Innovative treatment and alternative clinical endpoints

The benefits for patients and caregivers

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Executive summary

Clinical endpoints are the measured outcomes of a given treatment and are vital tools in clinical research that contribute to medical advancements. *Developments in medicine in general, and oncology in particular, have shifted practice away from the use of traditional outcomes such as survival, and towards the use of novel outcomes that can be measured sooner and allow new treatments to reach patients faster. This change has, however, brought challenges to all stakeholders involved throughout the lifetime of a new treatment.*

This report, commissioned by Bristol Myers Squibb, provides a foundation for ongoing discussions of the benefits and challenges of alternative clinical endpoint, *and in particular highlights the value of clinical endpoints, areas of consensus and areas where disagreement remains. This report also proposes measures to address key bottlenecks in regulatory processes. Our analysis is based on literature and publicly available data, interviews and focus group discussions with both clinicians and patient advocacy groups from across the Nordics (Norway, Sweden, Finland and Denmark), as well as a survey of cancer patients in Norway conducted in collaboration with the Norwegian Cancer Society. While this analysis mainly focuses on the case of oncology, the aim is to inform the discussion across disease areas.*

There are trade-offs to be considered. *Advances in cancer detection and treatment have significantly improved the lives of cancer patients, leading to transformative changes in the design and execution of clinical trials. The use of alternative clinical endpoints in these trials has become commonplace, accelerating drug testing and subsequently access to novel treatments. While this has benefits for patients, it poses a challenge to the involved stakeholders, who grapple with new concepts and methods, as well as increased uncertainty. Alternative or surrogate endpoints are, however, here to stay and are an integral part of contemporary drug discovery and testing. Learning how to deal with the challenges involved*

Key findings of this report

Alternative endpoints are here to stay

ACEs have the capacity to unlock innovation and get promising treatments to patients faster and are standard practice in clinical trials today.
Stakeholders must rise to the challenge and establish the necessary framework to deal with ACEs in a transparent and predictable manner.

Build capacity among all stakeholders

HTA bodies need a clear framework for the assessment of ACEs in different contexts. The ongoing NICE UK Task Force may be an inspiration.
Clinicians may benefit from improved decision support mechanisms.
Increased awareness of ACEs among PAGs will help them support patients more effectively

No one size fits all

Patients have different priorities for their treatment, which can be reflected by using multiple endpoints.
ACEs can accelerate clinical research, but their value may vary by treatment setting, disease stage, and degree of correlation with more traditional outcomes.
Assessment frameworks must account for this complexity.

Cooperation is key

Consistency in decision-making provides predictability to patients and clear incentives for producers. Cooperation between regional HTA bodies to establish clear frameworks can reduce uncertainty to patients and producers. Cooperation between regulators and producers in the design of clinical trials is also essential.

Real world evidence evaluation

Nordic countries have established uniquely valuable health registries with broad coverage and a high degree of data quality. They are in an ideal position to lead the way in the validation of alternative clinical endpoints using real-world data. Risk sharing agreements based on further evidence gathering can reduce uncertainty.

Notes: ACE: Alternative clinical endpoint. HTA: Health technology assessment. PAG: Patient group organisation.

in their use, including their careful validation are some of the ways agencies and pharmaceutical companies can work together to reduce this uncertainty, accelerate access to new treatments, and protect patients' interests.

Nowadays, many decisions on treatment reimbursement by the public health care system are being made based on alternative clinical endpoints. *Health Technology Agencies (HTA) across the Nordic countries are faced with challenging questions when assessing the cost-effectiveness of new treatments, and little formal guidance exists to assist them in this task. Concerns have also been raised regarding the reliability of using alternative clinical endpoints as a basis for HTA decisions. Regional cooperation across agencies may help establish a common assessment and acceptability framework for alternative endpoints, increasing predictability for patients, improving guidance for clinicians and clarifying incentives to pharmaceutical companies.*

Clinicians have a crucial role in designing the best possible treatment path for each of their patients, but it has become more complex over time. *That is mainly due to the constant development of new treatments, and the shift towards more personalized medicine. Supporting clinicians in keeping up with a changing treatment landscape, as well as in understanding new endpoints is crucial also for patient well-being.*

Patients' needs and priorities when it comes to cancer treatment vary widely and there is no one-size-fits-all solution. *Alternative endpoints, including Patient Reported Outcomes (PROs), can help provide a broader picture of the different ways in which disease and treatment can affect patients' lives. These endpoints have gained prominence in clinical research, offering deeper insights into patient well-being and treatment effectiveness. Improving patients' understanding of clinical research as well as the treatment they receive might help them feel more comfortable with their treatment and more informed.*

Our findings can be summarized in the five key points in the figure above. *They draw from our analysis and extensive interviews with healthcare professionals and patient advocates. First, we must acknowledge that alternative - or surrogate - clinical endpoints are by now standard practice in many fields, including oncology. All stakeholders involved in the development, testing and assessment of new treatments must ensure the building of capacity and infrastructure needed to fully exploit all benefits provided by innovative medicine, while keeping patient well-being at the forefront.*

This report would not have been possible without the participation of clinicians and patient advocacy groups from Norway, Sweden, Finland and Denmark, as well as the members of the Norwegian Cancer Society's user panel. We thank all of them for their time and insight.

Sammendrag

Tradisjonelt er effekten av et legemiddel målt ved ekstra levetid frem til død, omtalt som totaloverlevelse. Med stadig bedre overlevelse er andre utfallsmål tatt i bruk, både innen onkologi og på andre sykdomsområder. Disse omtales som alternative kliniske endepunkter eller surrogat-endepunkter. Fordi det kan ta lang tid før totaloverlevelse bekreftes, muliggjør bruk av alternative kliniske endepunkter som biomarkører i forskningsstudier, en tidligere evaluering av behandlingseffekt og tidligere tilgang til innovativ kreftbehandling for pasientene.

For både europeiske og nasjonale legemiddelmyndigheter medfører alternative kliniske endepunkter at de må forholde seg til økt usikkerhet ved beslutningstidspunktet. På noen områder er det entydige sammenhenger mellom positive funn ved tidlige utfallsmål og totaloverlevelse, på andre områder er sammenhengen mer komplisert og det er behov for økt bruk av registerdata og mer komplekse evalueringsmetoder.

Alternative endepunkter har blitt en integrert del av moderne legemiddelutvikling og testing, og ligger stadig oftere til grunn ved nasjonal beslutning om finansiering. Et endret informasjonsunderlag fører med seg utfordringer, særlig knyttet til å validere og kontinuerlig vurdere de langsiktige virkningene av ny behandling. Myndigheter og produsenter kan samarbeide om å håndtere denne typen utfordringer for å redusere usikkerheten, gi raskere tilgang til nye legemidler og ivareta pasienters behov. Samarbeid mellom myndighetene i Norden kan bidra til å etablere felles praksis i vurderingen av alternative endepunkter, noe som kan øke forutsigbarheten for pasienter, gi bedre veiledning for klinikere og tydeliggjøre produsentenes insentiver.

Klinikere ønsker å tilby det beste behandlingstilbudet for sine pasienter. For å gjøre det må man vurdere forventet effekt og ulemper ved behandlingen, opp mot pasientens livssituasjon. Legens rolle har blitt mer krevende over tid, med komplekse kliniske retningslinjer og overgangen til mer persontilpasset medisin. Dette gir behov for mer systematisk klinisk støtte for å sikre likeverdig og tilrettelagt behandling.

Kreftpasientenes behov og prioriteringer varierer og alternative endepunkter, inkludert pasientrapporterte utfall [2], kan bidra til å gi et mer utfyllende bilde av de ulike måtene sykdom og behandling kan påvirke pasientenes liv. Pasientrapporterte utfall har fått økt betydning i klinisk forskning og gir viktig innsikt i pasientenes vurdering av behandlingseffektivitet og livskvalitet. Økt forståelse av kliniske problemstillinger kan bidra til at pasientene blir tryggere og tar mer informerte valg.

Denne rapporten er initiert og finansiert av Bristol Myers Squibb med mål om å øke forståelsen av betydningen av alternative endepunkter. Rapporten ville ikke vært mulig å gjennomføre uten deltakelse fra klinikere og pasientforeninger i Danmark, Finland, Norge og Sverige, samt medlemmene av den norske Kreftforeningens brukerpanel. Vi takker for deres tid og innsikt.

1. Traditional and alternative clinical endpoints

Clinical endpoints, the measured outcomes of a given treatment, are vital in clinical research. Developments in medicine have shifted practices towards the use of novel endpoints allowing new treatments to reach patients faster. This change has, however, brought challenges throughout the lifetime of a new treatment.

1.1 What is a clinical endpoint?

Clinical endpoints are used in clinical trials to measure the efficacy of new treatments when compared to the current standard of care. They are meant to serve as objective measures that can be implemented consistently over time and throughout different contexts, as clinical trials are often conducted in multiple locations at the same time (Figure 1).

Some endpoints are relatively simple to understand. Has the patient survived? Have the symptoms disappeared? Other endpoints may be more complex and involve careful testing and monitoring of patients and of the disease that the treatment is meant to address. But in every case, their aim is to allow researchers to assess whether a treatment has a *significant impact on a disease, condition, or the well-being* of a patient.

