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Contents

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Abbreviations

EML	Essential Medicines List
EtD	Evidence to Decision
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
INCB	International Narcotics Control Board
IT	intervention type
LMIC	low- and middle-income countries
OAT	opioid agonist therapy
PICO	population, intervention, comparator, outcome
PDMP	prescription drug monitoring programme
WHO	World Health Organization

Glossary

Conflict of interest: Any interest that may affect, or may reasonably be perceived to affect, a person's objectivity and independence. Risks of conflicts of interest generally occur at two, non-mutually exclusive levels: organizational and personal. The scope of conflict of interest goes beyond financial interest.

Controlled medicines: Pharmaceuticals with an identified or emergent clinical application whose active principles are listed in the international drug control conventions and whose manufacture, possession and use is regulated by national law in order to promote rational therapeutic use or to prevent nonmedical use and dependence.

Diversion: Redirection of controlled medicines from the patients for whom they were intended for medical use to others, which may include transfer of prescription medications between individuals.

Essential medicines: Medicines that meet the priority health-care needs of the population and are selected according to their public health relevance, evidence of their efficacy and safety and their comparative cost-effectiveness *(1)*.

GRADE: Grading of Recommendations, Assessment, Development and Evaluation is a system for assessing the certainty (quality) of a body of evidence and for structuring considerations when formulating recommendations in clinical or public health guidelines.

Health professional: Health personnel who apply knowledge such as that relating to medicine, nursing, midwifery, dentistry and allied health and health promotion; they usually have a university undergraduate or postgraduate degree or the equivalent *(2)*.

Medicine: Any substance or combination of substances marketed or manufactured to be marketed for treatment or prevention of disease in human beings, for making a medical diagnosis in human beings or for restoring, correcting or modifying physiological functions in human beings *(3)*. Medicines may be of chemical or biological origin and include those obtained with or without prescription by a health-care worker. Often used interchangeably with the word "pharmaceutical".

Nonmedical use: Use of a prescription drug, whether obtained by prescription or otherwise, other than in the manner, for the reasons or period prescribed, or by a person for whom the drug was not prescribed.

Opioid: A generic term that encompasses the constituents or derivatives of the opium poppy *Papaver somniferum* and various synthetic and semisynthetic compounds, some related to morphine and others that are chemically distinct but the primary actions of which is on the μ opioid receptor. Examples of opioids include morphine, diacetylmorphine (heroin), fentanyl, pethidine, oxycodone, hydromorphone, methadone, buprenorphine, tramadol, hydrocodone, codeine and dextropropoxyphene. All opioids have analgesic properties of various potency and are central nervous system depressants *(4)*.

Opioid stewardship: Strategies and interventions involving appropriate procurement, storage, prescribing and use of opioids and also disposal of unused opioids, when opioids are appropriately prescribed for the treatment and management of specific medical conditions. The goal of opioid stewardship is to protect and optimize individual and population health. Specifically, the goals are to ensure the rational use of opioids; to prevent new addiction to opioid analgesics while maintaining access for patients when indicated; to meet the needs of individuals who require pain control and individuals with other relevant conditions (e.g. opioid use disorder), while minimizing harm to the individual and to other people and populations. The harm include those that may arise from opioid overuse, non-medical use and diversion *(5)*.

Pain: An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage *(6)*.

Palliative care: An approach to improve the quality of life of patients (adults and children) and their families with life-threatening illness. It prevents and relieves suffering through early identification, impeccable assessment and treatment of pain and other problems, whether physical, psychosocial or spiritual *(7)*.

Palliative care for children: Palliative care for children is a small, highly specialized field of health care that is different from, although closely related to, adult palliative care. Ideally, support for children who require palliative care starts at diagnosis, which, for many children with life-limiting conditions, is at birth. Palliative care for children consists of active total care of the child's body, mind and spirit and support to the family. It begins when an illness is diagnosed and continues regardless of whether a child receives treatment for the disease *(8)*.

Pharmacovigilance: The science and activities for the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem *(9)*.

Psychoactive substance: Any substance, natural or synthetic, or any natural material that has psychoactive properties *(10)*.

Rational use: Patients receive medications appropriate to their clinical needs at doses that meet their individual requirements, for an adequate period and at the lowest cost to them and their communities *(11)*.

Substance dependence: A disorder of regulation of use of a psychoactive substance arising from its repeated or continuous use. The characteristic feature is a strong internal drive to use the substance, manifested by impaired ability to control use, giving increasing priority to use over other activities and persistence of use despite harm or other negative consequences. The experience is often accompanied by a subjective sensation of urge or craving to use the substance. Physiological features of dependence may also be present, including tolerance to the effects of the psychoactive substance, withdrawal symptoms after cessation or reduction in use or repeated use of the same or pharmacologically similar substances to prevent or alleviate withdrawal symptoms. The features of dependence are usually evident over at least 12 months, but the diagnosis may be made if use of the substance is continuous (daily or almost daily) for at least 3 months *(5)*.

Substance use disorder: Disorders due to substance use comprise a broad category of health conditions that include substance intoxication, withdrawal syndrome and various substance-induced mental disorders.

Vulnerable populations: Groups and communities at higher risk of poor physical, psychological or social health due to inequitable access to resources and/or increased susceptibility to adverse health outcomes. Examples of specific and vulnerable populations include children, older people, pregnant women, indigenous populations, racial minorities, ethnic and linguistic minorities, migrants, people with substance use disorders, people with mental disorders or cognitive impairment, people who are homeless, people living in humanitarian and emergency settings, people in contact with the criminal justice system and other groups with special needs *(12)*.

Executive summary

Access to medicines is essential for attainment of universal health coverage, which is central to achievement of the health-related Sustainable Development Goals. Controlled medicines include those such as opioids, benzodiazepines, barbiturates, amphetamines and others with identified or emergent clinical indications. WHO recognizes that these medicines are necessary for pre- and post-operative care, for sedation, for the management of both acute and chronic pain, for palliative care, as anticonvulsants (anti-epileptics), for the management of anxiety disorders and for the management of substance use disorders, including as opioid agonist therapy (OAT).

WHO recommends that essential medicines, including those that are controlled, be available to all patients at all times at a price the individual and the community can afford. In line with their obligations under the United Nation's drug treaties, governments and health systems must ensure that people who need controlled medicines for medical and scientific purposes can access them and also ensure that these medicines are used safely and appropriately. Policies should seek to maximize access to essential and beneficial controlled medicines for all people who need them, while effectively restricting non-medical use, which poses serious risks to safety and has harmful consequences for individuals and societies *(13)*. This guideline is aligned with the WHO Roadmap for access to medicines, vaccines and other health products *(14)*. It provides evidence-informed recommendations on pharmaceuticals with an identified or emergent clinical application the active principles of which are listed in international drug control conventions and the manufacture, possession and use of which is regulated by national law.

Purpose of the guideline

The purpose of this guideline is to assist WHO Member States and their partners in developing and implementing balanced national controlled medicines policies to ensure their accessibility, availability and affordability for medical and scientific uses and to minimize the risk of harm arising from non-medical use. The guideline addresses policies for groups (of all ages, from neonates through to older people) affected by conditions in which use of controlled medicines is deemed to be medically appropriate according to evidence-based clinical practice guidelines.

Scope of the guideline

Populations

The recommendations in this guideline are relevant to policies addressed to groups (of all ages) affected by conditions for which the use of internationally or nationally controlled medicines is deemed to be medically appropriate according to evidence-based guidelines.

The guideline includes consideration of the necessity of adapting policies to meet the specific needs for access and safety of patients in various demographic groups, including neonates, children, adolescents, young people, adults and older people. The guideline also includes the needs of vulnerable populations.

Clinical contexts

Controlled medicines are most likely to be used in the following contexts:

- anaesthesia and procedural, pre- and post-surgical care;
- disease conditions associated with acute pain and chronic and non-chronic cancer pain;
- palliative and hospice care;
- management of mental health disorders;
- management of substance use disorders;
- management of neurological conditions, including seizures and severe spasticity;
- other relevant conditions, such as sickle-cell disease;
- clinical research on medical applications of controlled substances; and
- humanitarian emergencies and crises.

Some clinical conditions, notably acute and chronic pain, trauma surgery and acute mental health problems, are particularly likely to arise during humanitarian emergencies, including those due to climatic or geological disaster, political or ethnic conflict or serious infectious disease epidemics. These conditions and circumstances were considered during guideline development.

Types of controlled medicines

The recommendations in this guideline are intended to cover all types of controlled medicines with authorized medical or scientific purposes. They include opioids, benzodiazepines, barbiturates, dissociative anaesthetics, cannabinoids, hallucinogens and amphetamine-type stimulants.

Policy areas considered to be out of the scope of this guideline

This guideline addresses policies rather than clinical practice and therefore does not provide advice on clinical use of controlled medicines.

Guiding principles

The GDG agreed on several principles for making the recommendations and good practice statements in this guideline. The following apply to all national policies pertaining to controlled medicines.

1. All people have the right to enjoyment of the highest attainable standard of health, a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.
2. Controlled medicines are crucial for managing many health conditions and for treating illness. Access to essential controlled medicines is a component of the rights to both health and life.
3. National policies on controlled medicines should be balanced to ensure safe, appropriate use, ensuring access for medical and scientific need (that is not interrupted and is sustainable and continuous), while avoiding harmful consequences for individuals and societies.
4. All national policies should be tailored to the needs and requirements in the social context and the resources of the population, while recognizing individuals' right to the highest attainable standard of health.
5. Member States and health-care providers should ensure that patients, their families and caregivers know their rights to self-determination, non-discrimination, accessible and appropriate health services and confidentiality.
6. Governments should invite patients, advocacy groups, health professionals, academia, professional societies, civil society and other affected groups to participate in formulation of health policy.

Existing WHO guidance

The recommendations presented in chapters 4–6 (domains 1-3) are based on WHO guidance and are included in this guideline to provide support for development of national controlled medicines policies, pricing and financing of controlled medicines and related health-care services, and selection of medicines.

Chapter 4. Development of a national controlled medicines policy (domain 1)

WHO guidance (2001)

WHO recommends that all countries develop and implement a national medicines policy, that they regularly monitor implementation and update it to ensure that its goals remain in line with national medical needs and social priorities, as well as the most recent international norms *(15)*.

