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Understanding Health Technology Assessment: A Guide for Patients

Supporting Booklet

Thank you for completing the online eLearning module 'Understanding Health Technology Assessment'. This booklet provides further information and useful links in case you want to explore the topics covered in the online module any further.

Contents

What is Health Technology Assessment?

As you learned in the module, **health technology assessment (HTA)** is a process that evaluates the **clinical, economic and societal** implications of a new treatment.[1] The ability of patients to access cancer medicine is highly dependent on the allocation of appropriate and adequate funding or financial resources within healthcare systems to facilitate the availability of these medicines and the speed at which they may be accessed.

HTA aims to inform policy makers on how to use healthcare resources to benefit patients and achieve the best **value for money**.[1] To determine value, the costs and benefits of a new therapy can be weighed out. The process of assessing the **balance of costs and benefits** associated with introducing a new therapy to the healthcare system, compared to the current standard of care, is known as cost-effectiveness analysis.[2]

Cost-Effectiveness analysis

This analysis includes measuring the value of health outcomes known as **quality-adjusted life years (QALYs)**.[3] QALYs represent the clinical benefit of a treatment and take into account potential increases in life expectancy as well as possible improvements in quality of life (QOL) during treatment and follow-up.[3]

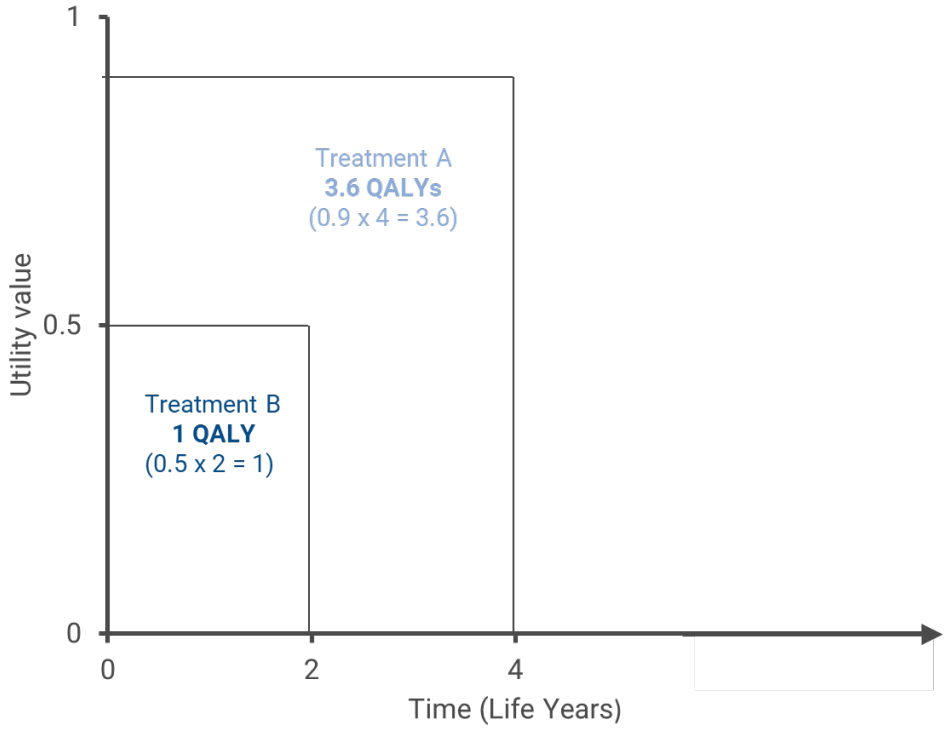
The cost per quality-adjusted life year (QALY) measure is not disease-specific, and therefore provides a standardised measure of clinical benefit. This allows comparison of the benefits of treatments across multiple disease areas.