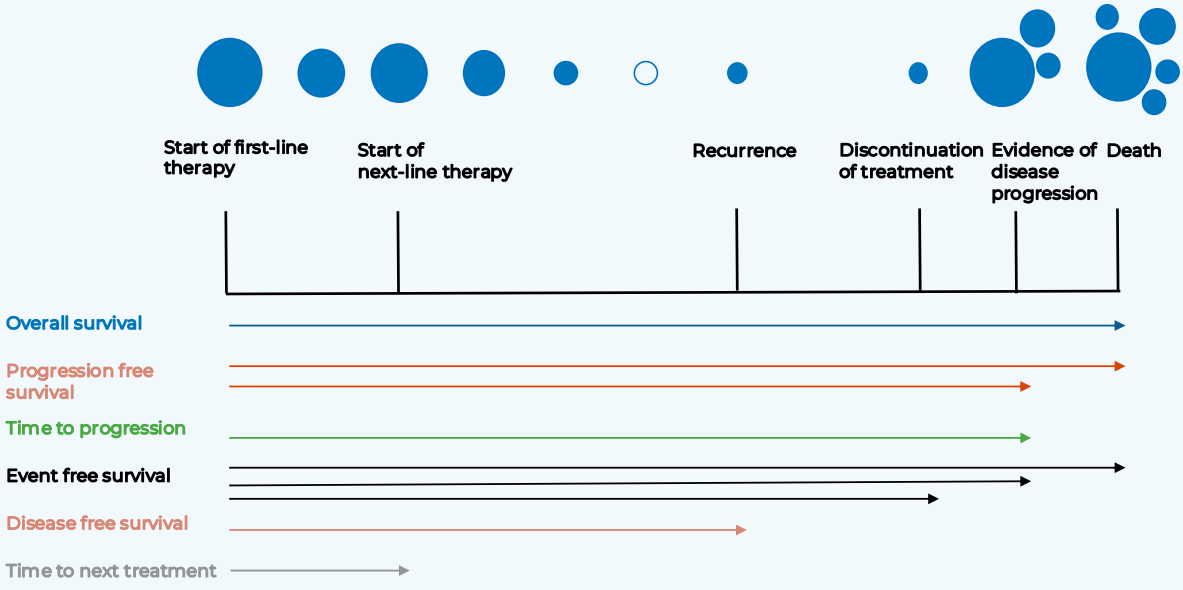
Across medical fields, these endpoints can vary, as the relevant outcomes to measure related to both patients and diseases can take different forms. In fields such as oncology, especially in advanced stages, whether a patient survives or not has been long considered the standard endpoint. The impact of a treatment on a patient's cognitive function is a common endpoint in neurology, while cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke are used as endpoints in research within cardiology. In other fields, the rate of hospitalizations could, instead, be the most relevant endpoint to measure.

1.2 Alternative clinical endpoints

Traditional clinical endpoints in medical research *directly* measure patient outcomes. One of the most common endpoints used in oncology, overall survival (OS), for example, tracks the proportion of patients alive after a certain time from starting treatment.

In contrast, *alternative* clinical endpoints may be used both to measure treatment benefits directly, or as proxy measures for benefits measured using traditional endpoints. They are thus sometimes also referred to as surrogate endpoints. This could be through radiological scans assessing disease progression, or the presence of specific biomarkers, for example. In many contexts, these measures can indicate whether a treatment is effective or not

Figure 1: Clinical endpoints commonly used in oncology and disease progression stages



Source: Oslo Economics, adapted from [3].

much earlier than traditional measures such as OS. As treatments advance and extend life, researchers increasingly rely on these alternative endpoints to accelerate clinical studies and better understand a treatment's effects on different populations. A shift towards more patient-centered research has also led to the more frequent inclusion of patient-reported outcomes [2], in the form of alternative clinical endpoints, as part of the evaluation of treatment impacts on quality of life.

1.3 Scope of this report

This report provides a foundation for ongoing discussions regarding the value of clinical endpoints, highlights areas of consensus and those where disagreement remains, and proposes measures to address key bottlenecks in regulatory and clinical processes. While the analysis focuses on oncology, the report's conclusions are intended to be valid for other disease areas.

Chapters 2 to 5 explore the opportunities and challenges brought about by alternative endpoints on a range of different stakeholders involved in different stages throughout the course of a treatment's lifetime (Figure). Our findings are summarized in 5 key conclusions in the final chapter of this report. Our analysis is based on literature and publicly available data, interviews and focus group discussions with both clinicians and Patient Advocacy Groups (PAG) throughout the Nordics, and survey of cancer patients in Norway.

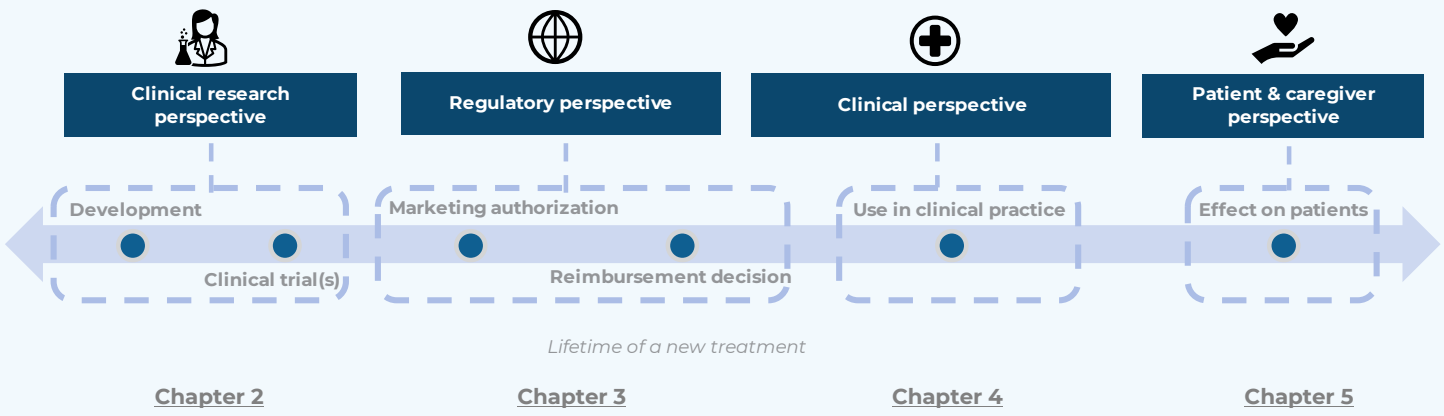
To better understand the value of endpoints from a clinical perspective, we interviewed 11 healthcare professionals from across the Nordics to understand their views and as well as the key challenges clinicians face. Our interviewees have experience in clinical research and in the treatment of breast, skin and lung cancer. We spoke with 7 PAGs from Denmark, Finland, Sweden and Norway (see Map) and asked them about their views on endpoints - and more broadly on which aspects of a treatment are most relevant to their patients. The PAGs' feedback is complemented with evidence collected via the Norwegian Cancer Society's (*Kreftforeningen*) user panel, consisting of current cancer patients and caregivers in Norway.

This report would not have been possible without the participation of clinicians and patient advocacy groups from Norway, Sweden and Denmark, as well as the members of the Norwegian Cancer Society's user panel. We thank all of them for their time and insight.

Map: Stakeholders interviewed across the Nordics

Source: Oslo Economics

Figure 2: The value of alternative clinical endpoints throughout the product lifetime.



Source: Oslo Economics

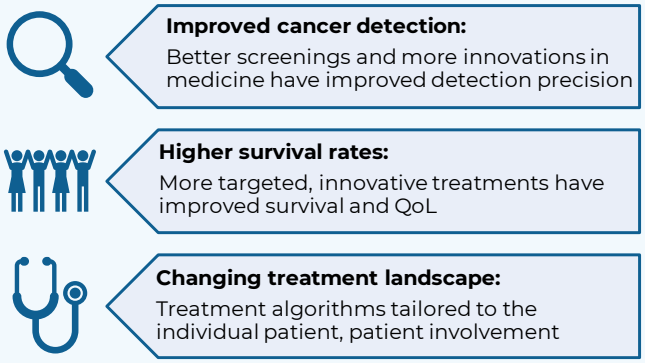
2. Alternative endpoints in clinical research

Advances in cancer detection and treatment have significantly improved the lives of cancer patients, leading to transformative changes in the design and execution of clinical trials. The use of alternative clinical endpoints in these trials has become commonplace, accelerating drug testing. While this creates benefits for patients, clinicians and regulatory agencies, there are uncertainties that need to be discussed and evaluated.

2.1 Drivers of change

In the last few decades, the field of oncology has witnessed remarkable advances that together have transformed patient outcomes as well as treatment approaches. These advances can be summarized in three key drivers that shaped how we design and conduct clinical trials (Figure 3).

Figure 3 Key drivers of change in oncology

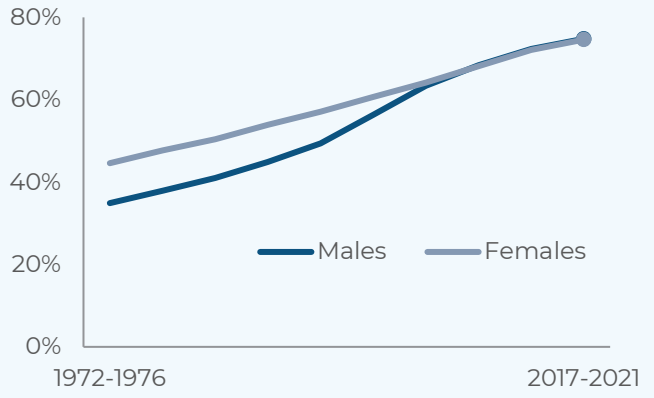


Source: Oslo Economics; QoL – quality of life

First, medical innovations and improved screening programs have significantly enhanced our capacity to detect cancer. This has led to a higher share of cancers being detected at early stages. Breast cancer serves as a prime example of this swift progress, with detection of the disease at Stage 1 in Norway today being about four times more common than in the early 1990s [11]. Similar progress has been seen in several other cancer areas and in all Nordic countries over the same period.