Chapter 5. Pricing and financing of controlled medicines and related health-care services (domain 2)

WHO guidance (2020)

WHO recommends that countries enable early market entry of generic and biosimilar medicines through legislative and administrative measures, with a view to encouraging early submission of regulatory applications, allowing for prompt, effective review and ensuring that these products are safe, efficacious and quality assured *(16)*.

WHO guidance (2020)

WHO recommends that countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are based on the cost of production.

WHO guidance (2020)

WHO recommends maximization of the uptake of generic and biosimilar medicines.

Chapter 6. Medicines selection (domain 3)

WHO guidance (2001, 2019)

WHO recommends that selection of all medicines be based on transparent, rigorous assessment of the latest available scientific studies *(15)*. In the case of controlled medicines that are not on the Essential Medicines List (EML), the review of evidence should explicitly include studies in which the risks of inappropriate and unsafe use are quantified in the national context, as well as the relative therapeutic value of different formulations of controlled medicines. When such evidence does not exist, WHO encourages its generation *(14)*.

WHO guidance (2019)

WHO's guidelines on medicine pricing recommend use of health technology assessment or equivalent tools or approaches in selecting medicines for public coverage, so that the process is transparent, assumptions are explicit and the perspectives of patients and buyers are taken into account *(16)*.

New recommendations and best practice to ensure safe, balanced access to controlled medicines (2025)

New recommendations and good practice statements published by WHO in 2025 are included in chapters 7, 8, 9, and 10 of this guideline. The recommendations are based on the best available scientific evidence and include ratings of the certainty of evidence *(17)*. The recommendations were formulated with methods that meet the highest international standards for guideline development *(18)*. Rapid systematic reviews were conducted to synthesize the evidence, and all components of the WHO INTEGRATE Evidence-to-Decision (EtD) framework

(balance of health benefits and harms, human rights and sociocultural acceptability, health equity, equality and non-discrimination, societal implications, financial and economic considerations, feasibility and health system considerations, as well as the quality of evidence) *(19)* were considered in developing the recommendations.

While the recommendations were based on the best available evidence, good practice statements were also formulated to present good practices in policies on controlled medicines. The good practice statements were supported by indirect evidence and do not include ratings of the certainty of evidence *(17)*.

Chapter 7. Procurement and supply chain management (domain 4)

7.1 Quantification of controlled medicines

Strong recommendation

Governments should ensure that reporting of current consumption and the potential need for controlled medicines for medical and scientific purposes, including ongoing adjusted estimates where necessary, are:

- accurate, timely and actively monitored; and
- based on need that is estimated from the best available epidemiological data (including morbidity and mortality), consumption data, clinical guidelines, service capacity and other relevant information.

Very low certainty evidence

Good practice statement

Governments should monitor the availability and affordability of controlled medicines and update estimates of need to ensure adequate supplies on an ongoing basis. If the national supply, demand or other area of availability changes significantly, updated quantitative estimates should be made and communicated to the International Narcotics Control Board (INCB) in a timely manner to allow corresponding changes to manufacture, importation and distribution.

7.2 Procurement guidelines, tools and mechanisms

Good practice statement

Governments should develop, implement and monitor their procurement policy for controlled medicines to ensure a sufficient, high-quality, efficacious, safe and cost-effective supply for medical and scientific needs, in compliance with rules and regulations for public sector procurement of health products.

Good practice statement

Governments should develop, implement and monitor good procurement policy to identify continually assessed and evaluated sources and achieve the best sustainable prices for quality-assured controlled medicines for medical and scientific needs.

7.3 Supply chain management systems, tools and mechanisms

Strong recommendation

Governments should use simple, appropriate technology and tools to:

- improve the traceability, efficiency and integrity of inventory management of controlled medicines;
- prevent waste and stock-outs;
- implement protocols for prevention of diversion; and
- reduce the administrative burden for front-line staff handling controlled medicines.

Very low certainty evidence

Good practice statement

Governments should have supply chain and distribution plans for controlled medicines that ensure full geographical coverage, prevent waste or shortages and avoid inequity in access.

Good practice statement

Governments should ensure that local and regional production hubs and supply chains are supported by adequate technologies, infrastructure, financial and human resources.

7.4 Local production of controlled medicines

Good practice statement

Governments should systematically collect and analyse information on the potential health, financial and social benefits as well as the risks and harms of producing quality-assured controlled medicines within their country to meet the health-care needs of their people.

Chapter 8. Medicines regulation and control (domain 5)

8.1 Medicine product safety

Good practice statement

Governments should ensure that controlled medicines are available in formulations that are acceptable, affordable and accessible for those with clinical need.

Good practice statement

Governments should ensure that packaging of controlled medicines prevents accidental use by children and vulnerable adults. The additional cost of ensuring such safety features should not result in reduced access for patients with clinical need.

Good practice statement

Governments that are considering adoption of tamper-resistant formulations or packaging should weigh their potential safety benefits against their higher cost and the risk that they may limit access and/or increase harm.

8.2 Possession and use of controlled medicines

Good practice statement

Governments should collaborate with health authorities, care providers, professional health organizations and patient advocacy groups to review laws and regulations regarding the possession and use of controlled medications. They should revise any laws that hinder access to these medicines for individuals with legitimate clinical needs.

Good practice statement

Governments, medicine regulatory agencies, health-care professional bodies and societies should ensure that permission to possess or handle controlled medicines is extended to all health professionals whose practice entails treating patients with a clinical need for controlled medicines.

Good practice statement

Governments should ensure that patients have adequate legal protection relating to the possession of prescribed controlled medicines for clinical need.

8.3 Drug scheduling

Good practice statement

Governments should ensure that changes to the scheduling of controlled medicines are based on robust scientific evidence relevant to the context of use, to achieve balance between ensuring access and preventing public health harm.

Good practice statement

Discussions of drug scheduling should include input from health authorities, associations of health professionals, patients, families and all relevant stakeholders. When reviewing drug scheduling, optimizing health outcomes should be the priority, balancing access for clinical need with preventing harm.

Good practice statement

Governments and relevant authorities should ensure that medicine scheduling does not impede access to controlled substances for use in ethically approved clinical research.

8.4 Regulatory procedures for import and export

Good practice statement

Governments and relevant authorities should review their requirements and procedures governing trade of controlled medicines to ensure that they are proportionate, do not obstruct the flow of medicines necessary to treat people with clinical need and competently minimize diversion.

Good practice statement

Governments should encourage universal use of electronic authorizations and reporting in implementing trade regulations for controlled medicines.

Good practice statement

Governments and relevant authorities should ensure that controlled medicines can be exported or imported rapidly for use by humanitarian response organizations that are duly authorized by relevant national authorities.

Chapter 9. Prescribing, dispensing and administration (domain 6)

9.1 Clinical practice guidelines

Good practice statement

Governments and relevant authorities should ensure that clinical guidelines that include controlled medicines are:

- developed or revised by independent experts according to a scientific process based on the best available evidence;
- designed to optimize access to controlled medicines that are safe, effective and appropriate for all patients with clinical need;
- non-discriminatory and address the needs of specific and vulnerable populations; and
- designed to protect the population from harm.

9.2 Regulations or policies governing prescription, dispensing and administration

Strong recommendation

Governments should develop and implement policies to ensure that prescription, dispensing and administration of opioid agonist treatment is available for people with opioid dependence in all types of settings in which there is clinical need and should ensure continued access throughout transitions of care. The settings include communities, prisons and other closed settings.

Low certainty evidence

Good practice statement

In settings where there is high prevalence of non-medical use of certain controlled medicines, with associated harm, policies for prescribing, dispensing and administration of controlled medicines should be implemented to limit diversion to non-medical use without reducing access for those with clinical need or for the purpose of scientific research.

Good practice statement

Governments and relevant authorities should ensure that regulations and guidelines on prescription, dispensing and administration of controlled medicines are formulated to optimize safe, effective, equitable, convenient access for those with clinical need, while maintaining proportionate safeguards against potential harm.

Good practice statement

Governments and relevant authorities should ensure that regulations enable health professionals to prescribe, dispense and administer controlled medicines without undue barriers, allowing them to work to the full scope of their practice, to ensure that controlled medicines are accessible to patients with clinical need.

9.3 Prescription monitoring programmes and pharmacovigilance systems

Good practice statement

Governments should ensure robust nationwide systems that allow monitoring of prescriptions for controlled medicines, with specific attention to the protection of patient privacy, to optimize access to and safe use of controlled medicines. Where feasible and affordable, electronic systems should be prioritized. The absence of these systems should not be a barrier to access clinically necessary controlled medicines.

Good practice statement

Governments should ensure that systems for monitoring prescriptions of controlled medicines are not used to expose caregivers, patients or prescribers to unwarranted scrutiny in the delivery or receipt of clinically indicated health care.

Good practice statement

Governments should ensure active monitoring of the safety of controlled medicines, including new formulations, through a robust pharmacovigilance programme.

9.4 Pharmaceutical industry relations

Good practice statement

Governments should implement national regulations to ban misleading or unethical marketing of controlled medicines to patients, health-care providers and other stakeholders involved in medicine purchase or supply.

Good practice statement

Governments, professional societies and international organizations should implement robust, transparent policies to prevent and manage conflicts of interest in the training, education and promotion of products to health professionals and in the development of clinical guidelines. This includes both direct and indirect commercial influence via patient groups or other stakeholders.

Good practice statement

Governments should implement policies to address undue influence, including preventing and managing conflicts of interest of legislators, regulators and other government officials who may formulate or vote on legislation or rules for controlled medicines.

Chapter 10. Education, knowledge and attitudes (domain 7)

10.1 Training for health-care professionals

Strong recommendation

Governments, academic institutions and other responsible bodies should promote comprehensive training in adequate access and safe use of controlled medicines, according to clinical guidelines, in core curricula and continuing professional education of relevant health-care disciplines.

Very low certainty evidence

10.2 Patient and public education

Strong recommendation

Governments should ensure, through appropriate authorities and institutions, the delivery of balanced, accurate information about controlled medicines to patients, families, caregivers and the public. Information should be provided about the potential benefits and risks of therapeutic use and also of the potentially serious risks associated with non-medical use.

Low certainty evidence

Chapter 1

Introduction

1.1 Background

Medicines are at the core of all health-care systems. Ensuring affordable, equitable access to safe, good-quality, effective medicines is therefore a central challenge for policymakers everywhere. Governments and health systems must ensure that people who need medicines can access them, while also ensuring that the medicines are used safely and appropriately, avoiding harmful consequences for individuals and societies.