Calculating quality-adjusted life years (QALYs)

A value between 0 (equal to death) and 1.0 (equal to perfect health) is assigned to the health status (QOL) experienced by people at different stages of their life.[3] This is known as the utility value. The assigned utility value is then multiplied by the number of years lived within each health status (quantity of life) to determine the QALY value.[4]

To illustrate this, we will look at the QALYs for example treatments A and B for a given medical condition, assuming treatment B is the current standard of care. Figure 1 shows that treatment A (3.6 QALYs) has an incremental improvement in health of 2.6 QALYs over treatment B (1 QALY), therefore, treatment A is more clinically beneficial to patients than treatment B.

Figure 1. Calculating QALYs for treatment A and treatment B



Abbreviations: QALY: quality-adjusted life year.

As cost-effectiveness analysis compares the health benefits and costs of a new treatment over the current standard of care, the cost of gaining an extra unit of effectiveness with a certain treatment must be assessed.[2] The most widely used method for assessing the cost-effectiveness in this way is the **incremental cost-effectiveness ratio (ICER)**.

Calculating the incremental cost-effectiveness ratio (ICER)

ICERs are expressed as a ratio of the difference in cost (**incremental costs**), between the new treatment (treatment A) and the current treatment (treatment B), to the difference in their effectiveness (**incremental QALYs**). When comparing treatments A and B, the ICER is €192.31 per additional QALY gained with treatment A (Figure 2).

Figure 2. Calculating ICERs

$$\text{ICER} = \frac{\text{Incremental costs}}{\text{Incremental QALYs}}$$

	COST	QALYs
Treatment A	€1,500	3.6
Treatment B	€1,000	1
Increment (of A over B)	€500	2.6
ICER of treatment A (€500 / 2.6 QALYs) = €192.31 per QALY gained		

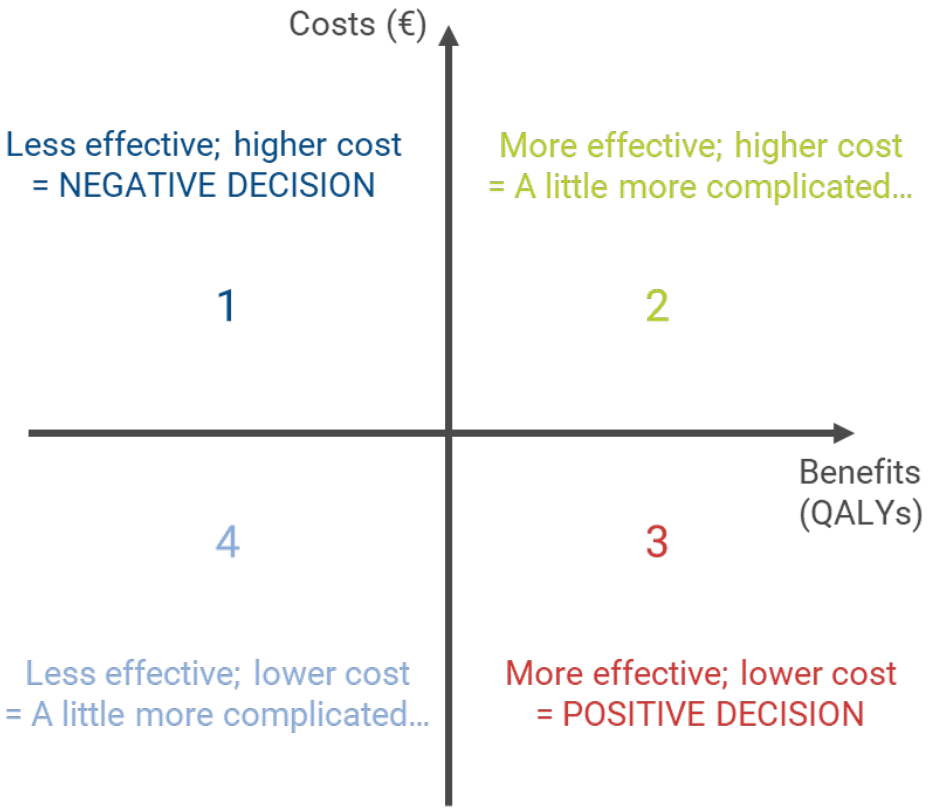
Abbreviations: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

