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**STEERING COMMITTEE FOR HUMAN RIGHTS IN THE FIELDS OF BIOMEDICINE AND HEALTH (CDBIO)**

# DRAFT WHITE PAPER ON EQUITABLE AND TIMELY ACCESS TO APPROPRIATE INNOVATIVE TREATMENTS AND TECHNOLOGIES IN HEALTHCARE

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# 1. Introduction

## 1.1. Background and context

Article 3 of the Convention on Human Rights and Biomedicine requires Parties, taking into account health needs and available resources, to take appropriate measures with a view to providing, within their jurisdiction, equitable access to health care of appropriate quality.

Equitable access should be interpreted in accordance with the meaning provided in Article 3 and clarified in paragraph 25 of its Explanatory Report. In this context, equitable access means first and foremost the absence of discrimination on any ground. Equitable access also implies that, depending on their medical needs and the available resources, individuals should be guaranteed access allowing them to effectively obtain a satisfactory degree of care. This involves removing barriers that may prevent access and providing appropriate support to individuals or groups who may be disadvantaged or exposed to a higher risk of harm to their health. In accordance with the Right to the protection of health enshrined in Article 11 of the European Social Charter (revised), the ultimate goal is health equity – i.e., the absence of avoidable, unfair, or remediable differences among groups of people – where ideally everyone should have a fair opportunity to attain their full health potential and no one should be disadvantaged from achieving this potential.

The principle of equitable access also applies to innovative treatments and technologies. In this regard, the Strategic Action Plan (2020-2025) emphasises that it is essential that these are made available in an equitable and timely manner. The intention was to elaborate a Recommendation on equitable and timely access to innovative treatments and technologies in healthcare systems. In the light of the Covid-19 pandemic and the ethical considerations concerning access to vaccines as a scarce resource, the Committee on Bioethics (DH-BIO) agreed, at its 17th plenary meeting (3-6 November 2020), to develop guidelines to promote equitable access to vaccines and to treatments and equipment. Considering the evolutions in vaccine development, the DH-BIO agreed to first prepare a Statement on Covid-19 and vaccines: Ensuring equitable access to vaccination during the current and future pandemics, which was issued on 21 January 2021. At its 18th plenary meeting (1-4 June 2021), the DH-BIO subsequently agreed to develop guidelines on equitable access to treatments and equipment in a context of scarcity, focusing on critical products the scarcity of which could cause serious harm to patients. These guidelines were included in Recommendation CM/Rec(2023)1 on equitable access to medicinal products and medical equipment in a situation of shortage, adopted on 1 February 2023.

At its 2nd plenary meeting (2-4 November 2022), the Steering Committee for Human Rights in the Fields of Biomedicine and Health (CDBIO), which took over the responsibilities of the DH-BIO, initiated work on Equitable and timely access to innovative treatments and technologies in the healthcare system. At its 3rd plenary meeting (6-9 June 2023), the CDBIO discussed the Concept note on equitable and timely access to innovative treatments and technologies in healthcare (CDBIO/BU(2023)8), noting the factual elements that challenge the decision-making process at the national level. These elements include that clinical evidence supporting safety and efficacy is often limited, making the evidence-based decision-making process uncertain. Other factors relate to the problem of affordability due to high prices charged by manufacturers and, more generally, to the need for an overall assessment of the clinical value and appropriateness for patients in the context of the healthcare system. The CDBIO noted that the scope of the work potentially includes a wide variety of healthcare products, processes, and medical procedures, and supported keeping a high-level strategical view on the issue, not limiting the scope of the work to the case of expensive medicinal products. It was also noted that the term innovative does not necessary endorse benefits for patients and can raise unrealistic expectations. The CDBIO agreed that Recommendation CM/Rec(2023)1 already covers most issues related to equitable access to innovative treatments and technologies. The Committee agreed therefore not to prepare a new draft

recommendation but to work on a discussion paper to assess any outstanding ethical issues relevant to innovative treatments and technologies to be taken into account when designing the process. The discussion paper should examine how the general and procedural principles of Recommendation CM/Rec(2023)1 apply to the decision-making processes ensuring equitable access to innovative treatments and technologies. It should also map and briefly analyse the work done by other international organizations such as the WHO, OECD, and the EC to avoid duplication, taken into consideration that the paper should take a human rights patient focus approach.

At its 4th plenary meeting (14-17 November 2023), the CDBIO discussed the draft discussion paper on Equitable and timely access to appropriate innovative treatments and technologies in healthcare. The draft discussion paper indicates that the general and procedural principles included in the articles of Recommendation CM/Rec(2023)1 are applicable also to access to innovative treatments and technologies. It also points out that, considering the specific characteristics of innovative treatments and technologies, some principles may be especially relevant or may raise challenges for their application. Delegations welcomed the draft discussion paper, the analysis carried out, and the summary of the work done by other international organisations. Delegations agreed on entrusting the drafting group to continue the work by elaborating a white paper including further information, analysis, and examples. The scope of the work should be extended beyond innovative treatments and technologies intended for severe or life-threatening health patient conditions, and should consider a broader range of patients' health conditions as long as the safety and efficacy of the innovative treatments and technologies concerned are supported by scientific evidence. In addition, the European Court of Human Rights jurisprudence should be considered, particularly for cases regarding experimental treatment. The white paper could also include considerations of the possible tensions created by innovative treatments and technologies between individual rights and public health needs and the long-term perspective of decision-makers choices. At its 5th plenary meeting (11-13 June 2024) the DH-BIO examined the outline of the draft white paper on equitable and timely access to appropriate innovative treatments and technologies in healthcare.

## 1.2. Importance of equitable and timely access to appropriate innovative treatments and technologies

Equitable and timely access to innovative treatments and technologies is crucial for addressing health inequities and ensuring that all individuals, regardless of socio-economic status or other social determinants of health, can benefit from advancements in healthcare. The importance of equitable access to innovative treatments and technologies is highlighted by **three critical considerations**.

First, ensuring that advances in healthcare truly benefit everyone is **a moral imperative and a human rights concern**, which can be alternatively grounded in the Right to the highest attainable standard of health (International Covenant on Economic, Social and Cultural Rights), the Right to the protection of health (European Social Charter), and the Right to equitable access to healthcare (Convention on Human Rights and Biomedicine). This means that everyone should have the opportunity to obtain a satisfactory standard of care, taking into account health needs and available resources. Within the context of achieving universal health coverage (UN Sustainable Development Goal, Target 3.8), access to the full range of essential health services, medicinal products, and health technologies should be provided, without causing financial hardship. As innovative treatments and technologies have the potential to transform, if not revolutionise, healthcare and drastically improve health outcomes, it becomes crucial to ensure that no one is excluded from their benefits. Innovative treatments and technologies may be particularly important in addressing complex, chronic, and life-threatening conditions, leading to earlier and more accurate diagnoses, and new interventions that can stop the progression of disease, offer long-term survival benefits, and in some cases, provide cures for previously untreatable diseases. However, without access to these

innovations in healthcare, individuals may continue to suffer from preventable diseases, delayed diagnoses, and deteriorating health conditions that could have been managed or treated more effectively.

Second, innovative treatments and technologies **may hold significant potential to reduce health inequities** by enabling more proactive, preventive, and tailored approaches to healthcare, compared to more traditional methods. Since disadvantaged populations often face higher rates of preventable diseases, delayed diagnoses, untreated medical conditions, and interruptions in ongoing treatments, these new pathways in prevention, diagnosis, and integrated care management could bring the greatest benefits to them. Moreover, when properly implemented and supported by efforts to bridge the digital divide, innovative technologies can create new care delivery models that may further reduce health disparities. For instance, telemedicine can enable remote consultations, diagnoses, and treatments for individuals in rural, hard-to-reach, or underserved areas, where healthcare services are often scarce. This may help eliminating geographical barriers to medical care that may have otherwise been unavailable. Additionally, wearable and implantable devices and health-tracking systems may allow continuous monitoring and personalised interventions for chronic conditions such as diabetes and heart disease. These technologies may provide more timely care for patients with limited access to healthcare services, helping to mitigate some of the most pressing healthcare inequities.

Third, several social determinants that directly influence the ability of individuals to obtain timely and appropriate healthcare, such as income, education, geographical location, and social support networks, play an even more critical role in determining access to innovative treatments and technologies. Innovative treatments and technologies are often expensive, depend on advanced infrastructure and highly specialised healthcare professionals, and require a high level of health literacy. Consequently, individuals who are already struggling financially, those living in rural or underserved areas with limited access to specialised healthcare services, and those with lower education levels and limited social support networks essential to understand the value of new treatments and technologies and to navigate complex healthcare systems, are at risk of being excluded from the advantages of medical innovations. Without comprehensive policies aimed at improving the availability, affordability, and accessibility of innovations in healthcare, **there is a real risk of exacerbating health inequities**. This concern is particularly relevant in light of the principles outlined in **Recommendation CM/Rec(2023)1**, which focuses on equitable access to medicinal products and medical equipment in a situation of shortage. Failing to address these barriers can lead to discrimination based on factors such as socioeconomic status, geographical location, and educational and literacy levels. Disadvantaged populations, who often already face barriers to healthcare, could see their exclusion worsen, deepening existing inequities. Importantly, the Recommendation also highlights the need for prioritisation based on medical criteria and the removal of barriers for systematically disadvantaged individuals in situations where innovative treatments and technologies are in short supply. Without targeted interventions, only the more privileged individuals, with the necessary financial resources, knowledge, and social support, will benefit from these medical innovations. As a result, rather than mitigating health disparities, innovative treatments and technologies risks perpetuating and exacerbating them.

## 1.3. Potential benefits and risks of innovative treatments and technologies in healthcare

Innovative treatments and technologies in healthcare present a broad range of benefits as they may improve diagnostic and treatment capabilities, patient care and outcomes, and efficiency and productivity in healthcare processes.

Innovative technologies offer the potential for more precise, timely, and individualised care, through tools such as precision medicine, genomic profiling, pharmacogenomics, and AI-based diagnostic platforms. These technologies allow treatments to be better tailored to a

patient's unique health profile, offering more targeted and effective interventions. Additionally, advancements in predictive analytics, genetic screening, and real-time health monitoring allow earlier detection of risks and diseases, and a more preventive and proactive approach to healthcare. AI-powered diagnostic tools may enhance both the speed and accuracy of disease detection and enable healthcare professionals to make informed decisions faster. Moreover, advancements in minimally invasive techniques, including robotic surgery and neurotechnology, may provide new ways to treat complex conditions with greater precision, reducing recovery times and complications. Furthermore, AI-assisted systems may help reduce medical errors in diagnosis, prognosis, and treatment planning, enhancing overall safety and improving patient outcomes.

Innovative treatments and technologies may also improve patient care and outcomes in different ways. For instance, telemedicine platforms, along with wearable devices and remote monitoring systems, may facilitate continuous care and rapid responses to health changes, even outside traditional clinical settings. Telemedicine platforms may allow patients in rural or underserved areas to access specialist consultations, diagnoses, and follow-up care without the need for in-person visits. In addition, mHealth and bioelectronic implantable devices may empower patients to have more control of their health by giving them access to real-time information and by improving chronic disease management and adherence to treatment plans. Advances in certain directions, for instance in the fields of gene editing, immunotherapy, antiviral therapy, and regenerative medicine, are pushing the boundaries of what is possible in healthcare, leading to cures for previously untreatable conditions and groundbreaking treatments, that can stop the progression of disease or offer long-term survival benefits.

Innovative treatments and technologies also hold the potential to significantly enhance efficiency and productivity in healthcare by streamlining diagnostic and treatment processes. Tools such as AI-assisted medical imaging analysis, predictive analytics for assessing disease risks, and remote patient monitoring systems can lead to faster and more accurate diagnoses and interventions, which can save valuable time and resources in patient management. Additionally, innovative treatments and technologies can lead to more targeted and timely interventions, reducing the need for frequent consultations and extended hospital stays, while also minimising complications and recovery times. This can in turn decrease the burden on healthcare facilities, reduce healthcare costs for both patients and providers, and allow healthcare professionals to treat more patients efficiently and with higher precision, increasing the overall capacity of healthcare systems to meet growing demands. Moreover, big data and AI may contribute to accelerating medical research and innovation by analysing vast and complex datasets, enabling the identification of new therapeutic targets, a deeper understanding of disease mechanisms, and the development of more advanced treatments and technologies, which could result in more effective and timely healthcare solutions for patients and more efficient and responsive healthcare delivery.

While innovative treatments and technologies in healthcare offer significant benefits in enhancing diagnostic and therapeutic capabilities, improving patient care and outcomes, and increasing efficiency, it is essential to remain aware of the limitations and risks they present. As these innovations move from the experimental stage to clinical application, challenges such as limited clinical evidence, lack of large-scale trials, and concerns about generalisability across diverse populations complicate the assessment of their long-term safety, efficacy, and potential superiority over conventional treatments, requiring ongoing evaluation and monitoring. In addition, issues such as disparities in access, data privacy and security concerns, scalability of solutions, potential over-reliance on technology at the expense of human judgment, the tendency to prioritise novel solutions over traditional treatments and technologies that may be equally or more effective, and the costs associated with implementing such advancements must be addressed to fully realise the potential of these innovations. This white paper will explore these limitations and risks in greater depth, with a particular focus on ensuring equitable access.

## 1.4. Scope and objectives of the white paper

This white paper focuses on the challenges related to equitable and timely access to appropriate innovative treatments and technologies in healthcare.

The scope of the white paper encompasses both innovative treatments and technologies that may or may not be intended for severe or life-threatening health patient conditions. The white paper is restricted to innovative treatments and technologies of which the safety, efficacy, and quality are supported by scientific evidence, and which have been approved or certified through an appropriate regulatory process provided for by law. It does not consider experimental treatments and technologies.