Balancing access to controlled medicines with safety in national policy

Achieving a balance between access to therapies for all people who need them and safe, medically appropriate use is especially important in the case of medicines that affect the brain and other parts of the central nervous system. Many of these medicines, including opioids, benzodiazepines, barbiturates and other types of controlled substances, are on WHO's model lists of essential medicines (EML) for adults and for children *(20, 21)*. They are needed by neonates, children, adolescents and adults, including older people, for pre- and post-operative care, sedation, prevention and relief of acute and chronic pain, palliative care, treatment of anxiety, agitation and insomnia, substance use disorder, attention deficit hyperactivity disorder, seizures and others (for instance, sickle cell disease). Without them, people of all ages and genders and all races, ethnicities and social groups may suffer avoidable pain, mental distress and other harms.

Because of the psychoactive properties of controlled medicines, they are also sought for non-medical use. When used non-medically, controlled medicines can seriously harm health and well-being and may contribute to mental health problems, high risk behaviour (resulting in physical injury, infections and road and industrial accidents), substance use disorder, premature death and other social harms.

The substances used to make controlled medicines are controlled under internationally agreed conventions. Parties to the conventions agreed to restrict the production, export, import, distribution and prescription of many medicines containing these substances (which are referred to collectively as "controlled medicines") to medical and scientific use. The purpose of the agreements is to reduce harmful non-medical use of controlled medicines while ensuring sufficient supplies of safe, effective medicines for people with clinical need.

The goals of ensuring access to and the safety of controlled medicines are not currently being met, according to the INCB, which is mandated to support Parties to the conventions in their implementation *(22)*. In its annual report for 2022, the INCB described the failure of current efforts to achieve a balance between maximizing access for safe and appropriate medical use, while minimizing unsafe and non-medical use globally.

> Despite the prominence given to the issue [of ensuring the availability of controlled substances for medical use] in the text of the conventions and the fact that the two conventions enjoy almost universal ratification, achieving adequate and affordable access to controlled medicines for the treatment of health conditions remains a distant goal in many countries, where people still suffer or die in pain or do not have access to the medications they need. At the same time as there is a lack of access to controlled medicines in many countries, other regions have experienced the negative health and social consequences of the non-rational prescription of controlled substances, resulting in an epidemic of opioid dependence and related overdose deaths *(22)*.

In its annual report for 2023 *(23)*, the INCB reiterated its commitment to supporting Member States in improving the availability of controlled substances for medical, scientific and industrial purposes, stating:

> ... there are notable disparities between countries in the availability of narcotic drugs, owing, among other reasons, to the issue that many governments do not accurately estimate their medical needs for opioid analgesics or have limited access to them. Consequently, and in line with the provisions and objectives of the 1961 Convention as amended, the Board emphasizes the importance of ensuring sufficient availability at the global level and calls upon countries with greater availability of and access to opiate raw materials and opiates to assist those countries with limited access and availability in their efforts to increase access to and availability of such substances and raw materials *(23)*.

The observations of the INCB are based on national consumption data collected from States Parties to the conventions. Between 2018 and 2020 in the USA, an average of over 20 000 standard daily doses of opioids were consumed for pain management per 1 million inhabitants per day *(22)*. In most western European countries during that period, consumption was 5000–10 000 standard daily doses per million inhabitants per day *(22)*, and in most countries in Africa and Asia, consumption was fewer than 100 standard daily doses per million inhabitants per day *(22)*.

While medical need differs among countries according to their epidemiological profiles, with sudden increases in cases of disasters and public health emergencies, the magnitude of the disparity in consumption indicates overuse in the countries in which the highest volumes are consumed and unmet need in countries with low consumption. This difference has real consequences for individuals and societies. High consumption without the necessary safeguards against inappropriate prescribing and diversion contributes to considerable opioid-related harm in some settings, while in countries with very limited access to opioids, millions of patients in need of pain management, palliative care, treatment of anxiety, agitation and insomnia, substance use disorder, attention deficit hyperactivity disorder, seizure disorders and other disorders suffer because controlled medicines are not available and accessible.

WHO's role in ensuring access to controlled medicines

Ensuring access to safe, effective, affordable medicines is one of the targets of the United Nations Sustainable Development Goals for 2030 *(24)*. Access to essential medicines is, however, a continuing challenge in much of the world. WHO supports Member States in extending access to safe, effective, affordable essential medicines for everyone who needs them. WHO has developed model EMLs for adults and for children *(20, 21)*; has provided clinical guidelines to ensure that countries have up-to-date evidence on optimal prevention and treatment regimens; and supports medicines regulators in ensuring that the medicines in circulation are safe and effective.

In low- and middle-income countries (LMIC) in particular, the gap between the need for and sustainable access to affordable, quality-assured medicines is higher for many psychoactive medicines than for other treatments. This may be due to restrictions imposed by the international conventions or how the conventions have been interpreted in national regulations, which make it more difficult to procure, prescribe and dispense medicines under international control *(25-27)*.

In 2018, it was estimated that 59.4% of the global need for pain medication to avert "serious health-related suffering" was unmet, which is, however, distributed unevenly. In high-income countries, the shortfall was estimated to represent under 2% of all need, whereas, in low-income countries, the shortfall reached 98% *(25)*.

In its annual report for 2022, the INCB noted that few reliable data are available on the unmet need for some psychoactive medicines for mental health, substance use or seizure disorders, partly because some countries were not fulfilling their obligations under the international conventions to provide information about consumption of these medicines *(22)*. This may be due partly to the fact that low-income countries with weak pharmaceutical systems lack the resources for such a complex exercise.

In a supplement to the annual report of the INCB for 2022 on the availability of internationally controlled substances, it was reported that OAT programmes provided services for fewer than one in 12 people who inject drugs in 50 countries that reported data to the Joint United Nations Programme on HIV/AIDS, reinforcing the statement of the INCB that, in some countries with a considerable number of people who inject drugs, "the presence of OAT services are limited or not present at all" *(28)*.

Treatment for neurological conditions is also lacking in much of the world. In 2019, WHO estimated that 75% of people living with epilepsy in LMIC had no access to the medicines they need to treat seizure disorders, including several benzodiazepines and barbiturates such as diazepam, lorazepam, midazolam and phenobarbital, which are on the WHO EML *(29)*.

Psychoactive medications such as methylphenidate and amphetamines, which are used for treatment of attention deficit hyperactivity disorder, are also often in short supply or inaccessible in LMIC, where strict regulations and limited resources make it challenging to adequately supply and distribute these essential medications.

In accordance with its mandate to support countries in achieving better health for all, WHO is committed to working with Member States to reduce the unmet need for controlled medicines and to implementing policies to ensure that use is safe and restricted for medical purposes and scientific research.

Controlled medicines and the right to health

The WHO Constitution asserts that all individuals have a right to health, defined as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity. Access to controlled medicines for those in need is an important part of the right to health. WHO Member States support this assertion, which is also enshrined in the constitutions of many Member States and in several World Health Assembly resolutions, such as those on surgical care, anaesthesia, palliative care and epilepsy *(30-32)*.

The right to health is also enshrined in the International Covenant on Economic, Social and Cultural Rights, which has been in force since 1976. General comment 25, adopted in 2020, states the right of people around the world, especially in more marginalized settings, to have access to affordable essential medicines, including to treat drug dependence *(33)*. General comment 14, adopted in 2000, stipulates the obligation of States Parties to ensure access to palliative care, reaffirming the importance of attention and care for chronically and terminally ill people, sparing them avoidable pain and enabling them to die in dignity *(34)*.

Controlled medicines and the international conventions

Medicines under international control: Controlled medicines are those with an identified or emergent clinical application the active pharmaceutical ingredients of which are listed under one or more of the schedules of the two international drug control conventions: the 1961 United Nations Single Convention on Narcotic Drugs as amended by the 1972 Protocol *(35)*; and the 1971 United Nations Convention on Psychotropic Substances *(36)*. The two conventions comprise different schedules, each of which indicates a different level of harm to health and medical or scientific usefulness.

The 1961 Single Convention on Narcotic Drugs includes opioids, opium and their derivatives, as well as synthetic or semi-synthetic versions. In the Anatomical and Therapeutic Classification system, these substances are classified as N01A, N02A or N07B, according to their use, or N02B when used in combination with other medicines *(37)*. These medicines are used for managing surgical, acute and cancer-related pain, palliative care and for treating dyspnoea and opioid use disorders.

The 1971 Convention on Psychotropic Substances includes medicines that have various effects on the central nervous system. They include benzodiazepines, barbiturates and psychostimulants, classified in the Anatomical and Therapeutic Classification codes as N03A–N07B *(37)*. They are used mainly to treat mood and psychotic disorders, hyperactivity disorders and seizure disorders and in palliative care.

Essential medicines under international control: Many controlled medicines that are under international control are considered by WHO to be essential medicines. Table 1 lists the internationally controlled medicines included on the 23rd EML and on the 9th EML for Children (both published in 2023) *(20, 21)*. These two lists name the medicines considered to be the most important in securing health in most countries. They are revised every 2 years; the current list can be consulted at https://list.essentialmeds.org.

Access to essential medications such as methadone and buprenorphine saves lives, reduces harm and exemplifies the principles of equity and human rights on which this document is based.

Table 1. **WHO-listed essential medicines under international control, according to the 23rd EML and the 9th EML for children, both updated in July 2023**

Medicine class	Medicine	International control	Therapeutic use
Barbiturates[a]	Phenobarbital	Psychotropic (Schedule IV)	Antiseizure medicine
Benzodiazepines[b]	Diazepam	Psychotropic (Schedule IV)	Antiseizure medicine; anxiety disorders; other common symptoms in palliative care
	Lorazepam	Psychotropic (Schedule IV)	Pain relief; antiseizure medicine; anxiety disorders
	Midazolam	Psychotropic (Schedule IV)	Antiseizure medicine; anxiety disorders; preoperative medication and sedation for short-term procedures; other common symptoms in palliative care
Opioids	Buprenorphine	Narcotic (Schedule III)	Treatment of opioid use disorders[c]
	Codeine	Narcotic (Schedule II)	Analgesic
	Fentanyl[d]	Narcotic (Schedule I)	Analgesic
	Hydromorphone	Narcotic (Schedule I)	Analgesic
	Methadone[d]	Narcotic (Schedule I)	Analgesic, treatment of opioid use disorders[c]
	Morphine	Narcotic (Schedule I)	Analgesic, preoperative medication and sedation for short-term procedures
	Oxycodone	Narcotic (Schedule I)	Analgesic

[a] Barbiturates: a class of controlled medicines derived from barbituric acid or thiobarbituric acid. Many are g-aminobutyric acid modulators, which are used as hypnotics and sedatives, as anaesthetics or as anticonvulsants.
[b] Benzodiazepines: a class of controlled medicines characterized by a chemical structure consisting of a group of two-ring heterocyclic compounds with a benzene ring fused to a diazepine ring; used for treatment of anxiety and seizures.
[c] These medicines should be used only for this indication in an established support programme.
[d] For the management of cancer pain

Other medicines under international control: Several controlled medicines are on the WHO EML; however, many others that are authorized for medical or scientific use are currently subject to international control. They includes barbiturates, benzodiazepines, opioids, dissociative-type medicines, amphetamines, cannabinoids and other classes of medicines that are authorized for medical uses in countries.