Consideration of the ICER along with the clinical evidence for the treatment forms a large part of HTA as cost-effectiveness analysis can support decision makers in comparing treatments and allocating resources effectively.[2] Some HTA systems utilise a **cost-effectiveness threshold** to make decisions. For example:

- If the ICER is below the given threshold, the introduction of the treatment will represent a cost-effective allocation of resources
- If the ICER is above the threshold, it would not be considered cost-effective

Using our previous example of treatments A and B, assuming treatment B is cheaper than treatment A, decision makers might consider treatment A to be **better value for money** than treatment B, even though it's **more expensive**, as it provides **greater benefit** to patients (3.6 QALYs). However, this is a difficult decision to make; as Figure 3 illustrates, treatment A would fall under quadrant 2.[2]

Figure 3. Decision making matrix



Abbreviations: QALY: quality-adjusted life year.

The outcomes of HTA are often summarised in a report with a specific recommendation on how the technology should be used; in which groups of people and under what circumstances. The report may recommend that the technology is not used at all or it may limit the group of patients for whom it is recommended.

Involvement of Patient Organisations in the HTA Process

Why is cancer patient involvement important?

Within any healthcare system, everyone is affected by decisions to pay for and use health technologies. In the governance of a healthcare system, patient involvement plays **four** major functions:[5, 6]

1. To improve the **quality of information** concerning the population's values, needs and preferences
2. To encourage **public debate** over the fundamental direction of the healthcare system
3. To ensure **public accountability** for the processes within and outcomes of the system
4. To protect **public interest**

The World Health Organisation (WHO) published a report on "Medicines Reimbursement Policies in Europe", encouraging more **patient involvement** in medicine reimbursement. The report strongly advocates for the inclusion of patient representatives who have an understanding of the rationale of policy makers.[5]

It is important for HTA bodies to understand **what matters most to patients**. No one knows what it is like to live with an illness better than the patients themselves and their carers. Patients can provide insights on the impact of their condition and its associated treatments on their lives that are:[6]

- Not identified or well represented in the published literature
- Not well captured in quality of life measures or other outcome measures that have been used in clinical trials
- Not well understood by experts in HTA

What are the barriers to patient involvement?

A **lack of education in HTA** is a major barrier to patient involvement:

- Patients often do not know how to get involved
- Regulators and payers need to be educated on why it is important to have patient involvement in HTA
- Patient organisations need to understand why it is important for them to be involved in this process

Advocating for patient involvement

There is no single way to involve patients in the work of HTA bodies and approaches to patient involvement vary according to the healthcare system and country. Before

submitting any patient evidence, please **check with the relevant HTA agency** what should be provided.

For example:

- The National Institute for Health and Care Excellence (NICE) has a useful guide for patients[7]
- The Scottish Medicines Consortium (SMC) has specific guidance[8] for end of life medicines to give patient groups a stronger voice in decision-making

In March 2017, the European Parliament passed a report[9] which focussed on the need for a **patient-centric approach** and **systematic involvement** of patients in all decision-making schemes. The report made several calls for action aimed at different institutions at both EU and national levels to address the most urgent problems in the issue of access to medicines.

In July 2018, ECPC published a detailed position paper[6] on the European Commission's January 2018 proposal,[1] calling for:

- Systematic involvement of patient organisations in HTA
- Formalisation of patient organisation involvement in all joint activities completed at EU level, as well as in the assessments of non-clinical domains that are conducted at national level
- Mandatory uptake of Joint Clinical Assessment reports

However, **strong advocacy is still needed** to turn reports and papers into reality at a national level.

What is the current state of play for patient involvement?

After gathering information from various experts and its members, ECPC has produced a short but comprehensive leaflet[10] summarising the state of play and how patients are currently involved in the HTA process in EU Member States. In particular, the leaflet explains how health technologies are assessed in **Belgium, England, Finland, Germany, Italy, The Netherlands, Romania, and Sweden**, and the level of patient involvement in each case.

How is the Value of Cancer Treatments Measured?

Cancer treatment is in most cases a **succession** of different therapies. After some time, treatment might cease to work, or patients might experience a relapse and will need to receive a succession of subsequent treatments to manage symptoms and disease progression.