Secondly, better cancer detection and improved treatment options have resulted in much higher cancer survival rates. Overall, survival rates have nearly doubled since the late 1970s (Figure 4).

Figure 4 Five-year survival rates in NORDCAN countries, all cancers, by year of diagnosis



Source: NORDCAN

Lastly, the overall treatment landscape has changed significantly. There are not only more treatments available to patients, but the patient as an individual is increasingly put into focus and involved in treatment decision making.

Taken together, this not only means that patients participating in clinical trials today are more likely to survive, they also often continue receiving treatment beyond the duration of the trial.

2.2 Alternative endpoints as a response to change

Two implications of the developments discussed above affect how clinical trials are designed and conducted, and which endpoints are used.

The first is that clinical trials in many cancer areas today test the efficacy of a treatment based on a sample of patients that are expected to live longer than they would have had they been diagnosed 20 years ago. Measuring survival outcomes in a clinical trial thus requires both more time and resources than before. Alternative ways of measuring how effective a treatment is, that can provide answers within a shorter timeframe, for example by studying

how the disease evolves (or stops evolving), have thus become much more valuable as they can speed up this process and get treatments to patients faster.

Secondly, these developments raise the question of what precisely is meant by "a *significant impact* on a disease, condition, or the well-being of a patient" and how it is supposed to be measured in a clinical trial. Is, for example, the slowing or halting of disease progression and extending progression-free periods considered a significant impact on a disease? These questions are not only relevant in research, but also for regulators, as well as clinicians and most importantly for patients and caregivers.

2.3 Overall survival: a fading standard in clinical trials

Traditionally, the effectiveness of new cancer treatments has been measured in terms of improvements in overall survival (OS), which tracks the time from diagnosis or treatment start until a patient's death from any cause. This endpoint is straightforward to measure and serves as the definitive and primary measure of treatment success in oncology trials, with the main goal being to extend the patient's life [3].

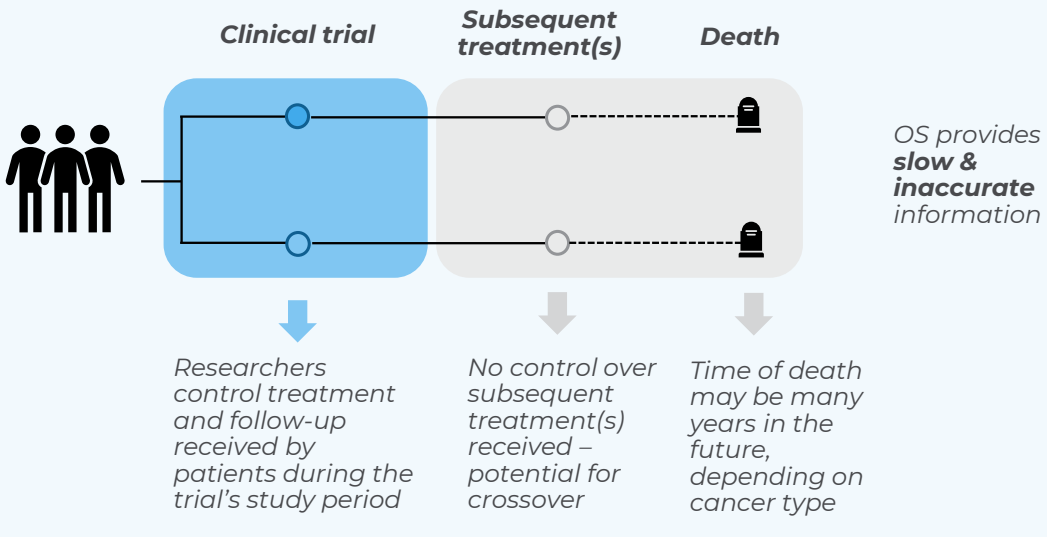
The developments described above, however, challenge the place of OS as the gold-standard clinical endpoint [12]. The longer follow-up periods needed to measure OS can, for one, delay trial results. Moreover, a lower number of expected deaths may require a larger sample size in order to document benefits measured in terms of OS. Taken together, this can make clinical trials significantly more expensive, and can threaten a trial's feasibility [3]. This questions the practicality of using OS as the sole endpoint in oncology. Furthermore, the evidence eventually collected using OS may be imprecise if researchers do not have full control over which subsequent treatments participants may receive after the trial. If, for example, patients from the control group also receive the treatment being studied, attribution of impacts measured in terms of OS becomes more speculative (see Figure 5), requiring additional statistical adjustments and consistency checks.

There are also important ethical considerations that should be considered. If the superiority of a new treatment over the current standard of care is clear using alternative endpoints in a short time frame, is it ethical to continue the clinical trial until OS data is available, and thereby prevent both patients in the control group as well as patients in the general population, from getting access to this superior treatment? The answer to this question is likely not binary and depends on the degree of uncertainty faced by decision makers at any point in time.

2.4 Alternative clinical endpoints are here to stay

Several alternative clinical endpoints, such as progression-free survival (PFS), event-free survival (EFS) or disease-free survival (DFS), were developed to provide researchers with information about the efficacy of a new treatment more efficiently. Outcomes that measure the time without progression of a disease or time until a new line of treatment begins (due to e.g. progression, side effects) have shorter follow up-periods than overall survival and can thus accelerate the testing of new drugs.

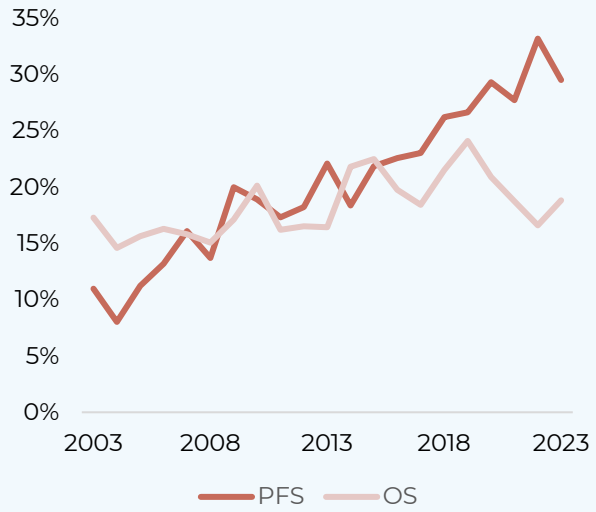
Figure 5 The challenge of measuring efficacy using OS



Source: Oslo Economics

In addition, most clinical trials make use of several primary and secondary endpoints, where primary endpoints measure the main research question and secondary endpoints assess other research questions of interest [13]. Among the assessed outcomes are also side effects and quality of life (QoL). This can give a clearer picture of the efficacy of a new drug and provide more and new information that can help to understand how a disease affects the patient and how the disease responds to the treatment, but also how a treatment affects QoL more generally.

Figure 6: Share of all interventional, phase III clinical trials in oncology containing PFS or OS as a primary endpoint by year of start.



Source: Oslo Economics based on data from the National Library of Medicine [5]

The outlined developments and changes have led to a visible increase in the use of alternative clinical endpoints in clinical trials over the last two decades. While in 2003 alternative clinical endpoints accounted for about 25 percent of the endpoints used in oncology trials globally, by 2023 this share had increased to about 43 percent [5]. The use of PFS in particular has increased dramatically over the past couple of decades. Its use as a primary endpoint in oncology trials has tripled from around 10 percent in 2003 to 30 percent in 2023 (see Figure 6). Over the same period, the share of trials using OS as a primary endpoint has remained constant.

2.5 The cost-benefit trade-off

The arrival of alternative clinical endpoints into the field of oncology has brought about a wide range of benefits. From the drug development and testing perspective, they allowed for a more practical and precise way of measuring disease response to new treatments, as well as providing deeper insight into how diseases evolve (see Figure 7). They have also contributed to more treatments being made available for patients faster, and this success is reflected in the constant development of new and more advanced endpoints in both oncology and other disease areas (see Box 1).

But some argue that these benefits have come at a cost of increased uncertainty. There is always a certain degree of uncertainty with respect to the measurement of a given outcome. It might, for example, be difficult to precisely measure how much a tumor has grown over a certain period. When using alternative endpoints as proxies of a treatment's impact on another outcome, there is also an additional source of uncertainty, related to how confident we can be about the alternative endpoint's relationship with this final outcome of interest (see Figure 7).

Figure 7: Benefits of alternative endpoints

A recent article, for example, questioned whether oncological treatments approved by the US FDA based solely on alternative endpoints such as PFS had similar documented impacts on patient survival [14]. However, only around 10% of these early approved treatments have so far been withdrawn based on further evidence [15]. Many of the accelerated approvals of novel treatments by the FDA would not have been possible with traditional endpoints such as OS, or at least not in this short amount of time. Alternative endpoints therefore provided incentives to the

pharmaceutical industry to develop new drugs, help research to better understand disease biology and have had clear benefits for patients in finding the right means to fight their disease.