Controlled substances for medical and scientific research: For medicines to be registered for clinical use by a national medicines regulatory authority, they must have been developed and tested in clinical trials. The international drug control conventions clearly state that controlled substances should be available for scientific as well as medical use. WHO supports research and development of health products that meet public health needs and increase the number of safe, effective treatments for mental ill health, substance use disorder, pain and other health conditions *(14)*.The development of innovative products for the prevention and treatment of mental ill health, pain and other areas of health require that the scientific research community can access controlled substances for clinical research.

International control of medicines: The conventions states countries' minimum commitments for managing scheduled medicines. Countries that have signed the conventions agree to implement policies that restrict the production, import, export or distribution of substances covered by the conventions, so that only medical and scientific needs are met (38). Countries must also apply certain legal measures for such medicines to prevent their diversion for non-medical use across international borders. For some controlled medicines, countries must report quarterly or annually the volumes produced, imported, exported and consumed to the INCB. In 2020, almost 80% of signatories to the conventions reported annual statistics as required (38).

National control of medicines: While the conventions require policies and set minimum requirements on issues such as prescription and reporting of controlled medicines, countries decide the details of the policies and how best to implement them. Countries thus adapt controlled medicine policies according to their health needs, their health system capacity and their physical access to substances and medicines. Some countries allow limited access to controlled medicines that have not yet received regulatory approval for specific conditions, under relevant legal frameworks. Additional flexibility allows adaptation of some globally mandated procedures in some settings and circumstances, such as during humanitarian emergencies *(39)*.

Countries are authorized to implement control measures that exceed the minimum requirements established by the conventions. More stringent controls should not, however, render controlled substances inaccessible for important medical or scientific use. Some countries may place additional medicines under control. WHO recommends that countries apply these guidelines to all medicines under both national and international control.

1.2 Purpose of the guideline

The purpose of this guideline is to provide recommendations and good practice statements developed by a multidisciplinary GDG and informed by the best available evidence, to support Member States in choosing national policies on controlled medicines. Each country should develop and implement policies that maximize access to controlled medicines for all people who need them, while effectively restricting harmful non-medical use that carries serious risks to the safety of individuals and communities.

This document replaces earlier guidance, published in 2011, which was not based on a systematic review of the evidence *(40)*, and was withdrawn in 2019.

1.3 Structure of the guideline

This guideline was developed in accordance with the WHO handbook for guideline development *(18)*. The GDG agreed on several principles to underpin the recommendations and good practice statements in the guidelines, which are stated at the beginning of the relevant chapters. Chapters 4–6 address areas of policy for which WHO has already issued guidance. They outline the policy area, provide links to guidance and describe any additional considerations of special importance to controlled medicines.

Policy recommendations in the remaining chapters (7–10) are based on a rapid systematic review of published studies and other quality-assured evidence to establish the relations between policy choices and two broad outcomes: access to controlled medicines for those who need them, and minimization of use that is not in accordance with the most recent, evidence-based clinical guidelines.

The methods for guideline development, including consultations and information on the guideline contributors, are summarized in chapter 2, with additional detail provided in Annex 1. The summary of findings and EtD tables are presented in Annex 2. The reports of the full rapid systematic reviews are available on request.

1.4 Intended audience

This guideline is intended for those who develop and/or implement evidence-based policies, regulations and best practices to promote access to safe, effective, affordable controlled medicines, while preventing non-medical use and harm to health. Target audiences include national and local health-care and social well-being policymakers and implementers and managers of national and local health and medicines supply programmes. They also include professionals involved in:

- health system financing;
- medicine regulation and registration;
- medicine selection and procurement;
- oversight and planning of medical supply chains and prescription policy;
- post-market surveillance and pharmacovigilance; and
- education and training of health professionals.

As outlined in the next section, every country should use the guideline to develop policies in discussion with the people most likely to be impacted by them: health professionals, patients and their families and carers, and other relevant community groups (for instance, faith leaders). The guidelines may also guide policymakers in the criminal justice and law enforcement fields and civil society when advocating for access to OAT.

1.5 Scope of the guideline

Populations: The recommendations in this guideline are for policies addressed to groups (of all ages) affected by conditions for which use of internationally or nationally controlled medicines is deemed to be medically appropriate according to evidence-based guidelines.

Development of the guideline included consideration of adapting policies to meet the specific access and safety needs of patients in different demographic groups, including neonates, children, adolescents, young people, adults and older people. The guideline includes the needs of vulnerable populations.

Clinical contexts: Controlled medicines are most likely to be used in the following contexts:

- anaesthesia and procedural, pre- and post-surgical care;
- disease conditions associated with acute pain, chronic cancer pain and chronic non-cancer pain;
- palliative care and care in hospices;
- management of mental health disorders;
- management of substance use disorder;
- management of neurological conditions, including seizures and severe spasticity;
- other relevant conditions, such as sickle cell disease;
- clinical research on medical applications of controlled substances; and
- humanitarian emergencies and crises.

Some clinical conditions, notably acute and chronic pain, trauma surgery and acute mental health problems, are particularly likely to occur during humanitarian emergencies, including those due to climate or geological disaster, political or ethnic conflict or epidemics of serious infectious diseases. These conditions and circumstances were considered during guideline development.

Types of controlled medicines: The recommendations in this guideline are intended to address all types of controlled medicines with authorized medical or scientific purposes. They include opioids, benzodiazepines, barbiturates, dissociative anaesthetics, cannabinoids, hallucinogens and amphetamine-type stimulants.

Policy areas considered to be out of the scope of this guideline: This guideline addresses policies rather than clinical practice. Policies outside the scope of this guideline include the following.

- Policies that do not cover any medical use of the controlled substance but relate exclusively to cultural, recreational or other non-medical uses and policies that permit or prohibit possession of controlled substances for these purposes are not considered, unless they also explicitly cover possession or use for medical purposes;
- Policies that govern psychosocial and other non-pharmacological interventions for treating conditions for which controlled medicines could be used (such as reducing anxiety or management of pain).
- Policies on veterinary medicine.
- These guidelines do not provide advice on the clinical use of controlled medicines. References to relevant WHO and partner guidelines and resources are provided in Annex 3.

Chapter 2

Methods

2.1 Overview

This guideline was developed in accordance with WHO's processes for guidelines, as set out in the WHO handbook for guideline development *(18)*. The recommendations are based on the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) *(41-43)* approach to reviewing evidence and formulating recommendations.

The main steps in the development of WHO guidelines are:

- identification of contributors to the guideline process;
- establishment of the general scope of the guideline and development of key questions;
- performance of rapid systematic reviews of the evidence to address the key questions;
- assessment of the certainty (quality) of the body of evidence for important and critical outcomes in the GRADE framework;
- formulation of recommendations within the WHO-INTEGRATE framework;
- drafting the guideline document for review and approval by the GDG and for peer review by the external review group;
- review and approval by WHO's quality assurance body; and
- publication and dissemination.

2.2 Contributors to the guidelines

Guideline development involved formation of several groups to guide and implement the process. Each group played a specific role, as described below. The members of these groups and other contributors are listed in the acknowledgements.

WHO steering group. The WHO steering group comprised members from relevant technical units at WHO headquarters, who provided technical guidance and support throughout development.

GDG. The GDG was responsible for finalizing the scope and key questions, interpreting the evidence and formulating the final evidence-based recommendations, including implementation considerations. The GDG convened in five informal preparatory meetings between June 2020 and May 2023 before convening in an in-person GDG meeting at WHO headquarters to formulate recommendations, on 28 August–1 September 2023. An informal follow-up meeting was held in June 2024.

The GDG consisted of 13 members balanced by gender and from all six WHO regions. GDG members were identified in a public call for experts and were selected according to their area of specialization, geographical representation, gender diversity and ability to serve as GDG members in an independent capacity. Their areas of specialization ranged from addiction medicine, palliative care, pain management, human rights, public health and harm reduction; they also covered care for both adults and children. The proposed membership list was posted for public review and comment and was then finalized.

External review group. The external review group was responsible for peer reviewing the guideline document. The group was selected to ensure geographical and gender balance and comprised members from academia, policy and research, programme implementation and networks of key and vulnerable populations. External review of the guideline was undertaken in November 2024.

External guideline contributors. Systematic review teams were commissioned to conduct reviews of evidence on the effectiveness and the factors affecting the implementation and impact of balanced national policies for access and safe use of controlled medicines. Guideline methodologists supported the WHO secretariat and the GDG throughout development of the guideline. Guideline writers summarized the GDG deliberations during the GDG meeting and drafted the chapters of the guideline.

2.3 Declaration and management of competing interests

Competing interests may occur in health care and could result in conflicts of interest leading to biased generation or assessment of evidence and to misinformed health-care policies. WHO has stringent policies for avoiding, or least limiting, conflicts of interest, particularly in the development of official guidance that affects health care. As declarations of conflict of interests are insufficient to neutralize potentially harmful effects, the Organization has accurate mechanisms for identifying relevant conflicts of interest and approaches for managing such conflicts. These include exclusion of members, recusal from participation in meeting sessions and restricting participation, thus ensuring the validity and transparency of WHO decisions and their credibility.

In order to improve management of conflicts of interest and to strengthen public trust and transparency in WHO meetings and activities involving the provision of technical or normative advice, the names and brief biographies of individuals ("published Information") being considered for participation in a WHO-convened GDG are disclosed for public notice and comment.

Before each informal and formal meeting, in accordance with WHO policy, all GDG and all temporary advisers attending the meeting submitted written disclosures of potential conflicts of interest that might affect, or may be reasonably perceived to affect, their objectivity and independence in relation to the subject matter of the meeting. The WHO secretariat received the disclosures and sought the advice of the Office of Compliance, Risk Management and Ethics. No disclosures that required measures to be taken with regard to participation in meetings. One expert who took on a government position after the guideline recommendations had been made self-recused from subsequent informal meetings.