The primary objective of the white paper is to explore the key barriers to equitable and timely access to appropriate innovative treatments and technologies in healthcare and to identify potential solutions based on guidance of the Council of Europe and other international organisations. Importantly, the white paper also examines the possible tensions between individual rights and public health needs when adopting innovative treatments and technologies, including insights from relevant case law of the European Court of Human Rights, as well as offering a long-term perspective on how decisions could be made by healthcare policymakers in accordance with the right to equitable access to healthcare.

# 2. Definition and characteristics of innovative treatments and technologies in healthcare

## 2.1. Definition

**Innovative treatments and technologies** refer to **treatments and technologies that adopt approaches which depart significantly from conventional medical practices**. They incorporate cutting-edge scientific discoveries and breakthroughs in engineering, with the aim of providing new therapeutic possibilities and better quality of healthcare. Innovative treatments and technologies have advanced through the various stages of research and development and have obtained regulatory approval for at least some specific indications or applications. In some cases, these treatments and technologies may already be available as standard treatment options.

**Experimental treatments and technologies** also use innovative approaches, but they are **still in the phase of research, development, or clinical evaluation**. These treatments and technologies might involve unknown risks and their effectiveness is often uncertain. Patients typically receive experimental treatments and technologies as participants in clinical trials, when existing treatments and technologies are either unavailable or ineffective. Access may be determined by different actors and subject to other criteria than those that apply to innovative treatments and technologies.

**Differentiating** between experimental and innovative treatments and technologies **may be complex**. For instance, with respect to certain treatments and technologies (e.g., immunotherapy, regenerative medicine, and neurotechnology), the boundaries between experimental and innovative may be dynamic, as these treatments and technologies may have received approval for certain uses while at the same time being evaluated for expanded indications and applications or for additional patient populations in the future. In should also be noted that, whereas some innovative treatments and technologies may be available in some countries, they may still be considered experimental or may not be available in other countries. This may be related to differences in regulatory approval processes, healthcare infrastructure and resources, national health priorities, and socio-cultural factors.

**Box I: Illustrative overview of innovative treatments and technologies**

This overview highlights the wide range of innovative treatments and technologies that are currently applied in healthcare. These technologies may either be integrated directly into therapeutic applications or function as stand-alone interventions.

**Precision medicine**, or personalised medicine, tailors healthcare to individual patients on the basis of their genetic and molecular profile, lifestyle, and environment to maximise therapeutic benefits and minimise adverse reactions. Precision medicine includes targeted cancer therapies, BRCA1 and BRCA2 gene testing, genomic profiling of tumours, and **pharmacogenomics (PGx)**, which explores how the patient's genetic profile influences their response to medications, and helps in selecting medication, determining the optimal dosage, or considering alternative treatment.

**Regenerative medicine** refers to innovative approaches to regenerate, repair, or replace damaged or diseased organs, tissues, and cells with a view to functional recovery and healing. Most regenerative medicine that is currently available is not innovative, but part of the established field of transplantation. In some fields established and in other innovative are bioscaffolds (i.e., an artificial structure implanted in the body to support tissue growth), used in orthopaedics, dentistry, cardiology, wound healing, and plastic and reconstructive surgery.

**Gene editing** is a medical approach to treating monogenic or polygenic disorders that involves replacing a defective gene with a healthy copy of that gene, manipulating or inactivating a defective gene, or introducing a missing gene. CRISPR-Cas9 is a modern technique that does not introduce new genetic material into a cell but employs molecular tools to make precise edits or corrections to the existing genetic material in the cell. Gene editing has clinical applications in, for instance, inherited retinal dystrophy, spinal muscular atrophy in infants, and certain types of blood cancers such as acute lymphoblastic leukaemia and non-Hodgkin lymphoma.

**Immunotherapy** is a treatment that is used to boost the immune system to target and destroy cancer cells, or to suppress the immune response to manage autoimmune diseases. Checkpoint inhibitors are used in the treatment of melanoma, lung cancer, and bladder cancer. In addition, monoclonal antibodies are used to treat autoimmune diseases such as Crohn's disease and rheumatoid arthritis, and CAR T-cell therapy is used to treat acute lymphoblastic leukaemia and non-Hodgkin lymphoma.

**Nanomedicine** focuses on using nanotechnology (i.e., involving the engineering of ultrafine particles between 1 and 100 nanometers in diameter) to diagnose and treat diseases at the molecular and cellular level. Nanoparticles can be functionalised with drugs to allow delivery of medications to specific cells or tissues, overcoming biological barriers, and release of medications in a controlled way. Nanomedicines have been approved for use in progressed ovarian cancer and metastatic pancreatic cancer. Nanoparticles are also used as contrast agents in medical imaging techniques to enhance visualisation of tissues, and used in biosensors to identify biomarkers for cancer detection.

**Artificial Intelligence** refers to systems that display "intelligent" behaviour by analysing their environment and taking actions to achieve specific goals. AI is often based on machine learning, which allows the predictive algorithms to learn from experience and automatically improve their performance, and which increasingly takes the form of "deep learning" models, composed of multiple layers of processing which allow the AI system to learn representations of data with multiple levels of abstraction so as to progressively refine predictions for accuracy. AI is used for automation of hospital processes, for remote patient monitoring, in machine vision embedded in robot-assisted surgery, for acceleration of drug discovery, in chatbot-based patient interactions, in personalisation of treatment plans, and in predictive algorithms based on self-learning to assist in interpreting medical imaging and predicting clinical outcomes.

**Neurotechnology** in healthcare refers to the application of neuroscience and technology to monitor, understand, diagnose or modulate neural activity with the aim to improve neurological and mental health conditions. Neuroimaging technologies are used to visualise brain activity to diagnose neurological disorders. Neuromodulation technologies can be non-invasive or invasive. They involve the targeted electrical or magnetic stimulation of specific brain regions to modulate neural activity, and are used to treat Parkinson's disease, dystonia, essential tremor, depression, migraine, and chronic pain. Additionally, brain-Computer Interfaces (i.e., computer-based systems that translate brainwave signals into commands that are communicated to an external device) are being developed to allow individuals with neurological and neuromuscular conditions to control prosthetic limbs, computers, or assistive technologies.

**Digital therapeutics (DTx)** refer to interventions that use digital technology to prevent, treat or manage health conditions, in conjunction with more conventional treatment. They are software-based, are delivered through wearables (mHealth), smartphone apps or web-based tools, typically collect real-time data, personalise interventions on the basis of user data and preferences, may be interactive, and can be integrated with healthcare systems and remote monitoring models that allow continuous management of patient status.

**Point-of-care (POC) diagnostics** refer to diagnostic tests conducted at the site of patient care, rather than in a traditional laboratory setting. These diagnostics are designed to provide rapid results to assist in immediate clinical decision-making. These include **biosensors** (i.e., devices that integrate a biological component with a physicochemical detector to detect and measure specific biological markers, such as glucose biosensors to manage insulin doses in diabetes) and biomarker tests, such as cardiac biomarker tests to diagnose heart attacks and rapid infectious disease tests.

**Telehealth** refers to the use of telecommunication and digital platforms to provide healthcare services remotely. Telemedicine is a subset of telehealth, involving remote clinical consultations, diagnoses, counselling, and follow-up care using real-time video conferencing. In addition, telehealth also encompasses services such as telesurgery, remote patient monitoring, "store and forward" (i.e., a method allowing healthcare providers to forward medical data or images for specialist review and timely diagnosis), and the use of electronic health records and digital health platforms to securely storage, access, and exchange patient information.

**Robotics** are used in healthcare in a variety of applications. Robot-assisted surgery allows surgeons to perform complex surgeries with minimal invasiveness and increased accuracy and control, resulting in reduced complications and faster recovery. Robotics exoskeletons and devices can help in rehabilitation by improving movement of patients with neurological conditions or mobility impairments, and assist healthcare providers in moving patients and minimise physical strain. In addition, robots can be used in telehealth to allow remote medical consultations, they can enable patients to longer maintain their independence at home, and they can be used to provide companionship and emotional support to patients.

**3D printing technology** is used in the healthcare context mainly to create customised medical implants, prosthetic limbs, orthotic devices, and braces tailored to the anatomy and the medical needs of the patient. 3D printing can also be used to produce models of patient anatomy to organise preoperative planning and the simulation of surgery, and to print specialised surgical instruments for complex surgeries.

## 2.2. Characteristics

### 2.2.1. Common characteristics

As compared to conventional treatments and technologies, innovative treatments and technologies (See Box I for an illustrative overview) have certain **characteristics that are different or more pronounced**.

#### a. Complexity

Innovative treatments and technologies in healthcare are inherently complex, often involving new mechanisms of action and advanced systems. Many innovative treatments, such as gene editing, immunotherapies, and regenerative medicine, operate through novel biological mechanisms. For instance, gene editing techniques such as CRISPR-Cas9 allow for precise modification of the genome by targeting specific genetic defects, which is radically different from conventional treatments that aim to alleviate symptoms rather than modify genetic material. Immunotherapies leverage the body's own immune system to recognise, target, and destroy cancer cells, which represents a fundamental departure from conventional therapies such as chemotherapy and radiation, which indiscriminately attack both healthy and cancerous cells. Regenerative medicine focuses on repairing or replacing damaged tissues by using the body's own healing capacity or using advanced biological materials, instead of managing symptoms or slowing disease progression. Furthermore, technologies such as robot-assisted surgeries, AI-driven diagnostic tools, and nanomedicine involve the integration of complex software and hardware systems that require highly specialised technical and clinical knowledge.

#### b. Multidisciplinarity

Innovative treatments and technologies rely on the convergence of knowledge and expertise from diverse fields such as medicine, biology, (bio)engineering, and information technology. This multidisciplinary collaboration is essential for the successful development and application of innovative treatments and technologies, as it allows for the integration of different perspectives that advance breakthroughs in patient care, and enables the incorporation of novel treatment methods, advanced diagnostic tools, and sophisticated data analysis techniques. This multidisciplinary approach can accelerate the pace of innovation and enhance the potential to address complex healthcare challenges more effectively.

#### c. Limitations in establishing effectiveness

As innovative treatments and technologies move from the experimental stage to clinical application, several challenges arise in establishing their effectiveness. One significant limitation is the lack of robust clinical evidence, as many innovative treatments and technologies are still in the early phases of use, with limited long-term data on their safety and efficacy. The absence of comprehensive studies and large-scale clinical trials makes it difficult to determine the durability of therapeutic benefits, identify potential side effects, and assess whether these innovations are superior to conventional approaches. This limitation complicates the validation process for regulatory authorities and healthcare professionals, posing obstacles to fully endorsing innovative treatments and technologies as viable alternatives. Furthermore, early trials often target narrow patient groups, raising concerns about the generalisability of results across diverse populations. The complexity and novelty of innovative treatments and technologies add to the difficulty in assessing their long-term impact, making continuous monitoring of evidence essential to ensure their safe and effective integration into healthcare.

#### d. Fragmented responsibility

The development, implementation, and management of innovative healthcare treatments and technologies typically involve multiple stakeholders, leading to fragmented responsibility.

These stakeholders may include researchers who drive scientific discoveries, biotech firms that translate these discoveries into market-ready solutions, hardware manufacturers and software developers who create the necessary technological infrastructure, data scientists who process and interpret large datasets, and healthcare professionals applying these innovations in clinical settings. Additionally, regulatory bodies are responsible for overseeing these innovations, ensuring they meet rigorous standards of safety, quality, and efficacy. This division of roles, while necessary for advancing complex innovations, can make it difficult to assign clear accountability when issues arise, such as serious adverse events or reactions.

#### e. Shift towards personalised healthcare

Innovative treatments and technologies are leading a shift towards personalised healthcare, where therapies are tailored to the unique genetic makeup, molecular profile, lifestyle, and environmental factors of each patient. This approach, driven by advances in genomics, artificial intelligence, and novel therapeutic techniques, aims to improve treatment accuracy and reduce adverse effects. In some fields, such as oncology, personalised approaches are already being successfully implemented, particularly through therapies targeting receptors, while in other areas, they remain aspirational. As a result, the timeframe for adopting personalised healthcare varies widely between treatments, with some still in early clinical stages and others advancing rapidly. For instance, precision medicine uses whole genome sequencing and pharmacogenomics to identify genetic predispositions to diseases and optimising medication choices and dosages for individual patients. AI also plays a vital role in the personalisation of treatments by analysing vast data sets to provide more accurate diagnoses and personalised treatment plans. While the personalisation of healthcare holds significant promise, it comes with challenges, including high costs and the need for sophisticated healthcare infrastructures.

### 2.2.2. Notable characteristics of selected innovative treatments and technologies

In addition to the general characteristics that distinguish innovative treatments and technologies from conventional ones, some innovative treatments and technologies also possess notable features that may pose challenges in assessing their quality, safety, and efficacy, or raise new or more pronounced ethical concerns.

#### a. Irreversibility of effects

Some innovative treatments and technologies introduce irreversible effects that are broader and more profound than those of conventional treatments, which are often reversible or more localised in their impact. Once administered or applied, these innovative treatments and technologies lead to permanent, systemic changes at a fundamental biological level, with little to no possibility of reversing the patient's condition to its pre-treatment state. For instance, gene editing techniques like CRISPR-Cas9 and immunotherapies such as CAR T-cell therapy operate at the genetic and molecular levels, aiming to fundamentally alter biological processes. These interventions can result in permanent changes to how genes express themselves or how the immune system functions. Similarly, neurotechnologies such as deep brain stimulation, which involves implanting electrodes in the brain to modulate neural activity, may have the potential to induce long-term or even permanent alterations in brain function.