Therefore, trials of new treatments often involve adding that treatment into a combination or replacing one treatment in an existing combination. Decision makers are often interested in the **effectiveness** and **cost-effectiveness** of inserting a new treatment into a treatment pathway as a whole, as in reality patients are likely to receive a sequence consisting of several treatments.[11]

As explained in the module, evaluating the value of new cancer treatments and making decisions about whether to reimburse a medicine can be difficult, especially for cancer treatments, due to a number of factors. These include subsequent treatments and crossover, as explained in the Use of surrogate outcomes section below.

The cost of cancer

The cost of cancer to society can be divided into both **direct and indirect costs**:

- Direct costs are the resources used for diagnosis, prevention and treatment[11]
- Indirect costs are resources lost due to an inability to work, including loss of production due to short-term absence from work, permanent disability and death before the age of 65. Despite the fact that most cancers occur in older persons, the indirect costs of cancer are still 2 to 3 times greater than the direct costs and constitute a major part of the total costs for all diseases[11]

Cost of cancer treatments

Statistics from the Organisation for Economic Co-operation and Development (OECD) allow estimation of the total healthcare costs for cancer in Europe. The total healthcare costs for cancer in 19 European countries covered by OECD was estimated to be **€54 billion** based on individual studies in 2002/2003.[11] France, Germany, Italy, Spain and the UK combined accounted for three-quarters of the total spending.

There are, however, challenges associated with estimating and reporting the cost of cancer treatments:[11]

- Many cancer patients have **non-cancer comorbidities** and receive multiple medications
- Payment methods for treatments are variable

For example, in some cases cancer treatments are used for hospital inpatients and therefore can be paid for through **different budgets**:

- The financing of inpatient care, based on days of hospital stay
- Global hospital budget
- A diagnosis-related groups system where budget is allocated for hospitalisation costs based on a classification of patients in different disease categories

In other cases, treatments are used in hospital outpatient departments and reimbursed separately.

Measuring health-related quality of life

As you learned in the module, there is no single, standard way to measure HRQOL, and so questionnaires are used to assess the patients' **physical, psychological, social and emotional function**. Examples of questions included in HRQOL questionnaires are shown in Figure 4. EuroQol-5-Dimenson (EQ-5D) is an example of a **generic** HRQOL questionnaire.[12] There are also two **cancer-specific** questionnaires that are widely used:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (**EORTC QLQ-C30**)[13]
- The Functional Assessment of Cancer Therapy-General (**FACT-G**)[13]

Figure 4. Example questionnaire questions for EORTC QLQ-C30, FACT-G and EQ-5D

EORTC QLQ-C30	FACT-G	EQ-5D
• Do you have any trouble doing strenuous activities? • Were you limited in doing either your work or other daily activities? • Has your physical condition or medical treatment interfered with your family life? • Did you feel tense, irritable, worried, depressed? • How would you rate your overall quality of life during the past week? ☐Not at all ☐ A little ☐ Quite a bit ☐Very much	• I am forced to spend time in bed because of my physical condition • I have trouble meeting the needs of my family • I am able to do work (including work at home) • I feel close to my friends • I get emotional support from my family • I worry that my condition will get worse ☐ Not at all ☐ A little ☐Quite a bit ☐ Very much	• Problems in walking about? • Problems doing my usual activities? • Level of pain or discomfort • Level of anxiety or depression ☐ None ☐ Slightly ☐ Moderate ☐ Severe ☐ Extreme

Abbreviations: EORTC QLC-30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D: EuroQol-5-Dimension; FACT-G: Functional Assessment of Cancer Therapy-General.