GDG members were invited to join the committee only after consideration of their declared interests, in accordance with WHO's protocols. Information about GDG members can be accessed at: https://cdn.who.int/media/docs/default-source/controlled-substances/ensuring-balance-gdg-members-list-23012020.pdf?sfvrsn=676961e6_2>.

2.4 Consultation and definition of scope

The scope of the guideline was decided by consultation. It was first discussed by the internal guideline steering group, which consisted of experts from WHO departments. The scope was further refined by the GDG, a panel of independent experts selected after an open call. The proposed scope was then opened for public comment, including in a public hearing in January 2020. Written and oral comments provided during this consultation were considered in finalizing the scope of the guidelines.

2.5 Rapid systematic reviews

For these guidelines, WHO commissioned rapid systematic reviews of the evidence to evaluate the effectiveness of and the factors that affect the implementation and impact of balanced national policies for access and safe use of controlled medicines. Given the broad scope and new conceptual terrain of the guideline questions and the fact that the literature was relevant to many disciplines and addressed both safety and access, several rapid review techniques were used:

- restricting the number of databases and languages,
- screening and inclusion by a single reviewer,
- sampling of eligible studies (for synthesis of the qualitative evidence),
- simplified study descriptions and quality assessments,
- data extraction by a single reviewer, and
- a descriptive (narrative) approach to data synthesis.

Tables summarizing the findings are presented in Annex 2. The full reports of the rapid systematic reviews are available upon request.

A rapid systematic review approach was used to address both primary effects (effectiveness) and qualitative studies and systematic reviews of effects and/or qualitative evidence. The protocols were made publicly available in Prospero for a rapid systematic review of evidence on the effectiveness of national policies for ensuring access to and safe use of controlled medicines (PROSPERO 2022 CRD42022362411) and a rapid qualitative synthesis of evidence on factors that affect the implementation and impact of national policies for ensuring access to and safe use of controlled medicines (PROSPERO 2022 CRD42022362391).

In accordance with the agreed scope, the GDG listed national policies for optimizing access to controlled medicines while ensuring their safe use. The objective of the review on effectiveness was to evaluate the effectiveness of national policies in ensuring access to and safe use of controlled medicines for patients with appropriate therapeutic needs and preventing or reducing non-medical use of controlled medicines. The objective of the synthesis of qualitative evidence (a systematic review of qualitative evidence) was to identify and explore the factors that affect the implementation and impact of national policies for ensuring access to and safe use of controlled medicines.

2.5.1 Formulation of key questions and prioritization of interventions and outcomes

Draft population, intervention, comparator, outcome (PICO) questions were first discussed and reviewed by the WHO secretariat, the Guideline Steering Group and the GDG. The final PICO questions were determined by the GDG. The population and intervention were identical for the two reviews (Evidence on the effectiveness of national policies and Factors affecting the implementation and impact of national policies for ensuring access to and safe use of controlled medicines); however, the comparator and the outcomes differed slightly, and they are outlined below separately.

Participants and populations

National policies should ensure access to and safe use of controlled medicines for patients who require access to:

- opioids for acute, procedural (anaesthesia and post-surgical pain) and chronic pain;
- opioids for the management of substance use disorder (in the form of OAT);
- benzodiazepines for the management of anxiety disorders;
- barbiturates for the management of epilepsy;
- amphetamines and other stimulants for the management of attention deficit hyperactivity disorder and narcolepsy;
- other controlled substances with emergent medical applications; and
- access to controlled medicines for patients in palliative care.

Policies should also ensure access for individuals at risk for non-medical use of controlled medicines, including those:

- with a therapeutic indication and legitimate prescription for controlled medicines use;
- with a prescription that is not indicated and/or not legitimate; and
- without a therapeutic indication or a prescription, who have accessed controlled medicines from other sources.

For synthesis of the qualitative evidence, most of the direct participants and populations in the eligible studies were policymakers, programme managers, clinicians, civil society and industry stakeholders and others involved in the design, implementation and evaluation of these policies.

Interventions and exposures

WHO identified seven relevant policy areas for these guidelines. The first three were not addressed in the systematic reviews, which addressed the next four, with 14 intervention types (ITs). (See Table 2 below).

Comparators and controls (Evidence on the effectiveness of national policies)

Research on the effectiveness of national policies included comparisons of the effectiveness of policies with other controlled medicines policies with the same objectives or outcomes, such as the absence of a controlled medicines policy, outcomes in the same setting (before-and-after studies), similar policies in other settings or another comparison. Studies with no comparison group or control condition of some kind were excluded.

Comparators and controls (Factors that affect the implementation and impact of national policies)

Most of the qualitative studies did not include an explicit comparator or control condition in the study design. Some studies included longer-term historical comparisons, shorter-term before–after studies of implementation or comparisons of different contexts (within or between countries).

Outcomes (Evidence of the effectiveness of national policies):

- the effectiveness of national policies on access to and safe use of controlled medicines;
- improving access by improving availability, accessibility, affordability, acceptability and/or quality (any such outcome was included); or
- improving safe use, by both improving the prescription, dispensing and administration of controlled medicines so that patients receive the appropriate medicines at the correct doses for the correct duration, and preventing or reducing non-medical use, including over-se, unintended use and diversion of controlled medicines (any such outcome was included).

Outcomes (Factors that affect the implementation and impact of national policies)

- any factor that affects the implementation or impact of national policies on access to and safe use of controlled medicines, through either the policies or interventions themselves or the contexts in which they are implemented;
- improving availability, accessibility, affordability, acceptability and/or quality; and
- improving safe use by both improving the prescription, dispensing and administration of controlled medicines so that patients receive the appropriate medicines at the correct doses for the correct duration and preventing or reducing non-medical use, including overuse, unintended use and diversion of controlled medicines.

The WHO-INTEGRATE EtD framework was used to code the findings.

Context

Studies were considered from any country and health system setting; conducted at national or sub-national (province or state) level or in large health systems; conducted in either in-patient and out-patient (ambulatory) settings; conducted in high-income, middle-income and low-income countries; or conducted in emergency and humanitarian settings.

Prioritization of interventions to guide synthesis of the evidence

Interventions of relevance to the guidelines were identified by the WHO secretariat and the GDG and organized into a framework to guide the evidence syntheses. Several iterations of the framework were designed, and it was further modified once the systematic review began to simplify the overall approach and to reflect assessments of the variety of interventions reported in in the scientific literature.

Seven broad areas of intervention (e.g. medicines regulation and control) were formed, and a number of different policy interventions were selected for which evidence of effectiveness was to be sought (e.g. drug product safety), see Table 2.

In view of the many areas in which controlled medicines are used and the urgency of replacing the earlier guidelines on access to controlled substances, the GDG approved a progressive approach, focusing the systematic review on the topics most specific to controlled medicines. Other topics that would be included in a comprehensive, balanced approach to controlled medicines, such as national policy formulation, programme financing and medicine selection and procurement, overlap considerably with areas in which WHO guidance is available. Such guidance is referred to in chapters 4–6, which indicate issues specific to controlled medicines that should be considered in applying the available guidance.

Table 2. **Framework of intervention and sub-intervention types**

Chapter	IT number	IT	Sub IT
7. Quantification, procurement, supply and production	7.1	Quantification of controlled medicines	–
	7.2	Procurement guidelines, tools and mechanisms	–
	7.3	Supply chain guidelines, tools and mechanisms	–
	7.4	Local production of controlled medicines	–
8. Medicines regulation and control	8.1	Drug product safety	Changes to formulations, labelling and packaging
	8.2	Possession and use of controlled medicines	Extended or explicit permission Pain clinic and related types of regulation
	8.3	Medicines scheduling	–
	8.4	Import and export regulations	–
9. Prescribing, dispensing and administration	9.1	National policies on clinical guidelines	–
	9.2	Prescription, dispensing and administration	Prescription practices (for providers) Prescription governance (for systems) New models of care and service delivery
	9.3	Prescription monitoring programmes and pharmacovigilance systems	–
	9.4	Industry marketing regulations	Regulation of direct-to-patient and direct-to-consumer marketing
10. Education, knowledge and attitudes	10.1	Training for health-care professionals	–
	10.2	Patient and public education	Patient education Public education

Prioritization of outcomes to guide the evidence syntheses

A framework for organizing and prioritizing the outcomes of interest in the evidence synthesis was initially developed by the GDG and the WHO secretariat. In view of the wide variety of intervention types and possible outcomes of interest to policymakers; however, a simplified framework was developed to structure the results of the evidence synthesis. The main outcomes were organized according to the focus of the outcome and the outcome category.

Outcome focus: To ensure that evidence was presented in an appropriately balanced form, outcomes were categorized as related to access or to safety, i.e. affordable access to quality-assured controlled medicines for patients with clinical need and safe use (and/or absence of unsafe use) of controlled medicines.

Outcome category: The broad outcome categories defined included: provider knowledge, provider practice, patient knowledge, patient practice, health outcomes and market outcomes. The summary tables (Annex 1) provide more detailed, specific information about the outcomes in each study. During development of the GRADE evidence profiles to evaluate the certainty of the evidence (see Assessment of the certainty of evidence, below, for a description), outcome evidence was grouped under these broader categories.

2.5.2 Quality assessment, synthesis and grading of the evidence

Assessment of risk of bias/methodological limitations of primary studies included in the reviews

For studies included in the systematic review of the effectiveness of national policies, assessment of risk of bias/methodological limitations was done using a rapid approach to risk of bias assessments based on GRADE's list of the four most significant threats to validity in observational designs *(44)*. Final assessments of risk of bias were categorized as "not serious", "serious" or "very serious".

The methods used in the systematic reviews of effects were assessed for quality with the Health Evidence Quality Assessment Tool of McMaster University *(45)*.assessment of quality was categorized as weak, moderate or strong.

For the qualitative studies included in the synthesis of qualitative evidence on factors that affect the implementation and impact of national policies, a simplified version of the Critical Appraisal Skills Programme tool *(46)* was used to assess methodological limitations. The methods used in published syntheses of qualitative evidence were assessed with the Health Evidence Quality Assessment Tool *(45)*. The final assessment of quality was categorized as weak, moderate or strong.