#### b. Opacity

Due to their novelty, complexity, or lack of transparency, some innovative treatments and technologies introduce a significant level of opacity. This makes it challenging for healthcare professionals and regulatory bodies to fully understand their mechanisms and potential implications, potentially leaving patients uncertain about their treatments. For instance, AI-driven diagnostic systems often operate as "black boxes" because their decision-making processes, based on complex, self-learning algorithms, are not easily interpretable or validated by clinicians, which can result in hesitancy in fully trusting AI-generated findings. Similarly, treatments such as gene editing and immunotherapy introduce novel mechanisms of action that may not be fully understood, particularly with regard to unintended effects and

long-term outcomes. Often, healthcare professionals may need to rely on external experts or cutting-edge research to interpret complex data or struggle to stay up to date with rapid advancements in the field, which can create knowledge gaps and erode confidence in the safety, efficacy, and quality of these innovations.

### c. Commercial stakeholder involvement

The introduction of some innovative treatments and technologies has resulted in a significant expansion of commercial stakeholder involvement in healthcare, including tech firms, data companies, and social media platforms. This increased involvement raises concerns about potential conflicts of interest, commercialisation of health data, and external influence on treatment choices. For instance, data companies may have a commercial interest in the health data they store and analyse. Large tech firms and social media platforms entering the domain of healthcare may drive healthcare professionals and patients towards technology-heavy solutions, potentially sidelining more traditional treatments and technologies that may be equally or more effective. This shift risks creating a technology-driven bias in healthcare delivery. In addition, these stakeholders can contribute to media hype and to the marketing of unproven therapies and technologies, fuelling unrealistic patient expectations and creating societal pressure on regulators to fast-track approvals.

### d. Big data

The rise of innovative treatments and technologies has made big data a central component of modern healthcare. The integration of big data involves the collection, storage, and linking of various types of datasets, such as electronic health records, genetic data, lifestyle data, and real-time patient monitoring, across diverse platforms and devices. The applications of big data are expanding rapidly, with the goal of enabling more efficient, proactive, and personalised approaches to patient care. Big data allows a transition towards precision medicine, where treatments are tailored to each individual based on their unique genetic and lifestyle profiles, leading to earlier detection of diseases, more accurate treatment plans, and better forecasting of health outcomes. A key advantage of big data is its ability to support real-time monitoring through wearable devices and sensors, providing continuous oversight of patient health outside of the clinical setting, allowing for quicker interventions and better management of chronic conditions. Additionally, big data facilitates predictive analytics, which can identify high-risk individuals before serious health issues arise, further advancing the shift from reactive to proactive healthcare. However, the extensive use of big data also introduces ethical concerns around privacy, transparency, and the potential for discrimination. The involvement of third parties, such as pharmaceutical companies, tech firms, and insurance providers, raises the risk of misuse of sensitive health information, highlighting the need for robust data protection measures.

### e. Digital integration

Many innovative treatments and technologies depend heavily on the digital integration and connectivity of healthcare systems, representing a paradigm shift in healthcare delivery and management, called Health 4.0. Digital integration in healthcare refers to the increasing use of interconnected digital tools, platforms, and technologies, such as electronic health records, telemedicine, wearable devices, remote patient monitoring, cloud-based platforms, and AI-powered diagnostic tools. These tools enable faster data processing, better communication, and improved collaboration between healthcare professionals, contributing to more efficient and coordinated healthcare management. This digital transformation also promotes a more integrated, personalised, and real-time approach to patient care, allowing for the identification of new treatment pathways and enabling more proactive, preventive, and customised interventions. This marks a departure from traditional, reactive models of care that often rely on slower diagnostic processes and generalised treatments, shifting towards a data-driven model of care that empowers healthcare professionals and patients to make better-informed and timely treatment decisions based on comprehensive patient data.

### f. Innovative care delivery models

In addition to the broader trend toward more proactive, preventive, and personalised care, innovative treatments and technologies related to big data and digital integration are driving the emergence of new care delivery models. A key example is telemedicine, which enables healthcare professionals to provide remote consultations, diagnoses, and treatment recommendations via digital platforms. This reduces the need for in-person visits, improving access to healthcare, particularly in rural or underserved areas. The COVID-19 pandemic further accelerated this shift, as telemedicine became essential when face-to-face consultations were limited. Another component of these innovative care models is continuous health monitoring through wearable devices and remote patient monitoring systems. Devices like fitness trackers, heart rhythm monitors, and blood glucose sensors can be integrated into healthcare systems, enabling real-time tracking of vital signs and health metrics. This data can be shared with healthcare professionals, allowing for more personalised and timely interventions, which is especially beneficial in managing chronic conditions like diabetes and heart disease.

> For example, cardiac patients can be given the option to use remote heart monitors, which are fitted with sensors attached to the skin to detect heart rhythm and electrical activity. This reduces the need for frequent hospital visits, as any significant abnormalities are immediately flagged to hospital staff, allowing for prompt intervention such as adjusting medications or, in more serious cases, fitting pacemakers or cardiac defibrillators.

### g. Technological integration with human body

Some innovative treatments and technologies are reshaping the relationship between technology and the human body, as devices and therapies not only interact with but increasingly integrate into biological systems. For instance, neurotechnologies are being developed to interface with the brain, modulating neural activity to improve cognitive and motor functions, with more experimental applications including brain-computer interfaces enabling individuals to control external devices, such as prosthetics or computers, using their brainwave signals. In addition, bioelectronic medicine merges biology and electronics by developing implantable devices that use electrical impulses to modulate nerve signals, aimed to restore or adjust normal physiological functions in chronic conditions such as diabetes and arthritis. In the field of regenerative medicine, innovations such as bioscaffolds, which are artificial structures that provide a framework for tissue growth and are gradually absorbed by the body, are being used in wound healing, surgeries, and orthopaedics.

### h. Access to mental states

Some innovative technologies are starting to offer unprecedented insights into cognitive functions and emotional states that were previously inaccessible or difficult to measure or treat. For example, neuroimaging technologies allow healthcare professionals to visualise brain activity and gain deeper understand of how emotions and cognitive processes, such as decision-making or memory, are influenced by specific brain regions or changes in neural connectivity. Other neurotechnologies, such as deep brain stimulation, are being used to alter brain function, potentially offering treatment for conditions like Parkinson’s disease, severe depression, and obsessive-compulsive disorder. Additionally, virtual reality is being used to access and treat conditions such as phobias, anxiety, and post-traumatic stress disorder by immersing patients in controlled environments where therapists can tailor treatment in real time based on their emotional and cognitive feedback.

# 3. Challenges related to assessing quality and superiority

Innovative treatments and technologies introduce significant complexities into healthcare decision-making, particularly due to their evolving nature and the uncertainties surrounding their long-term safety and efficacy. These challenges are crucial, as Article 3 of the Convention on Human Rights and Biomedicine emphasises the need for equitable access to healthcare of "appropriate" quality, meaning care that meets "a fitting standard in the light of scientific progress". Difficulties in assessing safety and efficacy and whether these innovations offer improvements over the existing standard of care make the validation process more complex for regulatory authorities and healthcare professionals. This section will examine these challenges, focusing on the potential barriers they present to ensuring access to innovative treatments and technologies.

## 3.1. Quality and superiority of innovative treatments and technologies

Evaluating the safety, efficacy, and potential advantages of innovative treatments and technologies is challenging due to a range of factors.

### 3.1.1. Limited availability of robust clinical evidence

A major difficulty is the limited availability of robust clinical evidence. Many innovative treatments rely on cutting-edge technologies that are still in the early stages of clinical application, meaning that long-term data on their safety and efficacy are often limited. Comprehensive studies are necessary to evaluate their effectiveness, to monitor their long-term effects, and to assess how they perform in broader clinical applications. Additionally, many of these treatments lack large-scale clinical trials and reliable longitudinal data, which are crucial for identifying the durability of therapeutic benefits and the potential for side effects, and for comparing these novel therapies to established diagnostic or treatment standards. This lack of robust data may make it difficult to determine whether these novel treatments are superior or even equivalent to more conventional treatment options. This may complicate efforts for regulatory agencies, reimbursement authorities, and healthcare professionals to validate these treatments and fully endorse them as viable alternatives to conventional treatments.

### 3.1.2. Concerns about generalisability of findings

Innovative treatments often encounter challenges in generalising their findings across diverse patient populations, as early clinical trials are typically conducted in controlled settings and focus on highly specific patient groups. These trials frequently lack sufficient representation of key demographics, such as women, older persons, ethnic minorities, or patients with rare diseases or pre-existing conditions, resulting in unequal treatment outcomes when applied in real-world clinical settings. This issue is especially relevant for innovative therapies, where treatment responses may be influenced by both intrinsic factors (e.g., genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction) and extrinsic factors (e.g., factors associated with the environment and the cultural background of the person). Since, for instance, differences in drug metabolism are well-documented across ethnicity, gender, age, and genetic variations, treatments that are introduced in the absence of large-scale, inclusive trials, may be less effective or even harmful for underrepresented populations. To promote equity in healthcare, it is essential to expand the diversity of clinical trial participants so that they more accurately reflect the diversity of real-world populations. This inclusive approach ensures that innovative treatments are safe and effective for all patient groups, avoiding the risk that certain groups disproportionately benefit from these advancements, thereby perpetuating or even exacerbating health inequities.

### 3.1.3. Algorithmic bias

AI systems used in healthcare have the potential to significantly improve clinical decision-making, but they also introduce the risk of algorithmic bias, particularly when these systems rely on imbalanced or incomplete datasets. Clinical trials and medical datasets historically lack adequate representation of certain populations, such as women, older adults, ethnic minorities, and people with rare diseases. When AI systems are trained, tested, or validated on such skewed data, the resulting algorithms may deliver biased outcomes, in that underrepresented groups risk being misdiagnosed or presented with less effective or even harmful treatments recommendations, in this way reinforcing health inequities. Mitigating algorithmic bias requires ongoing efforts to ensure that the datasets used for training AI systems are inclusive and representative of diverse populations and that AI systems are evaluated and monitored for biases in their outcomes through bias benchmarking frameworks and have diverse teams assessing data quality.[i] Additionally, improving the transparency and explainability of AI models is essential for enabling healthcare professionals to understand how AI-derived recommendations are generated, assess the appropriateness of suggested treatments, and detect potential risks of bias and risks of discrimination. These measures are crucial to ensure that the benefits of AI-based medical technologies are accessible to all patient populations and do not unintentionally reinforce or exacerbate existing health inequities.

### 3.1.4. Impact of external factors in assessing quality

During the initial phases of introducing of novel treatments or technologies, assessing their effectiveness and comparing them to existing alternatives can be complicated by external factors such as marketing hype, media interest, and patient advocacy, all of which can create unrealistic or misleading expectations. Companies developing these innovations often employ aggressive marketing strategies, framing their products as revolutionary breakthroughs, even when limited clinical data are available to support these claims. This may create a perception among patients and healthcare professionals that newer technologies are automatically superior to traditional treatments, despite a lack of robust data. Media outlets play a crucial role in amplifying this hype by focusing on promising early-stage clinical trials or experimental therapies, using headlines that fails to capture the nuanced reality of the medical evidence. This narrative can foster unrealistic expectations, presenting these innovations as definitive solutions to complex medical issues, even when substantial gaps in data still exist. Additionally, patient advocacy groups, while essential in promoting patient rights and pushing for timely access to promising treatments, may push for accelerated access to treatments based on anecdotal success stories or preliminary trial results. Their efforts, while well-intentioned, may lead to increased pressure on regulatory bodies to approve or reimburse treatments before there is sufficient evidence of their safety and long-term benefits. The combined influence of these external pressures can result in premature approvals or rushed adoption of treatments that have not yet undergone thorough evaluation, potentially leading to adverse patient outcomes or inefficient allocation of healthcare resources.

### 3.1.5. Difficulties in determining professional standards

As outlined in Article 4 of the Convention on Human Rights and Biomedicine, interventions in the health field must always be carried out in accordance with relevant professional obligations and standards. In this regard, the Explanatory Report clarifies that the professional standard is determined by the current state of the art and, “in following the progress of medicine, it changes with new developments and eliminates methods which do not reflect the state of the art.”[ii] Due to the rapid pace of advancements and the evolving nature of medical practice, healthcare professionals increasingly face challenges in determining whether an established treatment or technology has been superseded by an innovative one, prompting a shift in the standard of care. This challenge may be compounded by the limited availability of robust clinical evidence, as well as concerns regarding the generalisability of clinical findings across diverse patient populations, leaving healthcare professionals struggling to assess their actual

benefits for individual patients. Deciding when to integrate new treatments and technologies into healthcare practice is made even more complex by the potential implications for professional liability and regulatory compliance, as healthcare professionals must carefully navigate shifting standards of care while balancing the risks and benefits for their individual patients.

When it comes to aligning with professional standards based on the best interests of patients, the implementation of AI in healthcare introduces unique challenges, primarily due to the lack of transparency, explicability, and reproducibility. AI-models that function as “black boxes” may deliver highly accurate results but make it nearly impossible for healthcare providers to understand the rationale behind their decisions, impairing the ability to assess the appropriateness of AI-generated treatment recommendations and to detect potential errors and biases. As a result, healthcare professionals might either rely too heavily on AI or dismiss it altogether, both of which can negatively impact patient care. While the adoption of any new technology results in a loss of skills (deskilling) and simultaneously requires the acquisition of new skills (upskilling), the rapid adoption of AI technology in healthcare poses a particularly significant risk. Healthcare professionals might become over-reliant on AI recommendations without fully understanding the underlying medical reasoning, which could potentially lead to a decline in critical thinking and diagnostic skills over time. To mitigate these risks, it is crucial to carefully manage the transition to AI-enabled healthcare. Clear guidelines and regulations must be established for the development and use of AI systems, ensuring that these systems are rigorously validated through clinical trials and subject to regulatory standards to guarantee their safety and reliability. It is also essential to support and empower healthcare professionals during this transition, promote minimum standards for information and explainability in AI systems, and ensure that AI in healthcare is governed by meaningful human control. Furthermore, healthcare professionals should retain the discretion to distance themselves from or challenge AI system outputs when uncertainty arises, thereby preserving their core clinical skills while acquiring the necessary technological expertise.[iii]

## 3.2. Complexity in decision-making

The difficulties related to evaluating the safety, efficacy, and potential superiority of innovative treatments and technologies make decisions about their availability and prioritisation especially challenging. This process is made even more challenging as additional factors related to the distinctive nature and broader impact of these innovations must also be carefully considered.