2.6 Nordic countries can lead the way in the validation of alternative endpoints

The validity of alternative endpoints has been agreed upon in certain contexts in which their relationship with later outcomes is well understood (e.g. PFS in the adjuvant breast cancer setting) or in which survival is too long to remain a relevant measure, such as the treatment of multiple myeloma (see Figure 8) [16, 17].

The validation of clinical endpoints remains, however, an important objective, particularly since new endpoints are being developed and applied in new contexts. Developing robust methodologies for the validation of new endpoints is a necessary first step, since the methods applied in existing studies have been of varying quality [18].

The use of real-world data in the validation of new endpoints and the confirmation of benefits documented in clinical trials has thus become an active field of research. Nordic countries, with their extensive, high quality health registries, are in an ideal position to take a leading role in this effort.

Box 1 The use of biomarkers in clinical trials

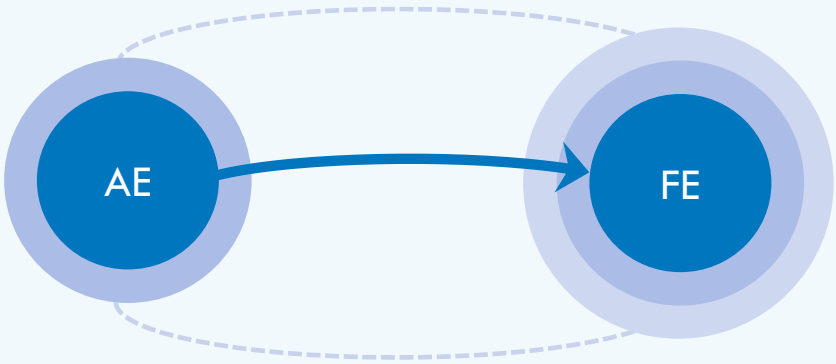
Biomarkers are objective, measurable signs of biological processes in the body. They show how the body interacts with potential hazards—whether chemical, physical, or biological—and can include changes in function, physiology, biochemistry, or molecular activity. Examples range from simple measures like pulse and blood pressure to more complex lab tests of blood and other tissues [1, 2].

Biomarkers do not necessarily reflect symptoms and thus may not always correlate with a patient's experience or overall well-being. In contrast, clinical endpoints reflect how a patient feels, functions, or survives, offering a very patient-centered perspective on health and well-being. In clinical trials, some biomarkers are therefore used to complement other endpoints. To do so, they need to have clinical relevance and should predict a clinical outcome. Like other alternative endpoints, using biomarkers provides early evidence of treatment safety and efficacy when primary endpoints like survival take too long. Biomarkers therefore allow efficient research and speed up the drug development process [1, 2].

Commonly used biomarkers approved by the FDA include *prostate-specific antigen* (PSA) used in prostate cancer to monitor disease progression and response to treatment, *low-density lipoprotein cholesterol* (LDL-C) used as a marker for cardiovascular disease risk and to evaluate the effectiveness of cholesterol-lowering treatments. In cancer trials, changes in *tumor size* can serve as a surrogate for disease progression or response to therapy.

Source: [1, 2].

Figure 8: Measuring impacts on a final endpoint (FE) based on impacts on an alternative endpoint (AE)



Source: Adapted from ISPOR US 2022 Issue Panel 3223 White Paper

3. From clinical trials to treatment

Regulatory agencies decide whether new treatments are safe and cost-effective and can thus be made available for patients. Many reimbursement decisions are now being made based on alternative clinical endpoints, but concerns have been raised regarding their reliability. Regional cooperation across agencies may help establish common frameworks, increase predictability for patients, improve guidance for clinicians and clarify incentives to manufacturers.

The European Union and European life science companies have established a public-private partnership (the Innovative Health Initiative) that aims, among other things, to accelerate the development of and access to innovative medical treatments. Europe's Pharmaceutical Strategy from 2020 also includes improved access to innovative treatments as an objective. As discussed in the previous chapter, alternative clinical endpoints are one possible way to accelerate drug testing, but their arrival has also brought challenges to existing regulatory agencies.

3.1 How do patients get access to new treatments?

Before a new treatment can be made available to patients, health authorities first assess whether the treatment is safe, and whether it has an effect on the disease. Drug developers thus submit clinical trial evidence to market authorization agencies like the U.S. Food and Drug Administration [19] or the European Medicines Agency [20], who check that the treatments meet international standards for safety, effectiveness, and quality. These agencies also ensure adherence to good clinical practice in the planning and reporting of clinical research.

Once a new treatment has been granted a marketing authorization, national health technology assessment bodies, such as the Norwegian Medicines Agency (NoMA), evaluate whether to introduce said treatments into their public healthcare plan. Their evaluation consists of comparing the proposed new treatment against the current standard of care to determine whether they deliver value for money.

3.2 The role of endpoints in regulatory decisions

Regulatory bodies like EMA and NoMA evaluate new cancer treatments by looking at how well they meet specific goals, such as improving patient survival or delaying disease progression. Marketing authorization agencies have in recent years acknowledged the value of alternative clinical endpoints for accelerating access to promising treatments. The FDA has for example published a guidance document for the industry with a discussion of the key advantages and disadvantages of a series of endpoints frequently used in cancer clinical trials, with recommendations on the suitability of different endpoints according to the disease context [19]. The EMA's most recent guidelines do not explicitly establish which endpoints are acceptable and which are not, but state that any selected endpoint should clearly document whether a treatment has a significant and positive impact on a patient's health, quality of life, or survival [20].

HTA bodies, on the other hand, often focus on whether a treatment's effectiveness justifies its costs compared to existing treatments. These assessments consider both how big and how certain the effects of a treatment are, since the outcome of their decisions may have large financial implications for their country's healthcare budgets. Perhaps because of this slight difference in focus, HTA bodies have shown a stronger preference for more traditional outcomes such as overall survival than marketing authorization agencies. Nevertheless, the joint European HTA body (EUnetHTA) recognized the challenges involved in the use of overall survival in their guidelines on clinical endpoints when they state that:

> *"Overall survival is the preferred clinical endpoint in survival analysis. If it is not feasible to measure final endpoints, then surrogate or intermediate endpoints may be acceptable provided there is compelling independent evidence of a strong association or correlation of effects on the surrogate or intermediate endpoint with the*

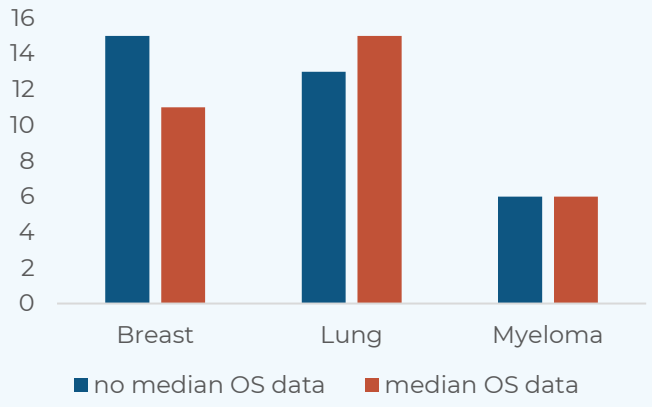
effect on the final endpoint of interest." [17]

In more recent documents, EUnetHTA has gone further and recognized, for example, that in the field of oncology, endpoints such as PFS are relevant in their own right [16].

NOMAs view on alternative endpoints are, in principle, in line with the EUnetHTAs guidelines: alternative endpoints are used when traditional endpoints cannot be measured directly or quickly. Traditional endpoints are, however, preferred for their direct measurement of clinical benefits, such as life extension [21].

Despite these preferences, reimbursement decisions by HTA bodies are not exclusively based on survival anymore: Figure 9 shows how, in Norway, a large share of approvals in oncology over recent years have been based on alternative clinical endpoints. More than half of the reimbursement decisions made since 2014 in breast cancer were based on data that did not report median OS. While median OS estimates can in some cases also be produced when data is not fully mature, a significantly large incurrence of deaths (around 50%) is still needed to provide sound OS estimates based on "mature" data [22]. Alternative endpoints, especially PFS, have been commonly used not only in the absence of mature OS data but also when mature OS data was available. Similar patterns can be observed for cases of lung cancer and multiple myeloma (Figure 9). Sister HTA agencies from other Nordic countries find themselves in a similar situation.

Figure 9: Number of new treatments introduced for breast, lung cancer and multiple myeloma by availability of median OS data in Norway (2014-2023)



Note: Bars show the number of positive reimbursement decisions made by the NOMA between 2014-2023 by disease area. The same treatment may be included twice if it was assessed (and introduced) for more than one indication. Blue bars show the number of decisions made before trial data was mature enough to provide estimates on median OS was estimated. Red bars show the number of decisions made with median OS data. Source: Oslo Economics, based on data from the NOMA

3.3 A way forward for HTA bodies

HTA bodies' acceptance of alternative endpoints differs across countries, and so do evidence requirements from different stakeholders [23]. Acceptance may also differ by disease, disease stage and the system's experience with both the proposed treatment and the used endpoint. EUnetHTA states that in the adjuvant setting (when patients are expected to live long after receiving the treatment), the use of PFS "appears acceptable", while this is not necessarily the case in the metastatic setting [16].