Synthesis of the evidence

For the effectiveness studies, an aggregative approach was used, in which the primary outcomes of studies and systematic reviews and basic descriptive information, outcomes measures, findings and general direction of the effect (in the intended direction or not) were summarized narratively.

The findings for 14 ITs were analysed and, as appropriate, for subtypes, as some of the 14 ITs included several distinct subtypes of interventions. For ITs or sub ITs, the findings were divided into safety and access outcomes, and the synthesis was further divided by broad outcome type (e.g. knowledge, practice, health). Synthesized findings from primary studies and from systematic reviews were presented separately.

Access and therapeutic contexts were noted for each set of synthesized findings. Some systematic reviews included meta-analyses of findings. In the few cases in which it was possible, pooled estimates of effect were extracted.

For the qualitative studies, an inductive approach was used for initial data extraction, with open coding to identify, organize and interpret factors that affected the implementation and impact of the policies reviewed. Concepts and themes were developed and refined in an iterative fashion in parallel with data extraction in the constant comparative approach. Although a broadly inductive approach was initially used to identify and organize the broad themes and concepts, this rapidly changed to organizing and developing the extracted data and emerging findings with the WHO INTEGRATE framework constructs *(19)*, which are described in chapter 2.5.3.

Many of the broad themes that emerged from this review were not directly linked to specific interventions or intervention types but rather to several or, in some cases, all intervention types and chapters. Qualitative findings that were directly related to an IT were included in the synthesis

for that IT. In addition, cross-cutting "contextual" qualitative evidence was found after the IT-specific chapters had been included. Such cross-cutting findings might not apply to all ITs but address more general aspects of intervention design and implementation.

Assessment of the certainty of evidence

The quality of evidence was assessed with the GRADE system for quantitative evidence. GRADE evidence profiles were organized into the main outcome categories (e.g. safety-related provider practice outcomes) rather than dividing the tables (or the underlying syntheses) by more specific outcome measures in that category (e.g. distinguishing prescription quantity from prescription rate). In the GRADE approach, randomized controlled trials were considered to provide high-certainty evidence, while non-randomized and observational studies were considered to provide low-certainty evidence. The evidence for each outcome was then downgraded if indicated by the assessments of risks of bias, inconsistency, imprecision, indirectness and publication bias. With this approach, the certainty of evidence for each outcome was rated as high, moderate, low or very low. A GRADE assessment of certainty is provided at the end of the narrative synthesis for each finding of effectiveness in studies of primary effects.

Assessment of the certainty of the findings from the systematic reviews was more complicated, as very few of the authors of systematic reviews had conducted and reported their own GRADE assessments of their findings, and the rapid approach used in this review precluded going back to the original studies and conducting our own GRADE assessment of each of these findings. Still, it was important for the GDG to have some indication of the certainty of findings from the systematic review evidence on which they based their recommendations. A tailored approach to assessing the certainty of the evidence was developed that included study design, estimates of effect, risk of bias or the quality and certainty of the findings from each of the underlying primary studies as well as the methodological quality of the review itself. An overall assessment of the certainty of the evidence was than made. These assessments are documented in Annex 1.

GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research was used *(47)* for findings from primary studies. In this approach, confidence in the evidence is based on four components: methodological limitations of the included studies; the coherence of the review finding; the adequacy of the data that contributed to a review finding; and the relevance of the included studies to the review question *(47)*. All the assessments were considered to be high confidence and were downgraded if important concerns were identified for any of the four components of confidence. The overall confidence was judged as high, moderate, low or very low.

2.5.3 Development of recommendations

Evidence for each intervention was synthesized into EtD tables for consideration by the GDG, within the WHO INTEGRATE framework *(19)*, which includes contextual considerations with technical evidence. The EtD tables (Annex 1) present the evidence identified in the systematic reviews and evaluated and synthesized for consideration by the GDG that was relevant for each WHO INTEGRATE criterion *(19)*. Although evidence was not collected for every criterion for each intervention, the GDG considered each in making a recommendation (Table 3).

Table 3. **WHO INTEGRATE criteria and their implications for making a recommendation**

Criterion	Question(s) addressed	Implications for a recommendation
Balance of health benefits and harms	Does the balance between desirable and undesirable health effects favour the intervention or the comparison? What is the certainty of the evidence of effects?	The greater the net health benefit associated with an intervention, the greater the likelihood of a general recommendation in favour of the intervention.
Human rights	Is the intervention in accordance with universal human rights standards and principles?	All recommendations should be in accordance with universal human rights standards and principles.
Sociocultural acceptability	Is the intervention acceptable to relevant stakeholders?	The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favour of the intervention.
Health equity, equality and non-discrimination	What would be the impact of the intervention on health equity, equality and non-discrimination?	The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favour of the intervention
Financial and economic considerations	Do financial and economic considerations favour the intervention or the comparison?	The more advantageous the financial and economic implications of an intervention, the greater the likelihood of a general recommendation in favour of the intervention.
Feasibility and health system considerations	Is the intervention feasible to implement?	The greater the feasibility of an option from the perspective of all or most stakeholders, the greater the likelihood of a general recommendation in favour of the intervention. The more advantageous the implications for the health system as a whole, the greater the likelihood of a general recommendation in favour of the intervention
Quality of evidence	What is the overall quality of the evidence?	The greater the quality of the evidence by various criteria in the WHO INTEGRATE framework, the greater the likelihood of a general recommendation.

The GDG reviewed the results of the systematic reviews and the EtD for each chapter at a meeting at WHO headquarters on 28 August–1 September 2023 (Annex 1) and agreed on recommendations by consensus. The GDG based the recommendations on their interpretation of the evidence, supplemented by information from GDG members with specific areas of expertise, as appropriate. Implementation considerations, statements on limitations of the data and recommendations for further research were also discussed.

According to WHO guidance *(18)*, the strength of the recommendations was classified as "strong" or "conditional" to reflect the confidence of the GDG in the desirable and undesirable consequences of implementing the recommendation. A "strong" recommendation reflects high confidence about the balance, while a "conditional" recommendation reflects some uncertainty. Caution is recommended in making strong recommendations when the quality of the evidence is low or very low. When the GDG considered that it was necessary to consider formulating a "strong" recommendation based on low or very low quality evidence, the WHO handbook (chapter 14) *(18)* was consulted (see Table 1). When the GDG considered that failing to make a "strong" recommendation could result in a life-threatening situation and the harm was probably immaterial, they made a "strong" recommendation, placing a very high value on an uncertain but potentially life-preserving benefit.

In accordance with the WHO handbook for guideline development *(18)*, when the GDG identified additional relevant evidence (either direct or indirect) when deliberating on each chapter and IT during the meeting on the criteria for developing a recommendation, it was presented and discussed. Such evidence is identified as having been submitted by the GDG in the EtD tables for each of the guideline recommendations. As such studies were not identified in the systematic reviews, their quality was not evaluated by the GRADE approach, and the evidence was therefore considered of "very low" quality.

2.5.4 Document review

The present document was drafted by the secretariat to present the recommendations of the GDG at the meeting on the results of systematic reviews. It was circulated to the GDG and to the WHO guidelines steering committee members for review and comment. After an online GDG meeting in May 2024, the guideline was refined and reviewed again with the Chairs, before being sent for review by the ERC. The final draft was reviewed by the WHO Guidelines Review Committee.

Chapter 3

Guiding principles

The GDG agreed on several principles as a basis for the recommendations and good practice statements in this guideline, which underly all aspects of national policies on access to and safe use of controlled medicines.

1. **All people have the right to the enjoyment of the highest attainable standard of health, a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.**

WHO remains committed to the principles set out in its Constitution, including that the enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition. The health of all people is fundamental to the attainment of peace and security and is dependent on the fullest cooperation of individuals and States.

2. **Controlled medicines are crucial for managing many health conditions and treating illness. Access to controlled medicines for people with clinical need, throughout their lifespan, is part of the right to health, which is a fundamental human right.**

Controlled medicines play a vital role in alleviating suffering and improving the quality of life. A number of controlled medicines are on the WHO EMLs, which are considered essential for alleviating pain and suffering, enabling surgery, treating mental health conditions, supporting dignified and comfortable end-of-life care, helping people to overcome addiction and saving lives.

Ensuring access to controlled medicines for those with clinical need is a medical necessity and part of the right to health, which is a fundamental human right. The International Guidelines on Human Rights and Drug Policy *(48)* states:

> ... in accordance with their right to health obligations, States should … take legal and administrative steps to ensure the adequate availability, accessibility, and affordability of controlled medicines…; and amend laws, policies, and regulations that unnecessarily restrict the availability and access to controlled medicines *(48)*.

Denial of access to controlled medicines can lead to unnecessary suffering and diminished health outcomes.

Fundamental human rights recognized in international human rights instruments include the right to be free from torture and from cruel, inhuman or degrading treatment or punishment. Member States therefore have an obligation to protect people from torture and maltreatment. This right is threatened if people do not have access to essential controlled medicines, including those for pain relief. A report by the Special Rapporteur on Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment in 2013 *(49)* affirms:

> … that the failure to ensure access to controlled medicines for the relief of pain and suffering threatens fundamental rights to health and to protection against cruel, inhuman and degrading treatment *(49)*.

Governments must therefore guarantee access to essential controlled medicines as part of their minimum core obligations under the right to health and take measures to protect people under their jurisdiction from inhuman and degrading treatment. There is also a medical and moral necessity of ensuring access to controlled medicines for use in response to humanitarian emergencies and crises of all types.

3. National policies pertaining to controlled medicines should be balanced to enable safe and appropriate use, ensuring access for medical and scientific need, while avoiding harmful consequences for individuals and societies.

Various governmental and inter-governmental bodies have stated the dual obligation of ensuring adequate availability of controlled medicines for medical and scientific purposes while at the same time preventing illicit production, trafficking and diversion of these medicines. The Preamble to the 1961 Single Convention on Narcotic Drugs *(35)* states that

> the medical use of narcotic drugs continues to be indispensable for the relief of pain and suffering and that adequate provision must be made to ensure the availability of narcotic drugs for such purposes *(35)*.

It also notes potential misuse of these medicines and the need to prevent and combat non-medical use with effective measures *(35)*. Opioid stewardship has been advocated as a mechanism to achieve this balance *(5)*, a principle that can be applied to all controlled medicines in the scope of this guideline.

4. Member States and health-care providers should ensure that patients and their families and caregivers know their rights to self-determination, non-discrimination, accessible and appropriate health services and confidentiality.