### 3.2.1. Difficulties in balancing individual and public health interests

The availability and prioritisation of innovative treatments and technologies can significantly impact both individual patient outcomes and broader public health. Advanced therapies, such as CAR-T cell therapy, gene editing, or immunotherapies, have the potential to greatly enhance or even save the lives of patients with serious conditions, especially when conventional treatments have failed. For these patients, access to groundbreaking therapies can mean the difference between life and death, making the decisions about their availability and prioritisation highly impactful. However, these decisions come with challenges. Some treatments, such as gene therapies or nanomedicine, may have far-reaching, unforeseen public health impacts, even when their benefits for individual patients would be clear. Additionally, decision-making is further compounded by the high cost of many innovative treatments and technologies. Healthcare systems must balance the immediate needs of patients with serious or life-threatening health conditions against long-term financial sustainability. This introduces an ethical dilemma: how to ensure access for those in need without overburdening the system or limiting future access to innovations. Moreover, given the complexity and technicality of these treatments, decision-making must involve a diverse group of experts from various disciplines. While interdisciplinary collaboration is essential, it also introduces additional layers of complexity. Stakeholders such as healthcare professionals, patient advocacy groups, regulatory bodies, and pharmaceutical companies often have

conflicting priorities, which can complicate the decision-making process. For instance, while healthcare professionals focus on clinical outcomes and patient safety, patient advocacy groups may prioritise rapid access to potentially life-saving treatments. Regulators, on the other hand, must ensure that these therapies meet safety and efficacy standards before they are made widely available.

### 3.2.2. Difficulties in defining what is "reasonable"

Defining what is "reasonable" in granting access is particularly difficult in the context of innovative treatments and technologies, due to evolving evidence, scientific uncertainty, diverse stakeholder views, and potential for future improvements. According to Article 10 of Recommendation CM/Rec(2023)1 on equitable access to medicinal products and medical equipment in a situation of shortage, access to medicinal products and medical equipment, and their prioritisation, should be guided by the best available evidence. This evidence should rely on parameters that are relevant, measurable, clear, objective, and consistent. However, compared to more established therapies, this poses distinct challenges for innovative treatments and technologies, as they often lack a robust body of evidence regarding their safety and effectiveness. This shortage of data, further complicated by the ongoing nature of clinical trials and the uncertainty surrounding long-term outcomes, creates difficulties in constructing sound arguments for their integration into healthcare systems and in determining the prioritisation of patients. Additionally, innovative treatments and technologies can be highly complex and novel in their mechanisms of action, making it difficult for decision-makers to fully understand their benefits, risks, and long-term implications. Moreover, confronted with the rapid pace of innovation, decision-makers must frequently revise their arguments about what is reasonable in order to incorporate new evidence and newly emerging treatments, technologies, and applications.

In addition, what is "reasonable" may be different depending on the perspectives of the different stakeholders. Patient advocacy groups and the public, influenced by media coverage and heightened expectations, may have different views on what is relevant and fair in terms of access, particularly when the treatments offer life-saving or life-changing potential where no alternative exists. This divergence in views can complicate the decision-making process, making it difficult to maintain a balanced, evidence-based approach. Furthermore, when assessing the reasonableness of an innovative treatment, especially one that initially offers limited benefits, it may be essential to consider its future potential. Some therapies that initially offer modest benefits, such as a few weeks of life extension in oncology, may later evolve to provide significantly improved outcomes as clinical experience grows. This dynamic nature of innovation requires a flexible and forward-looking approach in policymaking to accommodate the potential future value of treatments.

### 3.2.3. Challenges in maintaining consistency in policies of access

The principle, outlined in Article 12 of Recommendation CM/Rec(2023)1, that policies that define and implement priority-setting standards should be applied in a consistent way is also essential in the context of innovative treatments and technologies. The consistent application of policies based on predetermined criteria helps to prevent discrimination, promotes transparency in decision-making and, in this way, enhances trust in the healthcare system and decision-makers, enables the effective allocation of scarce healthcare resources, and provides predictability for patients and healthcare providers. However, the principle of consistency may be more challenging in the context of innovative treatments and technologies as compared to the context of more conventional treatment and technology, considering that policies may need frequent and ongoing adaptation in the light of rapid technological advancements and a changing evidence base. The policies that define and implement priority-setting standards should be designed to prevent corruption, arbitrary exceptions, access on the basis of financial means, activities such as lobbying, and political interference. This becomes particularly relevant in the context of innovative treatments and technology, where rapid access can be a matter of life and death. Patients, their families, and patient advocacy

groups may intensify lobbying efforts to secure approvals, reimbursements, or exceptional access to novel treatments.

### 3.2.4. Need for additional stakeholder involvement

According to Article 11 of Recommendation CM/Rec(2023)1, the process of determining access to medicinal products and medical equipment, as well as their prioritisation, should be inclusive to ensure that the views of all parties affected by these decisions are taken into account. While meaningful engagement is important for medicinal products and equipment, it becomes even more critical in the context of innovative treatments and technologies, as their introduction may have an impact on a broader and more diverse range of stakeholders. Unlike conventional treatments, these innovations often involve complex scientific advancements, incorporating cutting-edge scientific discoveries, breakthroughs in engineering, and digital tools that require collaboration across multiple disciplines, such as medicine, engineering, and data science. Input from a wide range of experts, clinicians, patients, and ethicists is necessary to evaluate the benefits, risks, and implications of these treatments, particularly in light of the uncertainties, evolving evidence, and rapid advancements in this field.

Moreover, innovative treatments and technologies can have far-reaching societal implications beyond their clinical applications. These therapies often raise more complex ethical, legal, and societal questions than conventional treatments. For example, discussions about the prioritisation of access to life-saving innovations, such as gene therapies or nanomedicine, can be more contentious, particularly when they involve potential impacts on future generations. Additionally, advanced treatments may raise healthcare budget concerns that are either non-existent or less prominent in conventional treatments. Public engagement is also crucial, not only to address these concerns but because biomedical advancements might more fundamentally impact public trust in biomedicine than conventional treatments and technologies. This may require gathering data on how different groups are affected by priority-setting decisions and identifying disparities that necessitate adjustment of policies.

However, fostering inclusiveness in the decision-making process also presents challenges. The diversity of stakeholders complicates efforts to ensure that all relevant perspectives are adequately represented. Additionally, ensuring that non-experts, including patient groups, have a meaningful say in the decision-making process will be resource-intensive and demanding. Significant efforts are required to educate these groups, considering the complexity, rapidly evolution, and potentially contentious nature of innovative treatments and technologies. Substantial efforts are also needed to inform these stakeholders about the available evidence and manage public expectations, while educating them on the nuances of the decision-making process. This inclusiveness requires careful coordination and transparent communication between diverse groups. Despite these challenges, providing all stakeholders, including patients, with a meaningful voice in the decision-making process is crucial for the development of balanced and fair policies. This inclusiveness also helps ensure that decisions are part of a broader deliberative democratic process, involving all groups who may bear the consequences. Public dialogue, as recommended in the Guide to public debate on human rights and biomedicine, offers a useful model for fostering this engagement and ensuring that the scientific, societal, an ethical dimensions of innovative treatments and technologies are appropriately addressed, making decision-making more transparent and equitable

# 4. Challenges related to equitable and timely access to appropriate innovative treatments and technologies

## 4.1. Affordability

The most significant barrier to accessing innovative treatments and technologies is often their high cost. While some innovations, such as mHealth applications and telemedicine, are relatively affordable and can even help reduce overall healthcare expenses, many advanced treatments remain prohibitively expensive for the majority of patients. Once these innovations receive market authorisation, access largely depends on the reimbursement policies in place in the healthcare system. For most patients, decisions about access to these innovations are therefore made at an earlier stage, when it is decided what treatment or technology will be reimbursed, as compared to conventional treatments, where access is often determined through priority-setting mechanisms. If a decision is made not to cover an innovative treatment or technology through public health insurance, access becomes virtually unattainable for the majority of patients. This creates a major disparity in access between patients with many financial means and those with limited financial means, reinforcing and exacerbating existing health inequities.

> Examples of innovative treatments and health technologies that are extremely expensive include gene therapies (e.g., Zolgensma as a gene therapy for spinal muscular atrophy in infants may cost more than €2 million per treatment; Luxturna as a gene therapy for inherited retinal dystrophy costs €850,000 per eye), CAR T-cell therapies (e.g., Kymriah and Yescarta as therapies for acute lymphoblastic leukaemia and non-Hodgkin lymphoma cost several hundreds of thousands of euros per treatment), immunotherapies (e.g., Keytruda and Opdivo as immunotherapies for melanoma and lung cancer can cost more than €100,000 for a year's treatment), precision medicine (e.g., Lynparza as a precision treatment for advanced ovarian and breast cancers with specific genetic mutations has a cost exceed €100,000 per year), and many treatments for rare diseases.

Several factors contribute to these high prices, including high development and production costs, expensive clinical trials and regulatory approval procedures, intellectual property considerations, the level of competition, market demand, and profit margins that are informed by the expected long-term cost savings offered by these treatments and the "willingness to pay" of individuals and society as a whole. The primary factor contributing to the high price is the market analysis, which is often not transparently connected to the proposed price. Since for most patients availability will depend on the reimbursement policies that are in place in the healthcare system, removal of financial barriers may in the context of innovative treatment and health technology need to involve optimisation of reimbursement policies and control of costs.

### 4.1.1. Principles in regulating financial coverage

Given the potential of innovative treatments and technologies to significantly improve health outcomes or even save lives, it is strongly recommended that national competent authorities thoroughly evaluate these innovations for their impact within healthcare systems. Based on the available clinical evidence regarding safety, efficacy, improvements over existing treatments, and cost-effectiveness, innovative treatments and technologies that have received market approval should, in principle, be considered for reimbursement, while carefully balancing available resources and other healthcare priorities. Doing so would promote equitable access to advanced therapies, while maintaining high standards of care and the sustainability of the healthcare system.

In the process of decision-making on reimbursement, several considerations are important, in line with the principles outlined in Recommendation CM/Rec(2023)1. First, the time gap between regulatory approval and public health coverage for innovative treatments can significantly impact patient outcomes. Delays of one or two years are not uncommon, as

reimbursement policies often take time to implement following regulatory authorisation. However, such delays may prevent patients from accessing these treatments, even when they have been proven effective and approved for use. Streamlining the process for reimbursement after market approval is therefore essential to avoid bottlenecks in access and ensure that patients can benefit from new therapies in a timely manner.

Second, reimbursement decisions for authorised innovative treatments and technologies should be transparent. In accordance with Article 13 of Recommendation CM/Rec(2023)1, all stakeholders, including patients, healthcare professionals, and policymakers, should understand the criteria and rationale behind reimbursement decisions. Clear communication about how evidence is evaluated is essential to maintaining public trust and accountability, particularly when high-cost therapies are involved. Article 9 of the Recommendation also highlights the importance of clearly defining responsibilities in the decision-making process, ensuring that healthcare professionals and the public are informed about the entities responsible for making reimbursement decisions and those which be consulted to address concerns. This level of transparency is especially important for innovative treatments, where delays in coverage can mean the difference between timely access to life-saving therapies and further deterioration of patient health.

Third, healthcare professionals need easily accessible and regularly updated guidelines on the reimbursement status of innovative treatments, enabling them to offer their patients the most effective treatments without uncertainty or delay. Additionally, they should be aware of any conditions tied to reimbursement, such as patient eligibility criteria or specific health outcomes that must be met.

Fourth, reimbursement decisions should be based on the best available evidence, relying on relevant, measurable, clear, and objective criteria, as outlined in Article 10 of Recommendation CM/Rec(2023)1. National regulatory bodies should establish clear thresholds for clinical benefit, such as the effect size required for coverage, to ensure that only therapies with proven value are reimbursed. In cases where clinical benefits are marginal, such as a minor extension of life expectancy, the costs should be carefully weighed against the outcomes to determine whether reimbursement is justified. This evidence-based approach helps maintain the sustainability of healthcare systems while ensuring that patients have access to treatments with real, demonstrable benefits.

Finally, the reimbursement status of innovative treatments and technologies should be subject to regular review, in accordance with Article 14 of Recommendation CM/Rec(2023)1. As more data become available through ongoing clinical trials or real-world use, healthcare systems should adapt policies based on new clinical evidence, changes in pricing, or the availability of alternative therapies. Regular reviews ensure that patients receive the most up-to-date and effective care without unnecessary delays or gaps in access.

### 4.1.2. Controlling costs

#### a. Reciprocity for public investment

Faced with the high costs of many innovative treatments and technologies, growing calls emphasise that, in setting prices, pharmaceutical companies and manufactures should take into account the substantial public investment that underpins much of their development. The expertise and knowledge driving these innovations are often rooted in research that is conducted at publicly funded universities and by highly educated professionals whose education and training were in large part supported by public resources. Moreover, the development of these treatments and technologies frequently relies on data and information provided by the public, whether through participation in clinical trials or the use of healthcare services. Considering this significant public contribution, there is an expectation of reciprocity, where pharmaceutical companies and manufacturers should recognise the essential role of the public by adopting pricing strategies that reflect these investments, including by offering discounts or other mechanisms to ensure broader, more equitable access.