While a global trend towards clearer guidelines on the use of alternative endpoints has been observed in recent years [23, 24], a more explicit, harmonized, framework for the acceptability of alternative clinical endpoints would be of great value for Nordic HTA bodies. First, it would provide patients with greater clarity, as they would not find themselves in a situation in which a promising treatment that is available elsewhere, is not available to them in their country. Secondly, for drug developers this would clarify incentives and facilitate decision making with respect to which treatments to explore and how to design the clinical trials to support them. Lastly, it would provide HTA agencies themselves with a clear roadmap, enabling more efficient processing of each individual case.

3.4 Regional cooperation

The development of a clear methodology for dealing with alternative endpoints in HTA practice is a challenging task, and one that should be conducted in cooperation across agencies and borders. The National Institute for Health and Care Excellence (NICE) in the United Kingdom is, for example, currently working together with partner agencies from Scotland, the Netherlands, Canada, Australia and Colombia to develop stronger guidance on the use and acceptability of these endpoints [25]. EUnetHTA is another umbrella organization of regional HTA bodies focused on this task which may provide a useful forum for discussion and methods development.

The Nordic countries have already established a specific platform for collaboration across HTA agencies that could prove beneficial for developing common standards: the Joint Nordic HTA bodies initiative. This platform may be perfectly suited for collaboration on developing common approaches to the assessment of alternative endpoints in HTA contexts.

3.5 Post market access evaluations

To address some of the uncertainties involved in making reimbursement decisions based on alternative endpoints, evaluations of treatments and their endpoints after they have been approved should be carefully considered. Such evaluations can be conducted using real-world evidence, such as data from national health registries, with which the effects of new treatments can be monitored for complete populations promptly.

The Nordic countries have some of the world's most valuable health registry records, often including all cancer patients in the country. These countries are in a unique position to take the initiative when it comes to evaluating new cancer treatments and the endpoints used to measure their efficacy.

This can help to reduce uncertainty by complementing clinical trial evidence with real-world evidence based on the actual patient population that experiences the effects of a new treatment.

4. Navigating treatment options

Clinicians have a crucial role in designing the best possible treatment path for each of their patients. This role has become more complex over time, with the constant development of new treatments, and the shift towards more personalized medicine. Supporting clinicians in keeping up with a changing treatment landscape and understanding new endpoints is crucial for patient well-being.

4.1 Clinicians face complex treatment decisions

Technological progress has changed clinicians' role in areas like oncology. Designing treatment plans for patients has over time become a much more complex and individualized task. Clinicians grapple with a new, personalized approach to treatment, using an ever-growing number of inputs, including novel treatments, new endpoints and a changing regulatory landscape that may introduce (or remove) treatment options at any time [26] (Figure 10).

Treatment decisions are based on both intuition and structured algorithms or guidelines. Structural procedures, such as clinical algorithms, standards and guidelines can facilitate the decision as they can help clinicians navigate and ensure that they have considered all relevant aspects of both the disease and the patient when deciding on a treatment course. National guidelines, as reported in many of our interviews with clinicians from across the Nordics, have an important role to play. Value assessment frameworks by professional associations such as the American Society for Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) play a similar role and have developed clear and overall consistent criteria for assessing evidence based on alternative endpoints to assist clinicians in their work [27].

These processes, guidelines and algorithms can, however, become very complex, and require regular updating and maintenance [10, 26]. Guidelines frequently refer to statistical methods used in research, which can be problematic if clinicians are not familiar with the underlying data, statistical methods applied or the clinical trial's design.

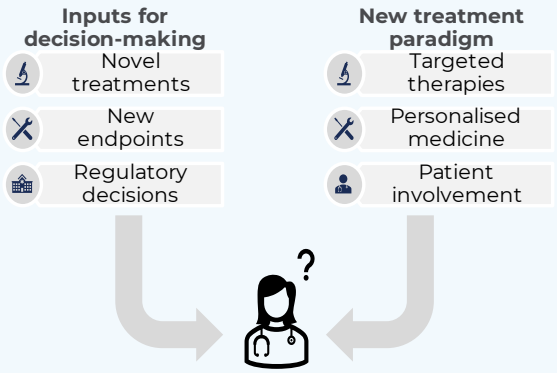
4.2 The need for better decision support systems

All the clinicians we interviewed as part of this project reported striving to keep up with the academic and regulatory landscapes in their fields. iIn times where treatment options progress fast and regulatory decisions are made regularly, this still proves challenging.

A more structured, effective approach to support clinicians in making these complex treatment pathway decisions, particularly in areas in which targeted therapies have become commonplace, such as lung or breast cancer, seems sensible. Clinical decision support systems (CDSS) is an umbrella term that covers several technical tools to assist clinicians and health care professionals in their day-to-day life. CDSS includes, for example, artificial intelligence-powered solutions to help choose the treatment options best tailored to a given patient in each country. These systems are described in more detail in Box 3.

Building capacity by tapping into existing knowledge and practice is recognized as the key to delivering the best treatment options to patients. Life-long learning, further medical education, attending conferences and congresses, as well as the use of CDSS when appropriate, can all contribute to an increased awareness of what the current options are for patients and clinicians.

Figure 10 Complexity of clinicians' treatment decisions



Actively encouraging involvement in clinical trials and connecting clinicians as well as other health care professionals with those involved in the medical research process could also be an effective approach to expand their know-how.

Likewise, fostering cooperation or exchange with regulatory bodies and PAGs could result in more effective market access and review processes. This may subsequently improve clinicians' awareness and knowledge with respect to prospective treatments in their country and help them find the optimal treatment strategies for their patients more effectively.

Box 2 Clinical decision support mechanisms and artificial intelligence

Clinical Decision Support Systems (CDSS) are computer-based programs designed to analyze healthcare data and provide guidance for clinical decision-making. By processing complex medical information, often through artificial intelligence (AI), these systems can enhance efficiency, accuracy, and improve patient outcomes. CDSS can offer features like reminders for preventive measures, diagnostic assistance, drug dosage suggestions, and disease management support [6]. A promising use of AI in oncology is early risk detection, with algorithms identifying cancer patients with high risk of short-term mortality or severe side effects [7, 8].
CDSS come in various forms including alerts, clinical guidelines, and focused patient reports, all designed to help clinicians make informed decisions at the point of care. This improves patient safety, boosts healthcare quality, and reduces costs linked to medical errors and inefficiencies [10]. At the same time, these systems are currently far from perfect. They may make biased decisions (especially if the algorithm is trained on a small, selected, set of data) or disturb the decision-making processes of health care professionals. Some of the key benefits and drawbacks are summarized below [6].

Benefits	Drawbacks
Improved patient safety: CDSS reduces medication errors by alerting clinicians to drug interactions and inappropriate dosages.	**Alert fatigue:** Too many non-critical alerts can overwhelm clinicians, leading to important recommendations being ignored.
Enhanced clinical management: These systems improve adherence to clinical guidelines, help with follow-ups, and support preventive care	**Workflow disruption:** Poor integration into existing systems can disrupt clinical workflows, adding time and complexity to care delivery
Cost containment: CDSS can cut unnecessary tests and duplicate orders, leading to significant cost savings for healthcare systems.	**Over-reliance on technology:** Excessive dependence on CDSS can reduce clinicians' independent decision-making skills and foster automation bias, the tendency to prefer suggestions made by AI, overlooking contrasting information gathered without the help of AI.

5. Living with cancer

Patients' needs and priorities when it comes to cancer treatment vary widely and there is no one-size-fits-all solution. When it comes to alternative endpoints, Patient Reported Outcomes (PROs), can account for this heterogeneity. These endpoints have gained prominence in clinical research, offering deeper insights into patient well-being and treatment effectiveness. Improving patients' understanding of clinical research as well as the treatment they receive might help them feel more comfortable with their treatment and more informed.

5.1 Patients' preferences

After speaking with cancer patient group organisations from across the Nordics, as well as collecting the views of patients themselves via survey, our key finding is that patients' concerns when it comes to their treatment can vary greatly, influenced by factors such as age, disease stage, and individual priorities. This insight can inform the development of future endpoints in the form of PROs, aimed at more carefully aligning how we measure clinical benefit to patients' priorities.

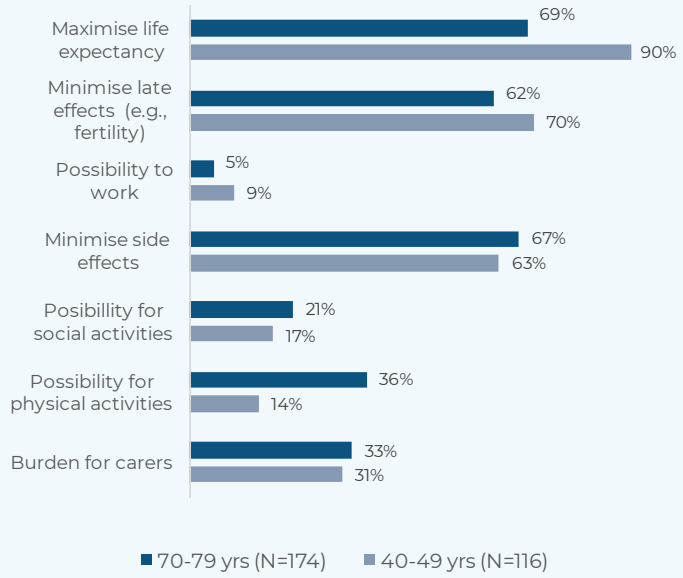
5.1.1 Patients' priorities are broad

By means of our survey and interviews we explored several aspects of cancer treatment and what patients value most when it comes to their treatment options (Figure 11). Life expectancy, side effects, and late effects of treatment appear to be the most discussed topics in consultations with health care professionals. However, aspects like relapse-free duration, work ability, and alternative treatments are less frequently addressed.