Combined assessment of a diagnostic and treatment

There is a growing interest in the field of **personalised medicine** in cancer treatment, prevention, diagnosis and prognosis.[14] Personalised medicine involves doctors learning about a person's genetic makeup and how their tumour grows in order to **customise treatment** and improve their survival outcomes.[14]

Targeted cancer therapy is an example of a personalised medicine, which utilise drugs or substances that block the growth and spread of cancer by interfering with specific molecules involved in tumour growth and progression.[3] Although targeted therapy allows greater tumour specificity and less toxicity, targeted agents are typically only effective in patients with one or two cancer types.[14]

Treatment with a targeted therapy depends on finding out whether the tumour has specific targets by testing a tumour sample. Therefore, targeted therapy involves the codevelopment of a test and a treatment, with the codevelopment making it possible to define the target population for the treatment more precisely.[3] This is an important step for HTA as the concept of the unmet medical need is clearer and the translation of results from clinical trials to clinical practice is defined.[3]

However, targeted therapies require the **joint assessment of a diagnostic and a treatment**. The number of combined testing and treatment strategies can, therefore, easily increase to a level where the result of the analysis becomes difficult to understand and communicate to administrative and clinical decision makers.[3]

Why do Some Countries Reimburse a Cancer Treatment and Others do not?

The scientific assessment of available data may be similar wherever the HTA is undertaken. However, the way in which a treatment is appraised may **vary from country to country**.[11, 15] As a result, different decisions are made concerning which technologies should be provided, leading to variations in treatment access.[11] Therefore, even if a new medicine is approved by the European Medicines Agency, this does not mean that it will be available to all patients across the EU as individual decisions for each Member State still depend on the verdicts of payers.

This can cause differences in:

- **Reimbursement decisions:** For example, NICE, the HTA body in England, have extended their threshold for drugs aimed at end of life care to facilitate cancer drug access to patients in the NHS[2]
- **The time it takes for new oncology drugs to reach patients:** For example, in Germany, drugs are usually available for reimbursement as soon as marketing authorisation is granted. In most other countries, pricing and reimbursement negotiations take place after marketing authorisation and this can take a year or longer[11]

Efforts to **harmonise HTA** at the European level are ongoing. In January 2018, the European Commission put forward a proposal for Member States to work together.[1] The vision of the proposal includes **more HTAs done, for less**, whilst making better decisions, making business easier for industry, better informing patients, and ultimately getting patients faster access to new medicines by ensuring efficient use of resources and strengthening the quality of HTA across the EU.[1]

The proposal aims to address a number of problems which cannot be sufficiently solved through continued project-based voluntary cooperation on HTA. These are listed below:

- **Impeded and distorted market access**[1]
  - The differences in national processes and methodologies of HTA bodies can lead to differences in how evidence is considered in assessments. This can contribute to delays and inequalities in availabilities of innovative medicine
- **Duplication of work for national HTA bodies**[1]
  - Clinical assessments of the same technologies (medicines) are being assessed in parallel or within a similar time frame by HTA bodies in different Member States, resulting in duplication of work and inefficient use of resources

- **Unsustainability of HTA cooperation**[1]

- The current Union-level cooperation on HTA is project-based. This means its funding is short-term and needs to be secured and renegotiated in every financial cycle. There is no guarantee for the continuation of activities in the long-term

At the September 2015 European Cancer Congress, ECPC presented the paper entitled 'Europe of Disparities', which included recommendations on the priorities for action to tackle inequalities in cancer care in Europe.[16] The proposed policy recommendations include:

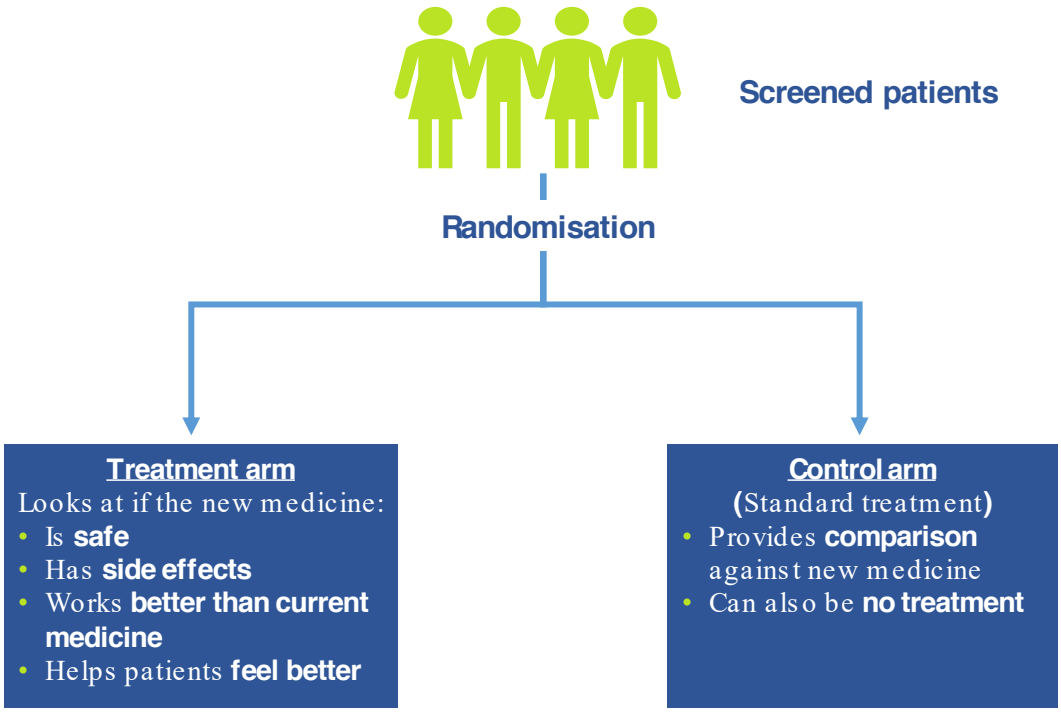
- Cancer control
- Cancer registries
- Multidisciplinary teams
- Cancer health literacy
- Screening and early diagnosis
- Access to optimal care
- Cancer survivorship and patient rehabilitation

Clinical Trials

New treatments for patients with cancer and other diseases have to be thoroughly tested to determine if they are safe and effective. Medical research studies involving people are called clinical trials. **Clinical trials are used to find out if the new medicine is beneficial compared to the standard of care**.

Randomised controlled trials are the ideal way to understand the efficacy and safety of new, innovative treatment regimens. Patients are screened to see if they qualify for the trial. Criteria can include many things like age, sex, health condition, whether they are pregnant and how close they live to the trial site. The patients are then randomly assigned to receive the new medicine (the treatment arm) or a control medicine (the control arm) (Figure 5). The patients are followed up, with outcomes being measured at specific times. Any difference in response between the groups is assessed **statistically**.

Figure 5. Randomised controlled Trials



Patient roles in clinical trials

Clinical trials are the most important tools of research in fighting cancer. ECPC strongly believes in the concept of patients as co-researchers, meaning placing the patient at the centre (rather than spectator) of scientific research.

Proper support of the patient role involves work to make sure that patients:

- Understand how clinical trials work
- Understand the impact of clinical trials on further research
- Understand the impact of clinical trials on cancer treatment
- Are able to provide information on the personal risks attached to trial participation

It is acknowledged that the patients' contribution to discovery, development and evaluation of medicine enriches the quality of the evidence and opinion available. Patients therefore have a moral right to be involved in the way clinical trials are developed, managed and evaluated.

European Patients' Academy (EUPATI) has developed guidance for covering patient involvement in:[17]

- Pharmaceutical industry-led medicines research and development (R&D)
- Ethics committees
- Regulatory authorities
- HTA

What do clinical trials measure?

The outcomes measured in clinical trials are called **endpoints**. A useful treatment is generally considered to be one that improves the quality and/or increases the length of patients' lives. Therefore, clinical trials of cancer treatments need to measure the **survival, quality of life and safety** of the participants. Each clinical trial usually has a **primary endpoint**, which measures if the therapy being studied can be considered a success. An example of an endpoint would be five-year survival.