### b. Greater transparency

In addition, there are also increasing calls for greater transparency in the pricing of innovative treatments and technologies, especially in light of their rising costs. Stakeholders, including patient advocacy groups, policymakers, and healthcare professionals, argue that the lack of transparency in how prices are set makes it difficult to assess whether these innovations truly offer value for money. A key concern is the confidentiality of price negotiations and agreements between pharmaceutical companies and public or private healthcare insurers, which often leaves the public and even some decision-makers unaware of the actual costs and of the discounts being offered. While confidentiality is sometimes justified to protect sensitive business information or to allow for flexible pricing arrangements, critics argue that it can lead to inequitable access and create disparities across different regions or countries. To address these concerns, many advocate for a more transparent approach to price setting, where the methodologies and justifications for pricing are clearly disclosed. This increased transparency would help ensure that prices reflect the actual value of the treatment, enhance accountability, and build public trust, while still safeguarding the necessary confidentiality in certain aspects of the negotiation process.

### c. Mechanisms to control costs

Apart from these general considerations, several mechanisms have been proposed for governments to control the costs of very expensive innovative treatments and technologies, thereby improving access. These mechanisms include implementing a system of reference pricing, negotiating innovative payment models such as managed entry agreements, fostering international cooperation in Health Technology Assessment to streamline evaluation processes, and promoting public-private partnerships to distribute the high development costs between public institutions and private companies.

**(1) Reference pricing**

A tool proposed to enhance the affordability of innovative treatments is reference pricing, where healthcare payers (such as government agencies, public health bodies or insurers) base the price of a new treatment on the cost of comparable treatments that are already available. This approach aims to control the pricing of high-cost innovative treatments, especially when there is uncertainty about their long-term effectiveness or value for money. In a reference pricing model, the price of an innovative treatment is compared to a benchmark price set by existing treatments that offer similar therapeutic benefits. By using this framework, governments can ensure that the price of new treatments remains in line with the value they deliver, preventing companies from charging excessively high prices simply due to the novelty of their treatments. Reference pricing also helps promote price transparency and accountability, as it forces pharmaceutical companies to justify why their innovative treatment should be priced significantly higher than existing alternatives. The system of reference pricing also encourages manufacturers to improve the cost-effectiveness of their treatments, knowing that they will be benchmarked against similar products. Since reference pricing can limit the financial impact of introducing expensive treatments, healthcare systems will be more able to provide access to cutting-edge treatments without overwhelming their budgets. This is particularly useful for healthcare systems operating under tight budgetary constraints, as it prevents them from overpaying for new treatments that may not offer significantly better outcomes than the alternatives. The model of reference pricing can be particularly effective when combined with other cost-containment measures, such as managed entry agreements.

**(2) Innovative payment models: managed entry agreements**

Managed entry agreements between healthcare payers and pharmaceutical companies provide a flexible framework in which payment for a new treatment is tied to specific criteria, helping to manage the high upfront costs that are often associated with these

treatments. Financial-based managed entry agreements focus purely on managing financial risk without considering clinical outcomes. These agreements help healthcare payers manage the budgetary impact through mechanisms such as price discounts, rebates, price-volume agreements, or expenditure caps. For instance, manufacturers may offer a predetermined discount on the list price of a treatment, or a rebate may be triggered once a certain usage threshold is met. In some cases, the price may decrease as the volume of the drug administered increases, or an expenditure cap may be set, ensuring the manufacturer provides the remaining doses for free or refunds the difference if spending exceeds this cap. These financial safeguards help prevent healthcare systems from bearing unsustainable financial burdens when adopting new, high-cost medical products. By contrast, outcomes-based managed entry agreements are tied to the clinical performance of the therapy, with reimbursement linked directly to the health outcomes in patients. In this model, payments are contingent on the real-world effectiveness of the treatment, and if the expected outcomes are not met, the manufacturer may provide refunds or adjust pricing accordingly. This approach reduces the financial burden on healthcare systems by only fully reimbursing therapies that are effective. Outcomes-based agreements are particularly useful when uncertainty exists about how a medicinal product will perform in real-world settings. Financial-based and outcomes-based elements can also be combined within a single managed entry agreement, providing flexibility to address both financial risks and clinical uncertainties and allowing for more efficient resource allocation.

Despite their advantages, managed entry agreements face significant challenges that limit their widespread adoption. Negotiating managed entry agreements can be complex and time-consuming, often involving high administrative burdens, detailed financial forecasting, and careful coordination between payers and manufacturers. A lack of consensus on how payments should be structured may further complicate these agreements. Outcomes-based managed entry agreements also require the collection of real-world evidence to assess treatment effectiveness, which adds complexity, as defining and tracking clinical outcomes is a resource-intensive process. Additionally, the confidential nature of these agreements, particularly regarding pricing terms, can reduce transparency and hinder comparisons across diverse markets. To overcome these challenges, a more standardised and transparent approach to managed entry agreements should be adopted to improve their effectiveness and encourage their broader adoption.

### (3) International cooperation in Health Technology Assessment

Fostering international cooperation in Health Technology Assessment (HTA) allows regulatory bodies to streamline processes, reduce duplication, and lower the costs associated with redundant reviews. By pooling resources, sharing expertise, and standardising regulatory and reimbursement requirements, countries can share the costs of HTAs, alleviating financial pressure on individual healthcare systems and making it easier to adopt innovative treatments without compromising financial sustainability. An example of this collaboration can be seen in the European Union's initiative for joint clinical assessments of health technologies, which harmonise the evaluation of newly developed therapies.[iv] This process reduces time to market and prevents duplication of efforts across member states. Smaller countries with limited HTA capacity can rely on assessments conducted by larger healthcare systems, allowing them to access innovative treatments more quickly and at lower costs. Harmonisation also prevents delays caused by separate national reviews, ensuring timely access to life-saving therapies for patients. By sharing the financial burden of HTA, international cooperation makes treatments more affordable and reduces disparities in the affordability of healthcare across different regions.

Sharing HTA results also improves the efficiency of decision-making, as it reduces the time and financial resources needed to bring effective treatments to the market.

Furthermore, cooperation strengthens the evidence base for evaluating new health technologies, especially those with uncertain long-term clinical outcomes or financial implications. By coordinating data collection and evaluations, countries can establish robust, internationally recognised standards for assessing the efficacy and safety of treatments. This allows healthcare systems to allocate resources to proven technologies while avoiding investments in those with insufficient value. Moreover, combining real-world data from diverse healthcare systems can further strengthen the evidence used to evaluate innovative treatments, as a broader assessment of performance is achieved, ensuring that only innovative treatments with significant clinical benefits are adopted. This reduces the risk of overspending on ineffective treatments, which is particularly important for therapies with limited or incomplete clinical trials. Additionally, countries can share best practices for designing and implementing managed entry agreements, linking payments to real-world performance, and ensuring that reimbursement decisions are based on strong evidence.

**(4) Public-private partnerships**

Public-private partnerships can help mitigate the financial risks and challenges by combining resources from public institutions, such as universities and public healthcare systems, with the expertise and investment capital of private pharmaceutical companies. These partnerships can play an important role in speeding up the development of cost-effective treatments, particularly for rare diseases, where traditional market dynamics may not result in sufficient investment. Through these collaborations, the high costs associated with research, development, and clinical trials are shared, reducing the financial burden on private companies and ensuring that public funds are used efficiently. For example, public institutions may provide access to scientific expertise, aggregate patient data, and research infrastructure, while private companies may bring investment capital, technological advancements, and strategies for commercialisation. This collective effort reduces inefficiencies, ultimately allowing treatments to reach the market at a lower price.

Public-private partnerships ideally include early agreements on pricing, intellectual property rights, and access so as to align public health objectives and the innovation incentives for private companies. This ensures that affordability is prioritised from the outset without undermining the commercial viability of the therapies. Public health bodies can negotiate pricing structures that reflect both the public health value of the treatment and the commercial interests of private companies, for instance by incorporating outcome-based managed entry agreements. By sharing both the risks and rewards of innovation, public-private partnerships help ensure that life-saving treatments are accessible to a broader patient population.

## 4.2. Availability and timely access

Innovative treatments and technologies also present unique challenges in terms of availability and timely access. Approval and reimbursement policies must strike a delicate balance between making groundbreaking treatments widely available, maintaining high standards of care, and ensuring the financial sustainability of the healthcare system. Delays in the regulatory approval process can significantly impact the timely availability of advanced therapies, leaving many patients waiting for care that could save or greatly improve their lives. Even after advanced therapies, such as CAR-T cell therapy and immunotherapies, have been approved and introduced on the market, they may remain prohibitively expensive for large segments of the population if reimbursement policies are not implemented swiftly and comprehensively. In regions where public healthcare systems lack sufficient funding or prioritise other areas of care, or where insurance policies do not cover these high-cost treatments, financial barriers may significantly delay or entirely block access. This creates a major disparity in access, disproportionately affecting lower-income and uninsured or underinsured populations. As indicated, these challenges can be mitigated by adopting more

transparent pricing strategies, fostering public-private partnerships, and implementing innovative approaches such as value-based pricing, where payment is linked to patient outcomes, and tiered pricing systems based on income or geographic factors. These efforts, combined with policies that promote timely approval and reimbursement, can help ensure that breakthrough therapies with proven effectiveness become more widely accessible, without compromising the sustainability of the healthcare system.

Innovative treatments and technologies also raise specific challenges due to the need for specialised infrastructure or highly trained healthcare professionals. Many advanced therapies require cutting-edge equipment and expert knowledge, which are typically concentrated in urban centres or well-resourced hospitals, making them difficult to access by individuals in rural, remote, and underserved areas. Patients living in these regions may need to travel long distances to reach these healthcare facilities, leading to delays in access and worsening health conditions. This geographic divide exacerbates existing healthcare inequities, as those living in underserved areas may be deprived of novel treatments that could drastically improve their outcomes.

Even when physical infrastructure is available, access to innovative treatments may still be restricted by a shortage of healthcare professionals with the specialised skills needed to administer these therapies. This creates a bottleneck in the healthcare system, where innovative treatments and technologies are technically available but cannot be delivered in a timely manner due to a lack of qualified personnel. Addressing these barriers requires significant investment in both infrastructure and human resources. Expanding and equipping healthcare facilities in underserved areas would help reduce the need for long-distance travel and improve equitable and timely access. In cases where the healthcare system cannot afford to expand specialised infrastructure beyond well-resourced urban hospitals, patients should be fully informed about these limitations and provided with guidance on how to timely access care at those centres.

Additionally, expanding training programs and providing opportunities for continuous professional development are crucial for enabling healthcare professionals to upskill and learn to effectively administer new, cutting-edge therapies. Offering incentives such as competitive salaries and improved working conditions could attract specialists to rural, remote, or underserved areas, further helping to reduce disparities in timely access to innovative healthcare. In some cases, innovative treatments such as immunotherapy could be made available in remote hospitals under the supervision and guidance of specialists working in larger centres. However, it should be noted that all investments in infrastructure and human resources for innovative treatments and technologies must be carefully balanced with other pressing healthcare priorities, ensuring that resources are allocated efficiently and equitably.

## 4.3. Accessibility

The issue of accessibility is particularly relevant in innovative treatments and technologies due to their complexity and the resources required to implement them. Many innovative treatments depend on access to reliable internet, digital devices, and specialised healthcare professionals, creating barriers for individuals in low-resource, rural, or remote areas. Additionally, limited health literacy and digital literacy may prevent certain populations from understanding and utilising these technologies, further exacerbating disparities in healthcare access.

### 4.3.1. Digital divide

With the rise of digital and data-driven healthcare technologies, a “digital divide” may emerge between individuals who have access to affordable digital devices and reliable high-speed internet services and those who do not. This digital divide can limit the ability of individuals in low-resource communities, as well as those living in rural or remote areas, to access technologies such as digital therapeutics (including mHealth apps), telehealth consultations, point-of-care diagnostics, and neurotechnology. This lack of access may delay diagnoses,

reduce treatment options, and exacerbate pre-existing healthcare inequities. For instance, during the COVID-19 pandemic, telemedicine proved invaluable in providing care remotely, yet patients without access to reliable internet or digital devices were unable to use these services, further deepening disparities in healthcare access. Moreover, digital therapeutics, such as apps designed for managing chronic conditions like diabetes, require stable internet access connections and smart devices to track health metrics, monitor symptoms, and adjust treatments in real time. Individuals without reliable internet or the necessary technology miss opportunities for early diagnosis, preventive care, and better disease management. This may create a significant gap in healthcare outcomes between individuals living in low-resource communities, rural or remote areas compared to individuals with consistent digital access.

Addressing this digital divide requires targeted efforts to promote equitable access to digital healthcare innovations. Investments in broadband infrastructure, particularly in rural, remote, and underserved areas, are crucial to enable telehealth consultations and other digital health services. Additionally, governments, private sectors, and healthcare organisations can collaborate to provide low-cost or subsidised digital devices for individuals who cannot afford them, while public-private partnerships or government subsidies should be implemented to ensure that affordable, reliable internet plans are available to all. By implementing these strategies, it is possible to bridge the digital divide, allowing more people to benefit from innovative healthcare technologies and ultimately improving health equity.

### 4.3.2. Limited health literacy

Access to innovative treatments and technologies can be significantly hindered by limited health literacy, which refers to an individual's ability to "access, understand, appraise, and apply information concerning healthcare, disease prevention and health promotion".[v] As highlighted in the Guide to Health Literacy, a lack of awareness about available healthcare services, and how to find and use them, poses a major challenge, preventing individuals from obtaining the care they need. This challenge becomes even more pronounced with innovative treatments and technologies, which often require access to up-to-date information about the latest medical developments, as well as the ability to understand complex treatment protocols, potential side effects, and instructions for follow-up care. Without these capabilities, patients might miss out on more proactive, preventive, and personalised approaches to healthcare that could significantly improve their health outcomes. In this way, limited health literacy is becoming an increasingly important social determinant of health.