Patients value different aspects of treatment based on their personal circumstances, with younger patients often prioritizing extended life expectancy and avoiding late effects more than older patients. When facing a poor survival prognosis, patients

Figure 11 Difference in treatment priorities for older and younger patients

Which of the following aspects would be most important to you during the treatment period (3 most important):



Source: Cancer Society's User Panel, 2024; Compiled by Oslo Economics

Figure 12 Key results from the Cancer Society's user panel

A good life for patients and caregivers

- Survival and physical and emotional symptoms as key outcomes from treatment.
- Minimising the burden for relatives and caregivers

Emotional burden matters a lot

- Strong emotional burden attached to relapses.
- Emotional impact was ranked most important factor affecting their QoL after a relapse.

Patients have different priorities

- 50/50: trying everything vs. stability with one treatment
- Elderly patients tend to prioritise stability, while younger patients more likely to want alternatives.

Patients want for more information

- More information on progression, long-term effects, treatment alternatives and possibilities to switch treatment.
- Patients are not familiar with ACEs

surveyed are divided in choosing between a stable, single treatment alternative or switching among treatments to potentially extend life, even if only by a few months. Older patients typically prioritize a more predictable treatment pathway during the remainder of their life with as few side effects as possible and predictable treatment outlook, whereas younger patients are willing to receive more aggressive treatments or switch treatment to extend life expectancy (see Figure A 4 in the Appendix). Gender-specific concerns, such as fertility impacts, also differentiate treatment preferences between young men and women. These findings highlight the importance of implementing multiple outcome measures in trials to ensure as broad a picture of a treatment's impact on a patient's life as possible.

5.1.2 The emotional burden of relapses

Being diagnosed with cancer and deciding on an optimal treatment places a substantial emotional burden on patients and their caregivers. Progression of disease, as well as response to treatment and the likelihood of severe side effects are all uncertain. Cancer treatments can fail, leading to a relapse, which imposes an additional emotional and physical burden on patients. Patients, particularly younger ones, often feel a sense of defeat when their disease worsens or recurs, and transitioning to new treatments can add significant stress due to the uncertainties around side effects and changes in the treatment regimen.

The emotional distress of a relapse, the physical symptoms of the illness, and the effects on caregivers, family, and friends were named the largest burdens of such relapses in our survey (see Figure A 3 in the Appendix).

Providing stable treatment options can help some patients to alleviate some of this stress. Specifically, periods of disease stability — progression-free periods — can be particularly beneficial in reducing patients' anxiety and stress levels, highlighting the potential value of PFS as an outcome in and of itself in field of oncology.

5.2 The need for capacity building

PAGs from across the Nordic countries have emphasized the importance of providing patients clear information about the implications of their treatment, to build trust and ensure patients' adherence to often complex treatment regimens. Patients particularly value information about the course of treatment, side and late effects, their ability to work and live a normal life, and any implications their treatment might have for their current or future fertility (see Figure A 2 in the Appendix). There is a general need among patients for more information related to various aspects and effects of cancer treatment, particularly when it comes to possible late effects, how long they expect to be able to live without a relapse and other treatment options.

Box 3: EUPATI - European Patient's Academy on Therapeutic Innovation

The European Patient's Academy on Therapeutic Innovation [4] is a pan-European project of 50+ partner organizations, universities, pharmaceutical companies and non-profit organizations, that was established in 2012 and is based in the Netherlands [9].

EUPATI provides tools and training to patients and patient representatives to better understand and contribute to the process of medical research and the development of treatments. Understanding patients' needs and experiences from living with a disease is in the eyes of EUPATI vital for the development and assessment of novel and effective medicines. Increasing capacity and knowledge of patient organizations and representatives helps them to adequately represent and guide patients [9].

In their toolbox, EUPATI, provides for example, information to help patients better understand and analyze clinical trial results. Aspects like who took part in the trial and how the sample might differ from the overall population, how well a treatment works (incl. basic information on hard and soft endpoints), what side effects occurred, how clinical trials can be designed [4].

To allow patients and the organisations they represent to maintain a strong voice when deciding between complex treatment options with many different implications requires educating and empowering patients as well as PAGs with respect to interpreting clinical evidence. This may help them become more active participants in key decisions affecting their future. In the past, initiatives like the European Patient's Academy on Therapeutic Innovation worked closely with PAGs to increase their competence and allow them to be more effective partners to their members (see Box 3). Similar programs aimed at building capacity related to alternative clinical endpoints may allow the patients voice to be heard more clearly in future discussions.

6. The way forward

Alternative clinical endpoints are standard practice in oncology clinical trials today, and that raises challenges for all stakeholders involved in achieving the best outcomes for patients and their caregivers. Below are five key recommendations for tackling this challenge over the coming years.

Our findings from the previous chapters can be summarized in the form of five key recommendations (Figure 13). Their aim is to serve as a basis for further discussions on how to maximize the value provided by alternative clinical endpoints to patients.

1. Alternative endpoints are here to stay

Alternative clinical endpoints have the capacity to unlock innovation and get promising treatments to patients faster than they would if relying solely on traditional endpoints such as overall survival. In some disease areas, the time it would take to measure a drug's effect in terms of overall survival may be longer than the period under which a said drug is under patent protection. Together with higher costs of larger sample sizes, this could remove all financial incentives to develop it in the first place. Alternative endpoints may also contribute to increasing our understanding of disease progression and its response to different treatments and are standard practice in clinical trials.

At the same time, alternative endpoints may introduce a higher degree of uncertainty for decision makers. This may be the case if the relationship between alternative and "hard" outcomes is less well understood or documented. Stakeholders must establish the necessary frameworks to deal with ACEs and the surrounding uncertainties in a transparent and predictable manner, ensuring that patients' interests are safeguarded.

2. Build capacity among all stakeholders

Assessing the value and limitations of novel clinical endpoints can be a daunting task for all stakeholders involved in delivering the best possible outcomes for patients. It is therefore necessary to set in place frameworks that enable stakeholders to be as effective as possible. HTA bodies, for example, could benefit from establishing a clear framework for the assessment of alternative clinical endpoints in different contexts. NICE UK has set up a Task Force to address this question, which is currently at work and could serve as an inspiration to Nordic HTA bodies.

Clinicians face ever more complex treatment decisions and may struggle to stay up to date with the latest research, regulatory decisions, and treatment guidelines. As a result, they may benefit from improved decision support mechanisms. PAGs

Figure 13: Key findings

Alternative endpoints are here tostay	Build capacity among all stakeholders	No one size fits all	Cooperation is key	Real world evidence evaluation
ACEs have the capacity to unlock innovation and get promising treatments to patients faster and are standard practice in clinical trials today. Stakeholders must rise to the challenge and establish the necessary framework to deal with ACEs in a transparent and predictable manner.	HTA bodies need a clear framework for the assessment of ACEs in different contexts. The ongoing NICE UK Task Force may be an inspiration. Clinicians may benefitfrom improved decision support mechanisms. Increased awareness of ACEs among PAGswill help them support patients more effectively	Patients have different priorities when it comes to their treatment. Alternative endpoints can accelerate clinical research, but their value varies by treatment setting, disease stage, and degree of correlation with other more established outcomes. Focus on settings with the most to gain from the use of ACEs	Consistency in decision-making provides predictability to patients and clear incentives for producers. Cooperation between regional HTA bodies to establish clear frameworks can reduce uncertainty to patients and producers. Cooperation between regulators and producers in the design of clinical trials is also essential.	Nordic countries have established uniquely valuable health registries with broad coverage and a high degree of data quality. They are in an ideal position to lead the way in the validation of alternative clinical endpoints using real-world data. Risk sharing agreements based on further evidence gathering can reduce uncertainty.

Notes: ACE: Alternative clinical endpoint. HTA: Health technology assessment. PAG: Patient group organisation.

have also reported that they do not always feel qualified enough to assess the value and limitations of alternative clinical endpoints. Capacity building programs aimed at PAGs could help make them more active participants in these discussions in the regulatory setting and more supportive partners to their patient members in the complex task of navigating treatment options.

3. No one-size fits all

Patients have different priorities when it comes to their treatment and their preferences cannot be summarized in a single measure of the likelihood of survival. Clinical trials now incorporate multiple primary and secondary endpoints, broadening the amount of information provided by each study. These outcomes have different significance to different patients, there is no one-size fits all.

Meanwhile, alternative endpoints can accelerate clinical research, though their value varies by treatment setting, disease stage, and degree of correlation with other more established outcomes. So, where should the work on establishing clear frameworks for the assessment of alternative endpoints start? We propose to focus on the disease settings and patient populations with the most to gain from the use of alternative endpoints. This may include areas in which the relationship between a given alternative endpoint and overall survival is clearly established, or in which the evidence based on alternative clinical endpoints is overwhelming, and thus where uncertainty is small. This may also include areas in which uncertainty is higher but the potential value of using alternative endpoints is also very high, such as the curative setting, in which waiting for overall survival evidence may be impractical.

4. Cooperation is key

Consistency in decision-making over time and across borders provides predictability for patients and clear incentives for producers. A consistent approach across the Nordic countries can be achieved by increased cooperation between regional HTA bodies in establishing clear frameworks for what kinds of evidence will be considered acceptable, and what degree of uncertainty will be tolerated.