Challenges to measuring the value of cancer medicines

Collecting evidence to demonstrate the effectiveness of cancer treatments is often difficult. This means that evaluating the value that new cancer medicines provide and making decisions about whether to reimburse them can be challenging. The reasons for this are:

- **Patient numbers**
  - Often cancer trials can only recruit a small number of patients. This makes it difficult to use statistics and therefore hard to draw conclusions about how effective the new treatment is
- **Standard treatment**
  - Standard treatment is often used in the control group. However, trials can run for years and the standard treatment may therefore not be relevant by the time of HTA
- **Third line therapy**

In third line or rescue cancer therapy, there are often no treatment options to serve as an appropriate comparator

Use of surrogate outcomes in clinical trials

One of the most commonly used primary endpoints in clinical trials is **overall survival**. However, for some cancers, it can take a long time before there is any survival data available. Healthcare systems will need to see this data before they can make a decision to reimburse the medicine and this can therefore **delay patient access** to beneficial treatments.

In order to speed up access to new cancer medicines, a **surrogate endpoint** can be used as a substitute for a clinical endpoint and they are often used in cancer clinical trials because the results can be measured much sooner than other endpoints, such as survival.[2]

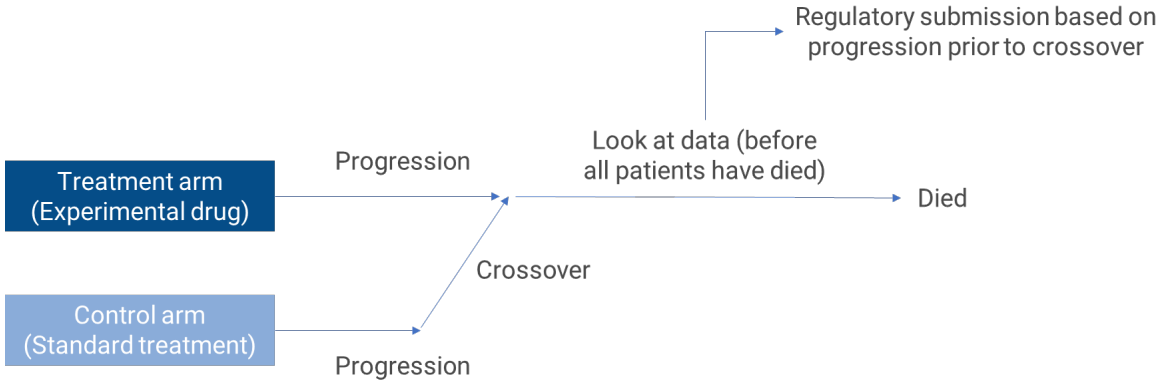
Examples of surrogate endpoints for overall survival include:

- **Disease-free survival**
  - This is the length of time between the start of treatment and tumour recurrence or death from any cause
- **Progression-free survival**
  - This is the length of time between starting treatment and a measurable worsening of the disease or death from any cause

The use of surrogate outcomes has **limitations**, making it difficult for HTA to assess whether the drug is likely to offer **real benefit** to patients given the lack of mature data on overall survival (OS).[2] Progression-free survival (PFS) is the most widely used surrogate outcome for OS in cancer clinical trials, with the number of QALYs gained often estimated on the basis of PFS data from a clinical trial.[2, 18] However, two aspects of cancer treatment make the evaluation of the quality of data on PFS problematic:

- **Crossover among trial arms** – if, in a clinical trial, it is sufficiently strongly believed that the treatment arm is outperforming the control arm, patients will often **switch from the control arm to the treatment arm** based on disease progression (Figure 6). Treatment switching makes it difficult to evaluate whether PFS improves OS.[19]
- **Multiple subsequent treatments** – in most cases, cancer treatment is a succession of different therapies. Therefore, there could be a PFS for several treatments but only one OS and the relationship between one particular PFS and OS will not be known.[19]

Figure 6. Crossover among clinical trial arms



Further challenges to measuring survival

In order to measure survival, it is important to state what the event is (death or relapse) and when the period of observation starts and finishes. This data might be difficult to collect for all patients in cancer clinical trials for the following reasons:[19]

- Some patients will be lost to follow-up
- Some patients will go on other treatments after the one being evaluated

Therefore, for some patients, the **true time to event will be unknown**, which makes analysis of survival difficult.

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