06 3015 1  
E-mail: rettorato@rm.unicatt.it

**Korea**

Committee for New Health  
Technology Assessment  
Tel: +82 31 543 2636  
E-mail: omy@cha.ac.kr

**Latvia**

VSMTA — Health Statistics and  
Medical Technology State Agency  
Tel: +371 67501590  
E-mail: agentura@vsmtva.gov.lv

**Lithuania**

State Health Care Accreditation  
Agency under the Ministry of Health  
of the Republic of Lithuania  
Tel: +370 5 261 51 77  
E-mail: vaspvt@vaspvt.gov.lt

**Malaysia**

Health Technology Assessment  
Section, Ministry of Health Malaysia  
Tel: +603 888 312 29  
E-mail: htamalaysia@moh.gov.my

**Mexico**

Centro Nacional de Excelencia  
Tecnológica en Salud  
Tel: +52 55 5208 3939  
E-mail: evaluacion@salud.gob.mx

**Netherlands**

CVZ — College voor  
zorgverzekeringen  
Tel: (020) 797 8555

**New Zealand**

Health Services Assessment  
Collaboration  
Tel: +64 3 345 8147  
E-mail: hsac@canterbury.ac.nz

**Norway**

Norwegian Knowledge Centre  
for the Health Services  
Tel: +47 23 25 50 00  
E-mail: Gro.Jamtvedt@  
kunnskapsenteret.no

**Poland**

Agency for HTA in Poland, AHTAPol  
Tel: +48 22 566 72 00  
E-mail: szkolenia@aotm.gov.pl  
CEESTAHC — Central and Eastern  
European Society for Technology  
Assessment in Health Care  
Tel: +48 (0) 12 357 76 34  
E-mail: sekretariat@ceestahc.org

**Scotland**

SMC — Scottish Medicines Consortium  
Tel: +44 141 225 5552  
E-mail: smcsecretariat@  
nhshealthquality.org  
NHS Quality Improvement Scotland  
Tel: 0131 623 4300

**Slovenia**

Institute of Public Health of  
the Republic of Slovenia  
Tel: +386 (1) 2441 518  
E-mail: knjiznica@ivz-rs.si

**Spain**

AETS — Agencia de Evaluación  
de Tecnologías Sanitarias  
Tel: + (34) 91 822 20 04;  
E-mail: aets@isciii.es  
AETSA — Andalusian Agency for  
Health Technology Assessment  
Tel: +34 955006638  
E-mail: aetsa.csalud@  
juntadeandalucia.es

CAHTA — Catalan Agency for Health  
Technology Assessment and Research  
Tel: +34 935 513 888  
E-mail: direccio@aatrm.catsalut.net

Galician Agency for Health  
Technology Assessment  
Tel (0034) 981 542 737

OSTEBA — Basque Office for  
Health Technology Assessment  
(AP) Servicio Canario de la Salud  
Tel.: +34 945 019250  
E-mail: Osteba-san@ej-gv.es

UETS — Unidad de Evaluación  
de Tecnologías Sanitarias,  
Agencia Lain Entralgo  
Tel: +34 913089480  
E-mail: uets.ale@salud.madrid.org

**Sweden**

SBU — Swedish Council on  
Technology Assessment in Health Care  
Tel: 08-412 32 00  
E-mail: info@sbu.se

**Switzerland**

SNHTA — Swiss Network for  
Health Technology Assessment  
Tel: +41 31 322 15 86  
E-mail: info@snhta.ch

**Taiwan**

Center for Drug Evaluation  
Tel: +886 2 2322 4567  
E-mail: wyshau265@cde.org.tw

**Thailand**

Health Intervention and Technology  
Assessment Program  
Tel: +66 259 0459  
E-mail: hatai.l@hitap.net

**USA**

Agency for Healthcare  
Research and Quality  
Tel: +1 301 427 1612  
E-mail: elise.berliner@ahrq.hhs.gov  
VA Technology Assessment Program  
Tel: +1 857 3644469  
E-mail: vatap@med.va.gov





1425 René Lévesque Blvd. W., Suite 1010 Montréal, Québec H3G 1T7 CANADA  
Tel.: +1 (514) 875-7944 Fax: +1 (514) 875-8916  
[www.wfh.org](http://www.wfh.org)