This common framework can then inform the development of future clinical trials in closer cooperation with pharmaceutical companies.

5. Real world evidence evaluation

Documenting improvements in terms of overall survival has become challenging for clinical trials in many cancer settings. While there is a consensus that alternative endpoints provide useful information in a research setting, the implications of some of these endpoints for patients are not always as clear. In some situations, this uncertainty can be reduced by using real-world evidence to further assess novel treatments and validate new endpoints.

Nordic countries have established uniquely valuable health registries with broad coverage and a high degree of data quality, especially when it comes to the specialist healthcare services. They are therefore in an ideal position to lead the way in the validation of alternative clinical endpoints using RWE. Post-marketing studies have also the potential to reduce the amount decision uncertainty that reimbursement bodies face, facilitating access to patients and limiting risks.

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Appendix

About the user panel

The Norwegian Cancer Society's user panel was established in 2016 and is an electronic panel consisting of 1 400 cancer patients, previous cancer patients, caregivers and bereaved. The user panel is used to collect cancer patients' and caregivers' knowledge and perspectives on various topics. The participants receive 8-10 survey questionnaires per year. Participants are continuously recruited through the Norwegian Cancer Society's website, social media, advertisements, or through various events. Participants must update their information every year. The Norwegian Cancer Society processes personal data in line with the Personal Data Act and the requirements set by the Norwegian Data Protection Authority. Key results from the Cancer Society's user panel are presented in Figure A 1-Figure A 4)

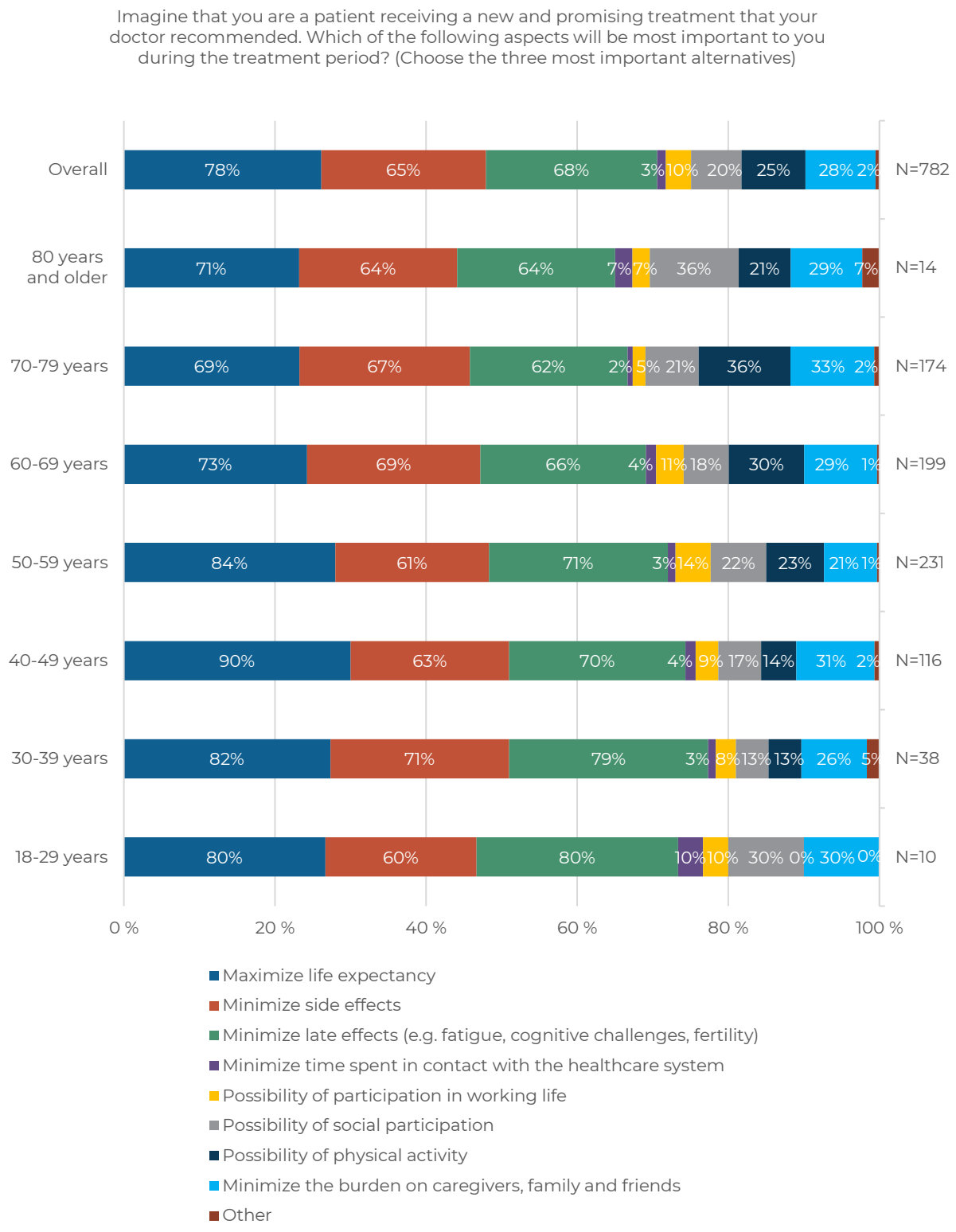
Respondents

The survey was sent to a total of 1 416 people, of whom 56,6 percent responded. Among those who answered the survey there is a larger share of women (64%) than men (36%). In comparison, data from Nordcan show that among those having or have had cancer in Norway, 46,5 percent are women and 53,5 percent are men [28].

Most (79%) respondents are 50 years or older. When it comes to education level, 30,4 percent state that they have completed primary school or high school as their highest completed education, while the rest have completed higher education at university or college. 36,8 percent state that they have completed higher education of up to four years, while 32% state that they have completed higher education of four or more years. According to Statistics Norway 37% of the population has completed higher education [29]. The respondents in this survey have a somewhat higher level of education than the general population in Norway.

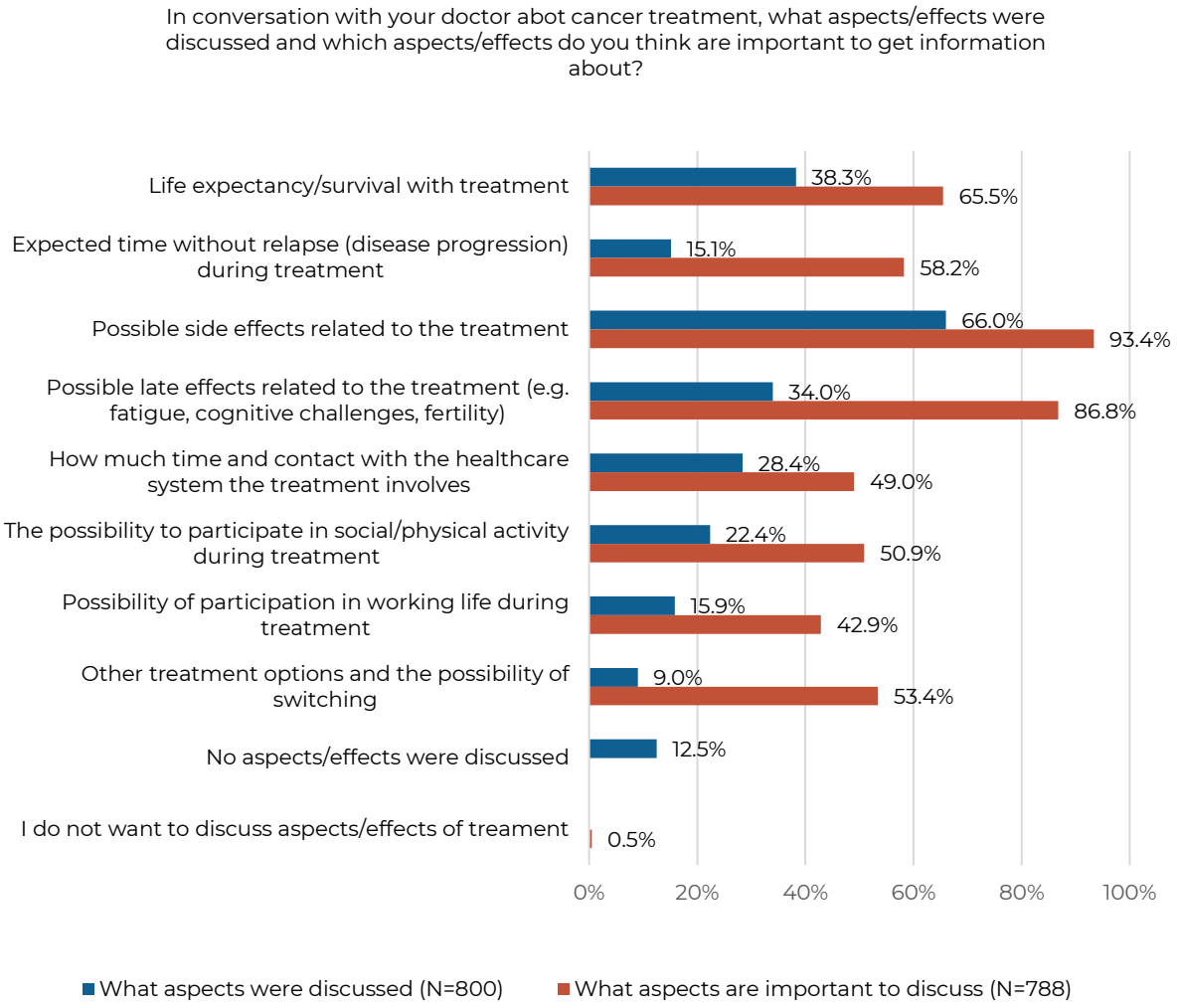
The survey was conducted in Norwegian, and all questions and answers have been translated into English in this report.