Access to information on their rights to self-determination, non-discrimination, accessible and appropriate health services and confidentiality enables people to advocate on behalf of another person or for themselves and to seek the care to which they are entitled, including care that may require treatment with controlled medicines.

5. All national policies should be tailored to the needs and requirements of the population, their social context, resources and health system characteristics, while recognizing the individual right to the highest attainable standard of health.

National health policies should be based on understanding of the unique needs and circumstances of the population they serve, acknowledging the diversity and complexity of social contexts and resources in order to be relevant and impactful, allowing everyone with clinical need to access the necessary controlled medicines and health services without discrimination.

6. Patients, patient advocacy groups, health professionals, professional societies and other affected groups should be encouraged and facilitated to participate in the formulation of health policy.

Governments are responsible for the health of their people, which can be fulfilled only by the provision of adequate health and social measures. Informed opinion and active cooperation of affected groups and the public in policy on the safety of and access to controlled medicines is of the utmost importance. Participatory approaches can ensure that controlled medicines policies reflect and address the population's needs and preferences.

Chapter 4

Development of a national policy on controlled medicines

The aim of a national medicines policy is to meet needs for medications and related services and to provide direction to public and private bodies on both the demand and the supply of the medicines market. The objectives generally include securing a sustainable national supply of quality-assured medicines that is adequate to treat all patients with medical need and for scientific needs, ensuring that the medicines are affordable and cost effective and that they are used rationally. A national medicines policy is a high-level framework, setting broad parameters within which more specific operational policies can be developed.

National medicines policies should include controlled medicines for patients in need of surgery, pain relief, palliative care, treatment for mental health or substance use, seizure disorders and other conditions for which controlled medicines are used. In addition, such policies should support access to controlled medicines for scientific purposes, in medical research. The restrictions placed on many of these medicines by international conventions and by national law mean, however, that more administrative procedures are necessary for securing access than for medicines that are not controlled. It may therefore be necessary to develop an additional national strategy for controlled medicines, which must remain within the parameters of the broader national medicines policy and be based on the guiding principles (chapter 3). It may also include policies specifically for identifying and addressing barriers to access to controlled medicines, creating a balance between maximizing affordable access for children and adults in need while minimizing the health and social risks associated with unsafe or non-medical use.

Development of a national medicines policy is rarely straightforward. Consideration must be given to existing policies and practices and to the national context. The interests of many groups must be balanced, including those who manufacture, engage in commerce, pay for, prescribe, dispense, administer and take medicines. With respect to controlled medicines, the group of interested parties may be extended to include groups such as border control, law enforcement and criminal justice systems, which are less frequently involved in formulation of broad national medicine policies.

4.1 WHO guidance on development of a medicines policy

WHO recommends that all countries develop and use a national medicines policy and that they regularly monitor implementation and update the policy to ensure that its goals remain in line with national medical needs social priorities and the most recent international norms *(15)*. The importance and utility of a national medicines policy is demonstrated by its inclusion as an essential element in the WHO Global Benchmarking Tool for national medicine regulation *(50)*. The recommendations for formulation of a broad national medicines policy also apply to medicines under international control.

WHO guidance suggests that national medicines policies have the following components:

- selection of essential medicines;
- pricing and affordability;
- drug financing and reimbursement;
- procurement and supply chain policies, including licensing, stocking and delivering;
- regulation and quality assurance;
- rational use, including rational prescribing and dispensing and safe elimination;
- research;
- human resources; and
- monitoring and evaluation.

Countries have also found it useful to include policies on institutional arrangements, industrial policy, pharmaceutical security and data systems *(51)*.

4.2 Locally appropriate, needs-based policies

WHO stresses the importance of ensuring that national medicines policies are tailored to maximize safe access to controlled medicines according to national circumstances, including epidemiology, health system structure and capacity, health system characteristics, health financing structures and social and cultural norms *(15)*.

This is particularly important in the case of controlled medicines, as historically determined, culturally embedded assumptions often affect their availability, acceptability and use. As controlled medicines are subject to international conventions that require national policy responses, however, policies used in other countries may be adopted. As countries often have widely different requirements and resources, access to precursors and raw materials from which controlled medicines are made may differ.

4.3 Multi-stakeholder consultation on policy development

Ensuring access to essential medicines requires collaboration among many stakeholders, including policymakers, law enforcers, health service providers, health professional organizations, health insurers and academics. People who need controlled medicines, their families, their communities, patient advocacy groups and the pharmaceutical industry should also be involved. WHO therefore recommends active involvement of a variety of interest groups in the development of national medicines policies *(15)*:

> The consultations and national discussions preceding the drug policy document are very important, as they create a mechanism to bring all parties together and achieve a sense of collective ownership of the final policy. This is crucial in view of the national effort that will later be necessary to implement the policy. The policy process is just as important as the policy document *(15)*.

WHO recommends active engagement of sectors not usually involved in human health from the start of policy formulation *(15)*. In the context of controlled medicines, these are likely to include:

- professional, patient and academic organizations for palliative care, pain management, cancer, mental ill health, substance disorders, humanitarian emergency health care, surgery, veterinary medicine and all other health sectors in which controlled medicines are commonly used;
- professional and academic organizations for the provision of care for demographic groups in which controlled medicines are commonly used, including neonatologists, paediatricians, gerontologists, pharmacy professionals and dispensaries; and
- representatives of security, border control and criminal justice systems.

4.4 Unique considerations for controlled medicines and issues in implementation

Balance: Involvement of all constituencies in policy development is likely to result in national policies that are feasible to implement and that achieve the best possible balance between ensuring access to quality-assured medicines for those who need them, while minimizing inappropriate use.

Inevitably, policies (including some of those described in this guideline) differ in their focus on those two goals, some with the principal aim of maximizing access to controlled medicines for those in need and others with the aim of reducing the risk of non-medical and unsafe use. The relative importance of each policy depends on the national context, but all should adhere to human rights standards.

As outlined in chapter 1 and emphasized in the INCB analysis *(28)*, access to and consumption of controlled medicines differs widely across the world. Countries with many unmet needs may choose to focus on ensuring that people who need controlled medicines can access them, including facilitating provision for the purpose of scientific research, and expanded access programmes intended to address unmet needs. Countries that meet their population's clinically indicated need for controlled medicines but in which there are also high recorded levels of harm associated with non-medical use may prioritize policies to reduce harm. The two goals are not, however, mutually exclusive but are complementary. All national policies on controlled medicines should include a mix of strategies to achieve an optimal balance of maximizing health and well-being while minimizing harm. Governments should also ensure that unbalanced policies do not limit health care for either patients who need essential medicines for symptom relief or for people vulnerable to non-medical use.

Evaluation and adaptation: WHO recommends that the impact of national medicines policies (particularly on sustainable access to affordable, quality-assured medicines) be monitored and that the policies be adjusted as necessary to achieve the goal *(15)*. Continuous close monitoring of policies and their impact is particularly important for controlled medicines, because clauses to maximize access and minimize harm may interact. It is therefore important to ensure that, during monitoring, data are collected on both goals and that they are evaluated holistically so that policies can be adjusted as necessary over time to achieve and maintain an optimal balance.

Timeframe: Inclusion of many groups with different perspectives and priorities with respect to controlled medicines will generally increase the usefulness but also the length of discussions and negotiation. Adequate time must be allowed for policy development.

Balance of views: In any negotiation, there is a risk that the views of those with the greatest political power will prevail. Policies on controlled substances have often been overseen by powerful constituencies such as law enforcement and for-profit pharmaceutical corporations. Although their involvement in formulation of national policies specific to controlled medicines is essential, processes must be in place to ensure that patients, patient advocacy groups, health professionals, professional societies and other affected groups have effective voices in policy formulation.

Chapter 5

Pricing and financing of controlled medicines and related health-care services

5.1 Adoption of national medicines pricing policies to ensure affordable, quality-assured controlled medicines

In general, the purpose of national medicines pricing policies is to provide the greatest therapeutic benefit for a given investment. They are intended to strike a balance between affordability and fair reward, maximizing the availability and affordability of essential medicines in the public (and sometimes private) health sectors, without disincentivizing investment in quality or innovation. Pricing policies may include those related to procurement (such as international or national reference pricing or open or limited tenders) and those governing transparency (such as publication of tenders, bid prices, public procurement or reimbursement prices).

5.1.1 WHO guidance on pharmaceutical pricing policies

In 2020, WHO published a guideline on national pharmaceutical pricing policies *(16)*, which includes the following strong recommendations.

- WHO recommends that countries enable early market entry of generic and biosimilar medicines through legislative and administrative measures, with a view to encouraging early submission of regulatory applications, allowing for prompt and effective review, and ensuring these products are safe, efficacious and quality assured.
- WHO recommends that countries use multiple pricing policies to achieve low prices for generic and biosimilar medicines that are informed by the cost of production. These policies may include:
  - internal reference pricing;
  - mark-up regulation;
  - direct price controls;
  - open, fair, transparent competitive procurement methods, including tendering;
  - promoting price transparency; and
  - lower patient co-payments.

- To maximize uptake of generic and biosimilar medicines, WHO recommends that countries implement, and enforce as appropriate, a suite of policies, including:
  - legislation to allow generic substitution by dispensers and, where applicable, biosimilar substitution;
  - legislative structure and incentives for prescribers to prescribe by International Non-proprietary Name;
  - dispensing fees that encourage use of low-price generic and biosimilar medicines;
  - regressive mark-up structure where lower rates of mark-ups are applied for higher-priced products, and appropriate financial and non-financial incentives for dispensers; and
  - education programmes for consumers and professionals regarding the quality, safety, efficacy and price of generic and biosimilar medicines.

The guideline also provides conditional support for the following policies: internal and external reference pricing, value-based pricing, regressive mark-up regulations, price transparency, tendering and negotiation, pooled procurement and price-cutting tax reductions.

5.1.2 INCB guidance on pricing of controlled medicines

The joint WHO–INCB publication, Guide on estimating requirements for substances under international control *(52)*, provides additional guidance on the pricing of controlled substances, noting that competent authorities should consult their national EMLs to identify substances recommended for specific conditions. Chapter 6 provides additional guidance on provisions for selection of controlled medicines. WHO–INCB additional guidance on the pricing of controlled substances is stated on p. 8 of the publication.