With the rise of innovative treatments and technologies, there is a growing responsibility to structure healthcare services in a way that ensures that individuals can access and understand essential information, regardless of literacy levels. Public health initiatives can play a crucial role in raising awareness about new therapies and technologies, ensuring that information is provided clearly and accurately. Healthcare systems and professionals should provide comprehensible information, free of medical jargon and difficult terminology, to make health information accessible in a user-friendly way. To achieve this, they should actively involve individuals with limited health literacy in designing accessible systems. Furthermore, collaboration with community advocates and mediators can facilitate the translation of complex medical concepts into language that is easily understandable for populations with limited health literacy.[vi] Abilities to access and understand health-related information can be developed from a young age through the school curriculum. In addition, health literacy should be developed as a professional skill among healthcare professionals. This can be achieved by incorporating health literacy training into the curricula of higher education and postgraduate programs, focussing on equipping healthcare professionals with the necessary knowledge, skills, and attitudes to effectively communicate with individuals with limited health literacy.[vii]

In the context of the digital transformation of healthcare, digital health literacy (or e-health literacy) has emerged as an essential component of overall health literacy, encompassing the skills needed to access, interpret, and use digital health information and tools. However, disparities persist in the skills and resources required to engage effectively with these digital

platforms. Overcoming these barriers involves not only ensuring that individuals have access to necessary equipment, such as reliable internet access and smart devices, but also ensuring that they possess the digital competencies to use them. This can be particularly challenging, as digital healthcare technologies, such as telemedicine and digital therapeutics, often involve new and unfamiliar interfaces. For example, patients may struggle to use apps designed to monitor chronic diseases or lack the confidence to participate in remote consultations via telemedicine platforms. For digital health services to be truly inclusive, they should be easy to use and tailored to individual needs. Otherwise, the result would be a growing gap in healthcare access, excluding individuals who are not digitally literate from the benefits of modern healthcare technologies, reinforcing existing inequities.

## 4.4. Acceptability

The provision of health services, including innovative treatments and technologies, should be acceptable to patients, culturally appropriate, and sensitive to varying levels of educational attainment. Cultural beliefs and language barriers can profoundly shape how individuals perceive and accept innovative treatments and technologies. In some communities, traditional beliefs or deep-seated distrust of the healthcare system, rooted in historical injustices or previous negative experiences, can lead to hesitancy or even refusal of novel treatments such as vaccines, gene therapy, or advanced surgical procedures. This resistance not only limits access to promising healthcare innovations but also exacerbates existing health disparities, leading to poorer health outcomes in these populations.

Language barriers further compound these challenges, as they can impede effective communication between healthcare professionals and patients. Patients with limited proficiency in the dominant language may have difficulty understanding medical diagnoses, treatment options, or the potential risks and benefits of innovative therapies. Consequently, they may struggle to follow medical instructions, fully comprehend the value of treatments, or adhere to prescribed therapies. To address these cultural and language barriers, a multi-faceted approach is essential. Healthcare professionals need to be trained in cultural competence, which involves understanding and respecting diverse cultural beliefs while delivering care. Offering translation services, multilingual resources, and access to medical interpreters ensures that patients fully understand their treatment options and can make informed decisions. Additionally, culturally tailored healthcare campaigns, using the influence of community leaders or trusted cultural figures who share information in ways that align with patients' cultural values, have proven effective in increasing the acceptance of new treatments.[viii] Public health initiatives that adopt culturally relevant communication strategies can play a crucial role in closing the gap in access, reducing health inequities, and ensuring that language and cultural differences do not prevent individuals from benefiting from medical innovations.

# 5. Balancing individual rights and public health needs

When considering the introduction of innovative treatments and technologies, healthcare systems must rely on three principles to ensure that health outcomes are optimised while keeping costs manageable. The “benefit criterion” prioritises treatments in accordance with the expected benefit in extending the patient’s life and/or enhancing the patient’s quality of life. The “resource criterion” prioritises treatments that require fewer resources to achieve a benefit. The “severity criterion” prioritises treatments for more severe conditions in terms of risks of mortality and morbidity. These criteria must be carefully weighed against each other. The more severe the condition or the more extensive the benefit of the treatment, the more acceptable it is to allocate more resources. Conversely, giving priority to conditions with low severity and treatments with limited benefit can only be justified if resource use is low.

The basis for decision-making on introducing a new treatment is the estimated opportunity cost. This refers to the potential health benefits to other patients that could have been realised with the same resources. The opportunity cost is typically measured in quality-adjusted life years (QALYs). Many healthcare systems use an estimated opportunity cost to guide decisions about which treatments should be funded. This threshold represents the maximum amount a system is willing to spend to gain one additional quality-adjusted life year. Any new treatment must be assessed against this threshold to evaluate whether it delivers sufficient value. To that aim, the cost-effective ratio of the treatment is determined, which calculates the costs of the treatment in providing one additional quality-adjusted life year. This figure is then compared to the opportunity cost threshold to determine whether the treatment is cost-effective. If the cost-effectiveness ratio of a new treatment is below this threshold, it is considered cost-effective because the health benefits justify the expenditure. However, if the cost-effectiveness ratio exceeds the threshold, it is considered less cost-effective, as the same resources could potentially generate more health benefits if spent on other treatments. This approach ensures that the introduction of innovative treatments does not lead to the displacement of more cost-effective therapies, helping to maximise the overall health benefits achieved with the available resources.

Importantly, the cost-effectiveness ratio is adjusted based on the severity of the condition being treated, reflecting society’s willingness to prioritise patients with more urgent health needs and to accept a higher cost per additional healthy life year gained. When a treatment targets a life-threatening or highly debilitating condition, such as advanced cancer or severe genetic disorders, healthcare systems are typically more willing to accept a higher cost-effectiveness ratio, given the urgency and potential impact of these treatments. In contrast, treatments for moderately severe conditions are given moderate weight, and those for low-severity conditions are accepted only with a lower cost-effectiveness ratio. This flexibility ensures that patients with the most severe conditions receive necessary care, even if the treatment has a higher cost-effectiveness ratio and might otherwise be declined.

This becomes particularly important when evaluating expensive new treatments. Treatments that require fewer resources are generally prioritised, but this principle must be balanced with considerations of benefit and severity. For instance, a highly effective but expensive new treatment may be justified through a Health Technology Assessment if it addresses a severe, life-threatening condition. Conversely, to ensure that treatments for less severe conditions are still introduced without straining the healthcare budget, innovative treatments targeting these conditions should generally be priced lower.

When introducing expensive new treatments, several concerns may arise. First, an expensive treatment that consumes a significant portion of the healthcare budget may limit the healthcare system’s ability to treat other patients. In a system operating within a fixed budget, introducing such a new treatment will inevitably displace other services, potentially resulting in the loss of a certain number of QALYs in other areas. If the budget impact is large enough, not only could less effective treatments be replaced, but more cost-effective and beneficial ones could also be displaced. If these treatments are introduced without considering their total effect on the

healthcare budget and their practical challenges, such as retraining healthcare personnel or reallocating equipment, their benefit may be less than that of the displaced healthcare services. This may lead to a reduction in the overall number of healthy life years that the healthcare system can provide with its available resources and could undermine the principle of equitable access to healthcare for all patients. Therefore, the overall budget impact of an intervention must be factored into a broader discretionary assessment.

Second, when a treatment consumes a large share of the healthcare budget and it will be difficult to apply it across the entire relevant patient group. However, permanently limiting such a treatment to only a subset of patients may also be unreasonable, particularly if it is likely to offer more benefit, in terms of resource use and severity, than other available treatments. In such cases, a gradual introduction of the treatment may be necessary. This approach could involve offering the treatment initially to a specific subset of the patient group, such as those who are most critically ill or stand to benefit the most. As capacity increases, the treatment could then be extended to larger segments of the patient group. The conditions for such a phased implementation should align with the principles of priority setting, ensuring that treatments are first offered to patients with the most urgent medical needs and/or those who are likely to gain the greatest benefit.

Third, concerns over efficacy are particularly relevant when there is a limited evidence base, and these considerations should be carefully factored into prioritisation decisions. Provided that all other factors are equal, greater uncertainty regarding the efficacy or quality of a treatment should result in lower prioritisation. However, an important exception arises in the assessment of treatments aimed at small patient groups with extremely severe conditions. These groups are often too small to conduct large-scale clinical trials, making it difficult to perform HTAs comparable to those conducted for larger patient populations. In recognition of this challenge a less stringent requirement for documented evidence may be appropriate. The legitimacy and sustainability of this approach depend on ongoing monitoring to document both the efficacy of the treatment and any associated risks, which could then serve as a basis for re-evaluating the continued funding of these treatments under the scheme after a certain period of time. Such a framework ensures that, while flexibility is offered in cases of limited evidence, the long-term effectiveness and safety of treatments remain a priority.

# Appendix

## 1. The social determinants of health and promoting equitable access to healthcare

### 1.1. "Access to healthcare" as a social determinant of health

#### 1.1.1. Social determinants of health

**a. Definition**

A person's health status is determined by a wide range of personal, socio-economic, and medical factors. **Personal factors** include biological elements (e.g., genetics, age, sex), behavioural aspects (e.g., dietary habits, physical activity, smoking, alcohol consumption), and environmental influences (e.g., pollution, exposure to harmful chemicals or radiation). **Socio-economic factors**, also known as the **social determinants of health**, are defined by the WHO as "the conditions in which people are born, grow, work, live, and age, and the systems put in place to deal with illness".[ix] Examples include a person's income, employment and working conditions, education, social status, housing and living conditions, social support networks, social inclusion, discrimination (e.g., on the basis of gender, religion, political or other opinion, sexual orientation, ethnic background, legal status), access to social protection, and access to healthcare. **Medical factors** include the quality, timeliness, and efficacy of medical interventions used to improve the person's health.

**b. Characteristics**

The social determinants that give rise to, perpetuate, and exacerbate inequities in health are **complex** and are **interconnected** in a number of ways. First, the material circumstances in which people live have a direct impact on their health.[x] For instance, poverty may force individuals to prioritise immediate financial concerns over health needs, resulting in inadequate preventive measures and delays in seeking healthcare. In addition, living in overcrowded or substandard housing, residing in violent neighbourhoods, and working in unsafe environments can significantly increase exposure to various health risks such as infectious diseases, pollution, injuries, and chronic stress, which can lead to acute or chronic health conditions.

Second, unhealthy **lifestyle choices** that negatively affect health are often **shaped by a person's socio-economic status**.[xi] For example, individuals with lower socio-economic status may face higher risks of poor nutrition, as healthy food options can be more expensive or unavailable in their area. They may have less time or energy to engage in regular physical activity or may lack safe spaces or affordable recreational facilities nearby. Additionally, behaviours such as smoking and excessive drinking may be adopted as coping mechanisms to manage the stress of financial insecurity or difficult living conditions. Furthermore, lower levels of education can limit a person's understanding of the importance of a healthy lifestyle and the resources necessary to support it. This means that the assumption that unhealthy lifestyles of socioeconomic groups are freely chosen is fundamentally flawed.

Third, beyond the material challenges that a person may face, the **social stigma** associated with poverty, unemployment, or social exclusion can intensify feelings of hopelessness, chronic stress, and anxiety. This emotional strain heightens susceptibility to depression and substance abuse, while also triggering physiological changes (e.g., higher blood pressure, weakened immune response) which in turn increase the risk of developing various illnesses.[xii]

Fourth, social determinants have a **cumulative impact** over the course of a person's lifetime.[xiii] Early disadvantages such as growing up in poverty and receiving poor education often translate into persistent socio-economic challenges, like unstable employment, poor nutrition, and inadequate housing. In this way, the compounding effects of social determinants perpetuate a cycle of disadvantage contributing to ongoing health disparities later in life.

Fifth, social determinants provide access to key resources such as money, knowledge, and social connections that impact health outcomes in multiple ways.[xiv] **Persons with higher socio-economic status can better mobilise these resources to protect and improve their health**, no matter what the prevailing health risks are. Consequently, even as health risks and treatments change, persons with higher socio-economic status will consistently have an advantage. This perpetuates health inequities over time.

### c. The social gradient in health

The social determinants of health explain why health status tends to follow a social gradient. The **social gradient in health** refers to the systematic and graded relationship between socio-economic status and health outcomes.[xv] Health outcomes improve progressively with higher socio-economic status, with individuals in the highest socio-economic group generally enjoying the best health, while those in the lowest groups typically experience the worst health. This gradient extends across all levels of society and is shaped by several interconnected factors: lower socio-economic groups often face precarious employment, poor living conditions, and greater exposure to pollution and stress. They typically have less access to healthcare and fewer resources that mitigate health risks, such as education and social support. Moreover, they may lack the knowledge or networks to effectively address health challenges or take advantage of new treatment options. As a result, disadvantaged groups experience the onset of chronic illness and disability at younger ages, and have a significantly lower life expectancy than more advantaged groups.[xvi]

Individuals and groups most disadvantaged along the social gradient in health are also the **most vulnerable** to worsening health **during a public health crisis**. This became evident during the COVID-19 pandemic, when those in vulnerable socio-economic situations faced multiple challenges: (1) their living and working conditions, such as crowded housing or frontline jobs, increased their risk of exposure; (2) they were more likely to experience severe health outcomes due to a higher prevalence of underlying conditions like diabetes, obesity, hypertension, and respiratory issues; and (3) they struggled to access timely healthcare and could be at risk of being deprioritised for life-saving treatments based on their perceived lower chances of survival.[xvii] As a result of these challenges, COVID-19 mortality rates in the most disadvantaged communities were around twice those in the least advantaged communities.[xviii] Moreover, the COVID-19 pandemic has exacerbated pre-existing inequities in society and created new vulnerabilities.[xix]

## 1.1.2. The social determinant “access to healthcare”

**Access to healthcare** is considered **one of the social determinants of health** because it directly influences the ability of individuals to obtain timely, effective, and appropriate healthcare, which is essential for maintaining and improving health. Without proper access to healthcare, individuals are more likely to experience preventable illnesses, suffer complications from untreated medical conditions, and face interruptions in ongoing treatments, all of which can significantly worsen their health over time.