Figure A 1: Valued aspects of cancer treatment



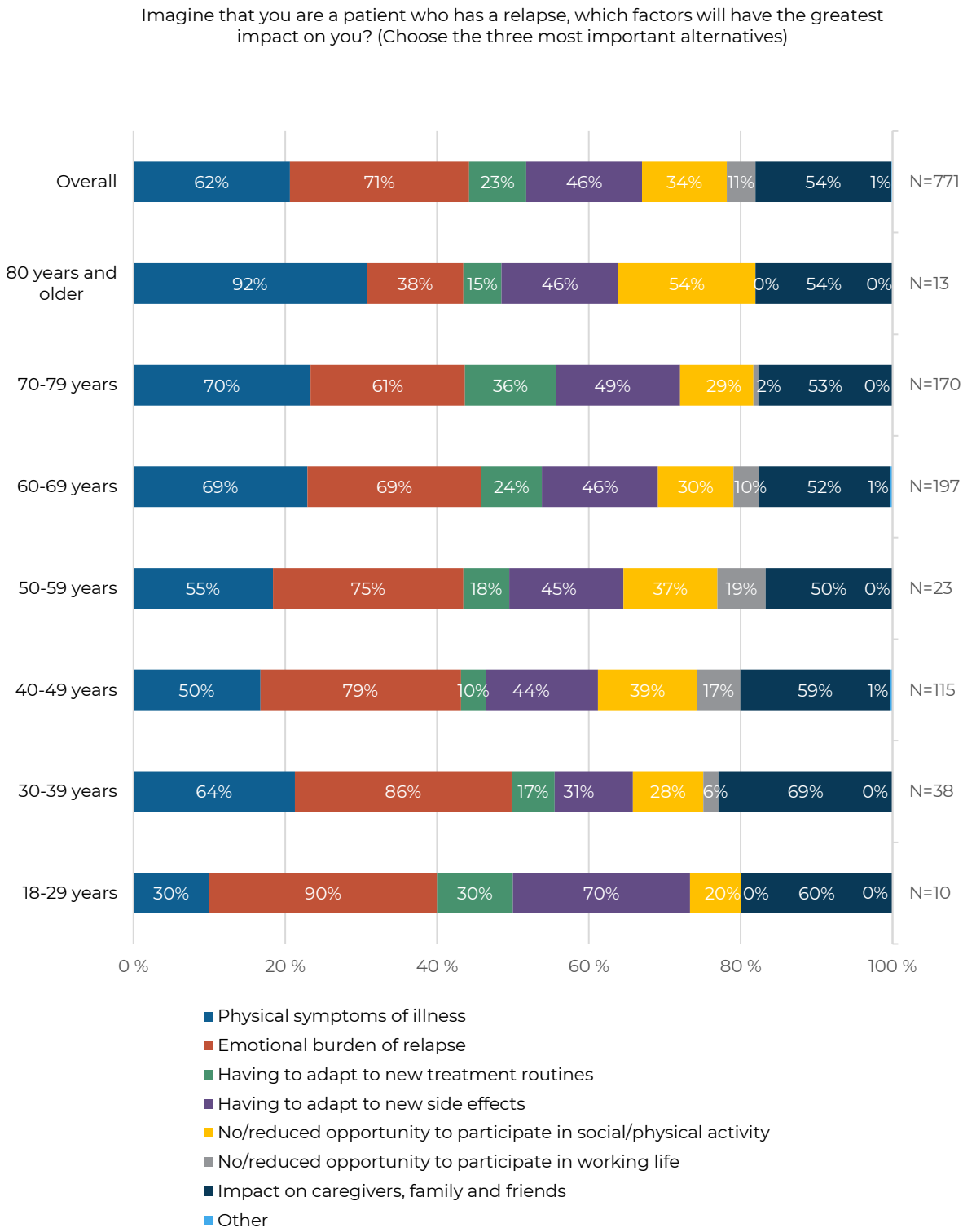
Source: The Norwegian Cancer Society's user panel

Figure A 2: Which information do patients (wish to) receive?



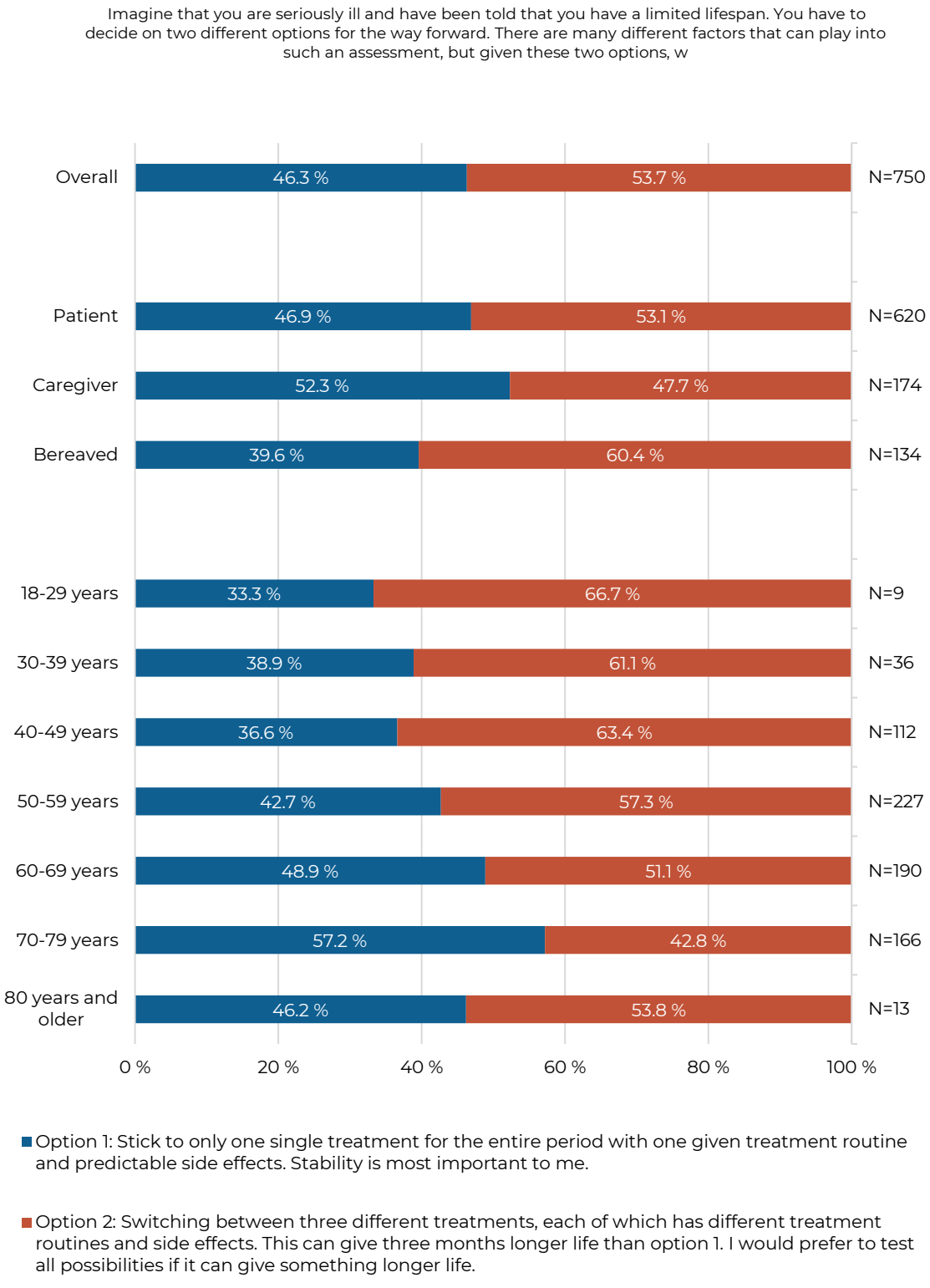
Source: The Norwegian Cancer Society's user panel

Figure A 3: Burden of a relapse



Source: The Norwegian Cancer Society's user panel

Figure A 4: Stability vs. trying every possibility



Source: The Norwegian Cancer Society's user panel

"There should be a longer expected lifespan before agreeing to something unpredictable. It is not the length of life that matters, but the quality of life"

"Side effects can significantly impair quality of life and the ability to engage fully, in addition to being a burden for the family and caregivers. I would be willing to try everything to extend my life as much as possible, but not at any cost."

"I am 80 years old and have come to terms with the fact that the end may be near. I prefer quality in the time that remains. However, when I was 64 and diagnosed with cancer, I might have considered option 2"

"Difficult choice. Quality of life is important here. It doesn't help to live longer if those 3 months are filled with side effects and low quality of life. At the same time, one wants as much time as possible with loved ones."

"I have young children. Any extra time I can spend with them matters. Hope is also important. Perhaps new medications are on the way that I could potentially participate in testing."

"Willing to try anything – the treatment could potentially yield valuable results for others, even if it may not benefit me personally."

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