Access to healthcare is **intertwined with other social determinants of health**, as barriers in one domain often intensify challenges in others, exacerbating health inequities both within and between populations. For example, individuals in lower-income groups face financial barriers that may prevent them from seeking timely medical care. Where health coverage depends on employment, individuals in precarious jobs or without stable work may find it more difficult to access healthcare services. Similarly, individuals living in rural, hard-to-reach or underserved areas may face difficulties accessing healthcare due to geographic barriers, lack of transportation, or limited availability of nearby healthcare facilities. Individuals without a strong social support network may struggle to navigate the complexities of the healthcare system or to find the emotional and material support needed to adhere to challenging or complex treatments. Additionally, individuals with lower levels of education are likely to have limited health literacy, making it harder for them to understand medical advice, engage effectively with healthcare providers, or recognise the value of preventive care and strict

management of chronic conditions. In turn, inequitable access to healthcare profoundly affects other social determinants of health. Delayed or limited access can result in escalating health issues, leading to economic instability as individuals may experience reduced productivity or risk job loss. Additionally, the lack of timely healthcare can result in poor educational attainment, as it increases absenteeism at school and may lead to learning difficulties caused by untreated health conditions. Furthermore, poor health resulting from inadequate access to healthcare can prevent individuals from fully participating in their communities, which can result in social isolation.

The cumulative impact of the social determinants of health often results in those who need healthcare the most facing the greatest barriers to accessing it, while those who need it the least tend to have the easiest access. This phenomenon is known as the "**inverse care law**", which describes how "the availability of good medical care tends to vary inversely with the need for it in the population served."[xx] The inverse care law highlights that, to reduce health inequities, healthcare policies should ensure that access to healthcare services is based on individual need rather than socioeconomic status or other social determinants of health. It **underscores the importance of equitable access to healthcare** as a fundamental human rights principle, which is essential to counteracting the inverse care law and mitigating the disparities it creates.

## 1.2. Strategies to address "inequitable access to healthcare" as a social determinant of health

### 1.2.1. Principles in addressing the social determinants of health

Since access to healthcare and other social determinants of health are interconnected in ways that reinforce each other, addressing one determinant without considering the others may not lead to significant improvements in health outcomes, as these determinants collectively shape a person's overall health. Following the Rio Political Declaration on Social Determinants of Health, the WHO Commission on Social Determinants of Health and the WHO Regional Office for Europe have developed an approach to improve health equity through action on the social determinants of health.[xxi]

First, this involves not only ensuring and safeguarding access to quality healthcare services, but **simultaneously addressing four other socio-economic conditions** that have the most direct impact on health and health inequities: (1) basic income security and social protection (e.g., reinforcing existing social protection policies and expanding coverage to populations that are typically excluded); (2) daily living conditions (e.g., ensuring safe and healthy housing, creating secure and accessible neighbourhoods, and improving public transport systems); (3) employment and working conditions (e.g., promoting full and decent employment and safe and fairly compensated work) and (4) social and human capital (e.g., strengthening social networks within communities, and guaranteeing high-quality education accessible to all).

Second, these policies should be implemented with the goal of **improving equity from the start**, focusing on interventions in early life and aimed at addressing health inequities **throughout the life course**, as the social determinants of health and their impact on health outcomes accumulate over time.

Third, the social determinants of health should be addressed in an integrated way in line with the principle of **"health in all policies"**. This means ensuring that health equity is a coherent consideration across all policies that may play an important part in shaping health, where appropriate, by using health and health equity impact assessment tools. This requires reconsidering the position of health policy in relation to other priorities and policies, and adopting new systems of governance with coordinated action, including accountability, at the highest levels across national, regional and local governments (**"whole-of-government" approach**), as well as across all sectors and stakeholders **("whole-of-society" approach**), focusing on all social groups (**"leave no one behind")**. In addition, in the aftermath of the COVID-19 pandemic, and with growing health challenges posed by climate change,

environmental degradation, and biodiversity loss, there have been increasing calls to also adopt a **One Health approach**. This approach emphasises the interdependent relationship between human health, animal health, and the health of the environment, and aims to progress towards sustainable development to mitigate the health threats that disproportionately affect socio-economically disadvantaged populations.[xxii]

Fourth, to effectively measure and address health inequities and the social determinants of health and to assess the impact of action, it is essential to implement robust, **routine monitoring systems**. These systems should be complemented by comprehensive training to policy actors, stakeholders, and healthcare providers, and investments in public awareness campaigns. To monitor policy actions, the WHO Regional Office for Europe has developed the **Health Equity Policy Tool**, which focuses on tracking within-country trends and inequities. The Health Equity Policy Tool outlines policy indicators across five key policy action areas that correspond to the five major social determinants of health: healthcare services, income security and social protection, living conditions, social and human capital, and employment and working conditions. These indicators leverage data disaggregated by factors such as income, education levels, and sex, enabling the monitoring of health equity across individuals in all population groups.[xxiii] + European Social Charter Monitoring System (Report)

Fifth, to effectively address the social determinants of health, resources should be allocated based on objective assessments of need, in line with the principle of "**proportionate universalism**". This principle asserts that to reduce the social gradient in health, "actions must be universal, but with a scale and intensity that is proportionate to the level of disadvantage".[xxiv] This means that, while policies should be available to everyone, they must be adapted to reflect the varying degrees of disadvantage along the social gradient, providing those with greater needs more intensive and tailored support.[xxv] This approach recognises that simply offering the same interventions to everyone will not be sufficient to "level up" the social gradient in health. Moreover, it highlights that concentrating solely on the most disadvantaged will not sufficiently reduce the overall gradient in health, as it will not improve the health of those who are moderately disadvantaged.[xxvi]

Sixth, to effectively address the social determinants of health, it is crucial to ensure accountability at all levels through inclusive and transparent decision-making. A key framework for guiding fair and accountable decision-making, particularly when resources are limited and difficult choices must be made, is the concept of "**accountability for reasonableness**".[xxvii] This concept emphasises that in situations of disagreement over resource allocation, decisions should be made through a fair procedure to ensure that they are viewed as legitimate. Such a procedure must meet four conditions: (1) publicity: the reasons and values behind the decisions must be publicly accessible and transparent; (2) relevance: decisions should be based on evidence and reasons that are to the greatest extent possible deemed relevant and justifiable by all stakeholders; (3) revisability: there must be a mechanism for stakeholders to challenge and revise decisions in the light of new evidence or arguments; and (4) regulation: a regulatory mechanism must be established to ensure that decision-makers can be held accountable when they fail to comply with the conditions of transparency, relevance, and revisability.[xxviii]

Seventh, policies that impact the determinants of health will only be effective when they are designed to increase **participation and engagement**, particularly among vulnerable groups, in their development, with the aim of identifying needs, barriers, and the values at stake.[xxix] When policies are developed and implemented without understanding the social, cultural, and economic challenges faced by disadvantaged populations, interventions may be mismatched, fail to deliver the intended benefits, and even exacerbate health disparities.

### 1.2.2. Promoting equitable and timely access to healthcare

#### a. Challenges related to equitable and timely access to healthcare

Individuals may face challenges in accessing healthcare, which may be caused or exacerbated by other social determinants of health. These challenges can be divided under the categories of availability, accessibility, acceptability, and quality, as defined by the UN Committee on Economic, Social and Cultural Rights in its General Comment No. 14 on the Right to the Highest Attainable Standard of Health.[xxx]

There might be insufficient **availability** of healthcare services to meet the needs of the population. This can be caused by geographical barriers, as rural and deprived areas often experience a scarcity of healthcare facilities and professionals. Individuals living in these areas may need to travel long distances to receive care, face longer waiting times, and have limited access to specialised treatments. Additionally, countries may encounter critical shortages of healthcare professionals due to inadequate training opportunities and challenges in attracting and retaining staff because of non-competitive salaries or brain drain. These factors can lead to the unavailability of certain specialised treatments, understaffing of critical departments, and further increase waiting times. Moreover, essential medicinal products and medical technologies may not be available due to delivery problems, stock shortages, and supply chain disruptions.

In addition, available healthcare services may not be accessible to everyone who needs them. **Accessibility** has four overlapping dimensions. First, patients may experience **discrimination** or stigma within the healthcare system, for instance when healthcare professionals provide them with less time, attention, or expertise compared to other patients or make biased assumptions based on factors such as ethnicity, gender, socio-economic status, or health conditions. In addition, stigma can discourage individuals from seeking medical care altogether, out of fear of being treated unfairly or judged. Second, health facilities and services may not be **physically accessible**, for instance when they are not within a reasonable distance from where people live and work, or when they are not designed or equipped to accommodate the needs of older adults or persons with mobility restrictions or disabilities. Third, healthcare services may not be affordable for everyone (**economic accessibility**), as individuals with limited financial resources may find it difficult to afford medical care and essential medications, forcing them to forgo necessary care or being pushed further into financial hardship. Fourth, **information accessibility** ensures that patients can freely seek and receive information about their health, medical treatments, and healthcare services, and share health information and ideas without barriers. However, this can be challenging for individuals with low health literacy, individuals with disabilities, or for those facing discrimination, language barriers, and stigma.

Moreover, the provision of health services should be **acceptable** to patients, meaning that it should respect medical ethics, be culturally appropriate, and be sensitive to gender and life-cycle requirements. However, healthcare services may fall short in several areas: they may fail to account for the cultural practices or beliefs of minority groups, healthcare professionals may have unconscious biases or discriminatory attitudes towards certain individuals or communities, healthcare services may lack the resources to provide information or care in a language the patient understands, they may fail to address gender-specific needs or concerns, and they may not be designed to accommodate individuals at different stages of life, such as children or the elderly, who often have distinct healthcare needs.

Finally, available healthcare services should also be of appropriate **quality**, which requires having skilled healthcare professionals with adequate training and ensuring that healthcare is delivered in accordance with relevant professional obligations and standards, as outlined in Article 4 of the Oviedo Convention. Healthcare should be “of a fitting standard in the light of scientific progress and be subject to a continuous quality assessment”,[xxxi] which implies that medicinal products must be approved through an appropriate regulatory process, and medical equipment must undergo a conformity assessment to ensure compliance with legal, safety,

and performance standards. However, several challenges may arise in ensuring quality care, particularly in disadvantaged areas. These include inadequate infrastructure, limited access to modern medical equipment, underfunding, a shortage of specialised healthcare professionals, overstretched staff struggling to maintain care standards due to heavy workloads, lack of continuous training to stay updated with the latest medical advances, and stock shortages of essential medicines.

### b. Addressing these challenges

To address these challenges and promote equitable access to healthcare, a set of cumulative approaches have been presented under the framework of **universal health coverage**, broadly defined by the WHO as ensuring that "all people have access to the full range of quality health services they need, when and where they need them, without financial hardship".[xxxii] Following the calls from the UN World Health Report 2010 and the 2012 UN Resolution on Global Health and Foreign Policy, achieving universal health coverage by 2030 was in 2015 set as a target of the UN Sustainable Development Goal 3 (Ensure healthy lives and promote well-being for all at all ages),[xxxiii] and the UN General Assembly reinforced this goal with resolutions in 2019 and 2023.[xxxiv] These resolutions emphasise addressing the social determinants of health through a health-in-all-policies approach and engaging all stakeholders in an integrated, whole-of-government and whole-of-society approach.[xxxv] While universal health coverage aims to improve the overall availability, acceptability, and quality of healthcare services, its primary focus is on ensuring accessibility, with particular emphasis on affordability (economic accessibility).

Achieving universal health coverage requires national health policies to ensure **universal and timely access to a nationally determined package of health services at all levels of care** – promotive, preventive, curative, rehabilitative and palliative care – **with financial protection for all**. With primary healthcare as the cornerstone, the aim is to "enable access to the full range of integrated, quality, safe, effective, affordable and essential health services, medicines, vaccines, diagnostics and health technologies".[xxxvi] Achieving universal health coverage demands strong, resilient health systems supported by sustainable financing that can respond to unmet health needs and remove financial barriers, with "special emphasis on the poor as well as those who are vulnerable or in vulnerable situations".[xxxvii] The WHO Consultative Group on Equity and Universal Health Coverage provided a strategic framework for progressively realising universal health coverage through **advancing in three dimensions**: (1) expanding coverage for healthcare services, with a focus on high-priority services; (2) including more people, with a focus on low-income groups, rural populations, and other disadvantaged groups; and (3) reducing out-of-pocket payments by shifting toward mandatory prepayment with pooling of funds, particularly for high-priority services and disadvantaged groups. Given resource constraints, strategic decisions must be made about which services to expand first, who to prioritise for coverage, and how to transition from out-of-pocket payments to prepayment models, as well as about acceptable trade-offs between these dimensions. The overarching principle is to prioritise equitable access to high-priority, prepaid healthcare services for all, particularly the worse-off, while avoiding policies that prioritise low-priority services or the well-off. Implementing universal healthcare requires **careful priority setting facilitated by robust public accountability and participation mechanisms**, guided by the principles of "accountability for reasonableness".[xxxviii] To promote accountability and participation, it is also essential to establish a strong monitoring and evaluation system that includes a comprehensive set of indicators that measure the degree of access to essential, quality health services, the degree of financial protection related to these services, the priority-setting processes in place, and the level and distribution of health outcomes.[xxxix]

Within the framework of universal health coverage, strategies are also promoted to ensure equitable and affordable access to innovative treatments and technologies. This includes encouraging innovative incentives and financing mechanisms for health research and development that separate the cost of investment from the price and volumes of sales, while

increasing price transparency across the value chain, through improved regulations and stronger partnership between the public and private sectors, academia, and civil society.[xl] In addition, promoting digital health and information and communications technologies, in accordance with the WHO Global Strategy on Digital Health 2020-2025, is recommended to improve and support health system functions and accelerate progress toward universal health coverage.[xli]

Complementing the framework of universal health coverage, tailored strategies are necessary to overcome remaining barriers. Improving the **availability** of healthcare services can be achieved by increasing investments and optimising resource allocation to expand healthcare infrastructure, particularly in underserved, rural, and hard-to-reach areas. This includes ensuring that healthcare facilities, professionals, medicinal products, and medical equipment are more adequately distributed. Addressing healthcare workforce shortages involves investing in education, employment, and retention strategies, while also addressing the root causes of professional migration and departure from the health workforce. Promoting equitable distribution of qualified health professionals requires offering incentives and creating a safe, supportive work environment with competitive remuneration.[xlii] To address supply chain challenges such as delivery problems, stock shortages, and disruptions, strategies should include enhancing supply chain management systems to forecast demand and monitor supply levels, diversifying supply sources by partnering with multiple manufacturers, promoting local production, encouraging regional collaboration, building regional stockpiles of essential medicines and medical equipment, and investing in logistics to ensure timely delivery of supplies.[xliii]

Strategies to improve **accessibility** (other than economic accessibility) and **acceptability** of healthcare services also require targeted measures. These include cultural competency training and diversity education for healthcare professionals to raise awareness about different cultural practices, beliefs, and the healthcare needs of minority groups, while focusing on eliminating unconscious biases. To better align healthcare services with the cultural backgrounds of local communities, community outreach initiatives and health education programs can be implemented with the support of community health workers, while cultural mediators can assist healthcare professionals in improving communication with minority patients. Language barriers may be addressed by establishing a network of trained interpreters, available both in person and through telehealth, and by providing written materials, consent forms, and digital tools in different languages. Health literacy should be a core component of these strategies, ensuring that patients are equipped with the knowledge and understanding they need to make informed decisions about their health. Additionally, healthcare services must be responsive to gender- and age-specific needs, which involves training healthcare professionals in gender- and age-sensitive care and communication. More generally, patient-centred care models should be adopted where the needs, values, and preferences of each patient are integrated into care plans.[xliv] Physical accessibility can be improved, not only by expanding healthcare infrastructure, but also by deploying mobile health clinics or use telemedicine units to reach underserved areas, cooperating with city planners and public transport networks to enhance transportation options to healthcare facilities, and designing healthcare facilities to accommodate children, individuals with disabilities, and older adults and improving assistive services.[xlv]

To ensure that healthcare services are of appropriate **quality,** several targeted strategies can be implemented, in addition to those mentioned above. To stay informed about the latest developments in medical science, patient care, and technology, healthcare professionals should be provided with regular training programs and encouraged to pursue lifelong learning.[xlvi] In addition, the regulatory systems of national health authorities should be strengthened to effectively oversee the approval of medicinal products and certification of medical equipment. This includes implementing robust processes for good manufacturing practices, overseeing clinical trials, pre-market approval, market authorisation, and post-market surveillance, aimed at maintaining high standards of quality, safety, and efficacy.

Moreover, it involves ensuring the licensing of health professionals, as well as the accreditation, auditing, and inspection of healthcare facilities to ensure compliance with quality and safety standards.[xlvii]

By implementing these strategies, healthcare systems can make significant progress in addressing health disparities by removing barriers and providing tailored support, with the aim of ensuring more equitable access to healthcare based on each patient's specific needs.

## 2. Requests for pre-approval access to investigational treatments

Before a medicinal product can be marketed, it must undergo a rigorous process of market authorisation by the relevant competent authorities. This process ensures that the product's safety, efficacy, and pharmacological quality have been established, primarily through clinical trials.[xlviii] These safeguards are crucial in protecting patients from potential harm caused by medicinal products that could have significant side effects, be ineffective, or be of poor quality. However, under certain circumstances, patients may gain access to medicinal products that are either unlicensed or not specifically licensed for their particular health condition. For instance, off-label uses involves a scenario where a medicinal product that has been licensed for a specific indication or patient group is prescribed for another, non-approved use. In such cases, while the product is licensed, its application falls outside its initially approved parameters.

Additionally, there are situations where patients can access completely unlicensed medicinal products, such as in certain early-phase clinical trials or compassionate use programs. Phase I clinical trials primarily focus on evaluating the safety of the medicinal product, by examining metabolism, toxicity, and the effects of different doses. While these trials are not designed to assess the product's efficacy, for patients with a serious or terminal disease, such as cancer, who have no remaining treatment options, participation may still offer potential benefits if the investigational product shows early promise. Despite limited information on efficacy information, participants in Phase I trials are afforded certain protections, including ethical review, informed consent processes, and clinical trial insurance coverage. Phase II trials, involving larger patient populations, aim to provide preliminary evidence of efficacy while continuing to assess safety, side effects, and risks. These trials usually involve several hundred participants and generate more concrete data about how effective the treatment is at addressing the targeted condition. In Phase III trials, typically involving thousands of participants, the aim is to confirm the treatment's efficacy and further evaluate its safety in a more extensive patient population. The data from these trials are used by regulatory bodies to determine whether the medicinal product should receive full approval for its intended use. In some cases, products aimed at treating serious or life-threatening diseases may receive accelerated approval after successful Phase II trials. This approval is granted on the basis of a positive effect on a specific surrogate endpoint, such as causing tumour shrinkage, that is reasonably likely to predict clinical benefits. After this approval, the manufacturer must still conduct post-approval clinical studies to demonstrate the effect of the product on more definitive clinical endpoints, such as extended survival, thereby ensuring continued patient safety and efficacy of the treatment.

Patients with life-threatening or seriously debilitating conditions who have no remaining treatment options and cannot participate in clinical trials sometimes can get access to experimental medicinal products through compassionate use, also known as expanded access. This allows them to get access to experimental medicinal products, which usually are in phase III trials, through a compassionate-use program, depending on their physician's willingness to apply for it and the manufacturer's willingness to supply it. At the European level, the regulatory framework permits member states to make an unauthorised medicinal product available for compassionate use to patients with a chronically or seriously debilitating disease or whose disease is life-threatening, when no authorised treatments are satisfactory. The product concerned must either be undergoing clinical trials or the subject of a marketing authorisation application, with preliminary data suggesting that it is likely to be effective and

does not pose unreasonable risks.[xlix] However, implementation of compassionate use programmes remains within the competence of a member State, resulting in considerable variability in procedures and requirements. For instance, some countries impose additional conditions, such as requiring that the product is authorised in another country or that its therapeutic efficacy is verified by a recognised scientific body.[l]

The question of when seriously or terminally ill patients should be granted access to unproven medicinal products through compassionate-use programmes is a subject of ongoing debate and controversy. This is illustrated by the cases of *Hristozov and Others v. Bulgaria* and *Durisotto v. Italy*, in which the European Court of Human Rights ruled that the refusals by the Bulgarian and Italian governments to allow access to experimental treatments did not violate the European Convention on Human Rights.[li] In *Hristozov*, a group of Bulgarian cancer patients sought access to an unapproved anti-cancer drug which had been permitted for "compassionate use" in other countries. However, the national authorities denied access, as Bulgarian law stipulated that compassionate use could only be approved if the medicinal product had already been authorised in another country. In *Durisotto*, an Italian father sought access to experimental stem cells therapy (the "Stamina" method) for his daughter, who was suffering from a degenerative brain disorder. A court decision to provisionally grant the applicant's request had been revoked under new national legislation, which stipulated that access to experimental treatments would only be allowed for medicinal products undergoing clinical trials and verified for therapeutic effectiveness by a recognised scientific body. In this case, a scientific committee established by the Ministry of Health had issued a negative opinion regarding the "Stamina" method, concluding that the treatment lacked a scientific basis.

Applicants in *Hristozov* and *Durisotto* claimed that the refusal to grant them access to these products violated Article 2 of the Convention (right to life), contending that by denying access, the State had failed to take appropriate steps to safeguard the lives of those under its jurisdiction. Specifically, in *Hristozov*, the Court underlined that national regulations for compassionate use were already in place and held that Article 2 cannot be interpreted as requiring States to provide access in the specific manner patients demand.[lii] The applicants also invoked Article 8 (right to respect for private and family life), arguing that the refusals infringed upon their autonomy to choose, in consultation with their physicians, how they should be medically treated, even if that choice involved potential harmful consequences. The Court dismissed this claim, stating that States have a broad margin of appreciation in regulating access to unproven treatments, for two key reasons.

First, the Court noted that the issue requires States to balance competing private and public interests. The Court observed that the applicants had a clear interest in accessing experimental treatments as a last resort, even when these treatments posed significant risks. However, there is also a countervailing public interest in regulating access to experimental products in a way that protects terminally ill patients from harm. The lack of clear data on the potential risks and benefits of experimental treatments and the vulnerable state of these patients make it crucial to ensure that patients are not exposed to risks which may prove harmful to their own health and life, even when they are terminally ill. The Court further highlighted that balancing these conflicting interests touches upon complex ethical and risk-assessment issues, against a background of fast-moving medical and scientific developments.

Second, the Court noted that, despite a growing trend among European countries to permit the use of unauthorised medicinal products under certain exceptional conditions, this emerging consensus had not been uniformly implemented across jurisdictions, as the legal frameworks governing such access vary in strictness.[liii] The Bulgarian authorities have chosen to balance the competing interests by allowing patients to obtain access only if products have already been authorised in another country. This solution tilts the balance between potential therapeutic benefit and medicine risk avoidance decisively in favour of the latter, favouring the use of products that have already undergone rigorous testing for safety and efficacy elsewhere. By making access to medicinal products that are still in the development stages

entirely inaccessible, Bulgaria did not exceed the wide margin of appreciation afforded to it.[liv] Moreover, the Court emphasised that it is not the role of an international court to substitute its judgment for that of national authorities in determining what level of risk is acceptable in such cases. This reasoning was later echoed in *Durisotto*, where the Court declared the application inadmissible.[lv]

With the rise of innovative treatments, there has been a significant increase in the number of patients seeking access to experimental drugs outside the context of clinical trials, especially among those with life-threatening diseases.[lvi] Compassionate use programmes may offer these patients a therapeutic option of last resort and a greater sense of control and participation in their treatment. From an ethical perspective, one could argue that compassionate use respects patients' autonomy by allowing them to make informed decisions about their health, even if that choice involves taking on the risks associated with unproven treatments. For instance, in the context of the World Health Organization's End TB Strategy, guidance suggests that exhausting all possible treatment avenues, including compassionate use, honours the dignity of patients by recognising that their lives are valuable and worthy of protection. This approach supports the idea that patients have the right to take calculated risks when no other viable treatments exist. However, while compassionate use programs aim to respect autonomy, patient safety remains a paramount concern. WHO guidance stresses the need to minimise risks through stringent pharmacovigilance and robust monitoring, ensuring that, in accordance with the principle of nonmaleficence, patients are not subjected to excessive harm without adequate safeguards.[lvii] The need to balance patient autonomy and safety creates tensions.[lviii] On one side, some advocate for broader access to experimental treatments, viewing it as a right grounded in dignity and autonomy. On the other side, others argue that patient safety and well-being should take precedence, emphasising the importance of strict controls to prevent harm and preserve the dignity of these vulnerable patients, even when they are willing to accept those risks.

In this context, it is important to acknowledge that clear restrictions must be established when granting requests for access to experimental treatments. The UN Committee on Economic, Social, and Cultural Rights, in its General Comment on the right to the highest attainable standard of health, emphasises that health services and products must be scientifically and medically appropriate and of high quality, which includes ensuring that medicinal products are "scientifically approved and unexpired".[lix] Similarly, the Explanatory Report to Article 3 of the Convention on Human Rights and Biomedicine stresses that "care must meet a fitting standard in light of scientific progress and be subject to continuous quality assessment".[lx] These provisions highlight the need for treatments to meet a baseline of safety and efficacy as confirmed by scientific standards, as advocated in the EU regulatory framework. However, the question of what constitutes "scientifically approved" and "a fitting standard" remains complex. A significant concern is that only a very small percentage of medicinal products that enter clinical trials ultimately receive approval. For instance, studies show that only 13.8% of all drugs and a mere 3.4% of cancer drugs that begin clinical testing are eventually approved, with most failing due to toxicity or lack of efficacy.[lxi] A notable example is the 2007 phase III trial of minocycline for ALS, where disease progression in patients taking the drug was 25% faster than in patients on placebo.[lxii] These findings underscore the potential dangers associated with experimental medicinal products and caution against further expanding "right to try" laws to include treatments based solely on Phase I testing and preclinical evidence.[lxiii]

Another critical issue is the concept of free and informed consent.[lxiv] While patient autonomy is often cited as the primary justification for granting access to experimental treatments, seriously or terminally ill patients may not always be in the best position to weigh the risks and benefits of unproven treatments, particularly when they might have unrealistic expectations or believe they have nothing left to lose. This emotional vulnerability can compromise their ability to make well-reasoned decisions.[lxv] Additionally, the role of physicians in providing clear and impartial information about the risks and benefits of these treatments is crucial but often complicated. The uncertainties surrounding experimental drugs can be profound, and

physicians may themselves struggle to fully understand or communicate these risks. Furthermore, when physicians have ties to the sponsor or are actively involved in clinical research, there is a potential that their presentation of the potential benefits and risks may not be entirely objective. The financial implications of compassionate use programmes can also be significant. In the absence of pharmaceutical company supply schemes or subsidies by public or private payers, patients may face substantial out-of-pocket costs. Moreover, if these programmes would expand considerably, the broader impact on healthcare systems could place significant financial strain on already limited resources, raising concerns about the long-term sustainability of these initiatives.[lxvi] Given these ethical, medical, and financial considerations, a cautious and balanced approach to compassionate use is essential. Rigorous oversight, transparent communication of risks, and careful balancing of patient autonomy with the principles of beneficence and nonmaleficence are crucial to ensuring that these programmes serve the best interests of the patients involved.[lxvii]

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