- The cost of one medicine [has] a large influence on the selection and quantification of other medicines. Selection, quantification and procurement should be based on the most cost-effective medicines in order to make the most efficient use of financial resources. Ensuring that the most effective medicine is available at the lowest possible cost for patients is a critical element of rational use.
- It is important to consider the health insurance and financing systems, as well as the controlled substance suppliers, including their prices and other costs that may be passed on to the purchaser. For example, if there are few suppliers to choose from, an oligopoly will be created and the suppliers may ask for relatively high prices... In such situations, Government authorities have sometimes stepped in to identify suppliers willing to sell the medicines at lower prices so that the fundamental medical needs of the population can be met.

In its annual report for 2022 *(22)*, INCB states:

> We encourage major producing countries to consider lowering the prices of medicines for low- and middle-income countries and to provide low- and middle-income countries with the option of purchasing affordable morphine instead of more expensive synthetic opioid analgesics *(22)*.

Unique considerations for controlled medicines and implementation

Additional regulations may impede international pooled procurement of controlled medicines. Broadly, pooled procurement involves consolidation of purchases among several institutions, regions or countries. International pooled procurement requires extensive regulatory harmonization among buyers. This is particularly difficult to achieve in the case of controlled medicines because these products are often subject to national laws and regulations that are beyond the purview of a national medicine regulator and differ widely among countries. Information-sharing should be encouraged, and joint procurement should be promoted

Special measures for reporting, storing and disposing of controlled medicines may increase costs in the supply chain.

Under the international conventions and national law, most controlled medicines are subject to specific regulations on how they must be transported, stored, disposed of and reported. The aim is to protect public health by reducing diversion of medicines into illegal markets. Many such measures have additional costs and bureaucracy, which disincentivize distributors, retailers and health facilities from handling controlled medicines *(28)*. Countries that apply price caps or mark-up policies in the supply chain should take such additional costs into account. They might be obliged to establish exceptions or other measures for controlled medicines to avoid reducing access. They must also, however, consider the impact of any such adaptation on end users, as allowing retailers to recoup their costs through dispensing fees may make medicines unaffordable to patients.

The practical issue of storage of opioids should be included in policy, as, in some countries, it is often a factor in accessing medicines.

5.2 National financing of controlled medicines and related services

Ensuring access to any medicine for all those with clinical need depends on the funds available to procure the medicine and for the human and other infrastructure that ensure its distribution and safe use. Financing of medicines and health services depends on a country's resources and the structure of its health system, particularly the contributions of the public sector, the not-for-profit sector and the profit-driven private sector to the provision of services and financing health care.

In any health system, resources are distributed unevenly among services. Distribution is affected by many factors, including the burden of disease, public demand, political priorities and social and cultural attitudes. In some countries, these factors may result in relative under-funding of services in which controlled medicines are most frequently used, such as palliative care, mental health and treatment of substance use disorders.

Some of the special control measures required for medicines under the international conventions are implemented in specific infrastructure, which must in turn be financed.

5.2.1 Guidance from WHO and partners on national financing of health services

WHO recommends that governments plan health financing holistically, designing strategies for raising revenue, purchasing and rationing all aspects of a national health system, rather than a piecemeal approach to financing by individual service *(53)*. As controlled medicines are necessary to treat patients with various conditions, however, including some that are socially stigmatized, services for such patients may require special attention. The services include pain relief and palliative care, treatment for seizure disorders, mental health care and treatment of substance use disorders.

Negative perceptions of these vital services sometimes place them at risk of exclusion from negotiations on the distribution of health funding. It is therefore important that professionals in these fields and patient advocates participate actively in development of the national health financing plans currently recommended by WHO. It is also important that external donors support governments in early co-financing of such activities to help ensure a smooth transition from donor to state funding.

The following documents provide overall guidance on holistic national health financing: Developing a national health financing strategy: a reference guide *(53)*; and Assessing country health financing systems: the health financing progress matrix *(54)*. WHO also provides guidance on financing the services in which controlled medicines are most frequently used.

National financing of tools and systems for prescribing, dispensing, administering, procuring, supply and use of controlled medicines: The INCB notes that countries must have sufficient human, technical and institutional resources to maintain effective systems to ensure adequate supplies of controlled medicines to meet patient needs *(52)*. Such systems allow countries to estimate their needs accurately and to track controlled medicines through the supply chain to ensure safe use. There is currently no international guidance on calculating the cost of effective control systems or other guidance on financing decisions for building, maintaining or operating them.

The advice provided in the 2021 WHO guideline on antimicrobial stewardship, WHO policy guidance on integrated antimicrobial stewardship activities, particularly chapter 5.5 on surveillance, monitoring and evaluation, could be adapted by countries seeking guidance on funding and other resources for effective monitoring of controlled medicines *(55)*.

National financing of health professional training programmes in the use of controlled medicines: WHO issued an evidence-based review of policy issues for building and maintaining a sustainable health workforce in 2013 *(56)*. Chapter 3.3 of that document discusses policy challenges in financing these efforts. It concludes that

> The affordability of additional expenditures generated by the scaling up [of health workforce education] is a matter for political decision based on value choices as well as on economic criteria, and consideration of the benefits in terms of health outcomes *(56)*.

National financing of treatment involving controlled medicines for substance use disorders: The WHO Consolidated guidelines on HIV, viral hepatitis and sexually transmitted infections for key populations – 2022 *(57)* classifies opioid agonist maintenance therapy as an "essential" health intervention for reducing the spread of HIV and hepatitis among people who inject drugs. On p. 81 of the document, links are provided to tools for estimating the cost of implementing this and other interventions *(57)*.

National financing of mental health care: WHO provides guidance on financing for mental health services in the following publications: Mental health financing (58) and subsection 2.6 of Improving access and use of psychotropic medicines (59).

National financing of pain and palliative care services: WHO provides similar practical guidance on providing resources for palliative care.

- Planning and implementing palliative care services: a guide for programme managers *(60)*;
- Integrating palliative care and symptom relief into primary health care. A WHO guide for planners, implementers and managers *(61)*;
- Integrating palliative care and symptom relief into paediatrics. A WHO guide for planners, implementers and managers *(61)*; and
- Integrating palliative care and symptom relief into the response to humanitarian emergencies and crises. A WHO guide for planners, implementers and managers *(61)*.

Chapter 6

Selection of medicines and associated policies

Medicines are selected at national level by decisions in two broad areas.

- the medicines (molecules, doses, formulations) to be authorized for sale on the national market according to clinical criteria selected by the national authorities and to standard national or international treatment guidelines, such as from WHO; and
- the medicines to be provided through publicly funded health services, which should be chosen from the WHO EMLs for adults and children, include controlled medicines, and be designed to ensure more rational or appropriate prescribing and use and lower costs for both health-care systems and patients *(20, 21)*.

Market authorization of a finished pharmaceutical product is initiated by medicine manufacturers or distributors, who submit their application to national medicine regulatory authorities for permission to sell the product in a country. The regulator usually evaluates the safety and efficacy of each finished pharmaceutical product for treatment of clinical conditions specified by the company and authorizes sale on the national market if it is considered that the health benefits outweigh the risks to patients.

Authorized medicines potentially become eligible for provision through public services, free or at a subsidized prices, as decided by national authorities. In the case of new medicines, the authorities usually consider how well a product performs as compared with existing treatments and the cost per unit of the benefit gained. In many countries, however, payment out of pocket may limit the access of people in need *(62)*.

Molecules and formulations considered to deliver the most net health benefits at the lowest cost are often included on national EMLs, which are adapted to local epidemiological needs and to economic circumstances and political priorities. Many countries base procurement of medicines for the public sector on their EMLs. They may also develop national reimbursement lists, which specify the medicines to be covered by public payment and the level. Ideally, the cost of all medicines on a national EML is reimbursed.

6.1 WHO guidance on selection of medicines and associated policies

Medicine selection

Since 1977, WHO has issued EMLs grouped by therapeutic area, for both adults and children (the latter since 2007), and updated them every 2 years. The 2023 versions were the 23rd EML in the series and the 9th EML for children *(20, 21)*. They list medicines by generic name, dosage form and strength and the indications for which they are considered to be the most effective, safe and cost-effective for relevant age groups.

Development and dissemination of independent, scientifically robust information on the efficacy and safety of controlled medicines

WHO recommends that all medicines be selected after transparent, rigorous assessment of the latest scientific studies *(15)*. In the case of controlled medicines that are not on the EML, the review of evidence should explicitly include studies in which the risks of inappropriate and unsafe use and the relative therapeutic value of different formulations, including of controlled medicines, have been quantified in the national context. When there is no such evidence, WHO encourages its generation *(14)*.

Assessment of controlled medicines in health technology assessments or by equivalent methods and inclusion on national EMLs

WHO's guidelines on medicine pricing recommend use of health technology assessment or equivalent tools or approaches for selecting medicines for public coverage, to ensure that the process is transparent, the assumptions are explicit and the perspectives of the patient and the buyer are taken into account *(16)*.

Implementation considerations

Controlled medicines must not be excluded from national EMLs, routine health technology assessments or other means for selecting medicines simply to prevent their use for non-medical purposes. Their omission from health technology assessments makes it difficult for countries to make informed decisions about the relative therapeutic value of different formulations of controlled medicines. This, with pressure from industry, can facilitate unwarranted use of formulations that are unnecessarily costly or that increase the risk to public health. It may also reduce the likelihood that formulations that meet the needs of specific subpopulations such as children are listed and procured or even developed and manufactured.

Some WHO EMLs include products that deliver comparable results at different prices. Countries can choose more expensive products because they are more convenient, better suit a specific indication or accord better with local cultural preferences. In choosing the most appropriate version for inclusion in national EMLs, countries should consider potential trade-offs. For example, transdermal fentanyl is indicated for the management of cancer pain but is more costly than oral morphine. In some countries, use of more expensive products limits or precludes access to pain relief for part of the population because of the high cost. If higher-cost products such as transdermal fentanyl are included on a national EML, affordable therapeutic alternatives such as oral morphine should also be listed and readily accessible.

Chapter 7

Procurement and supply chain management

Efficient procurement and supply chain systems for managing health products are necessary for a strong, reliable health-care system. Adequate human resources, sustainable financing, comprehensive information management systems and coordinated health-care partners and institutions ensure the uninterrupted availability and accessibility of controlled medicines.

WHO and the INCB advocate for integrity and efficiency in procurement and supply chain management to improve the availability of and access to essential medicines and to reduce shortages and stock-outs. There are additional requirements for controlled medicines to ensure accountability in supply due to the risk of diversion and non-medical use.

The policies discussed in this section govern aspects of medicine procurement and supply chain management for which special measures are required by the international drug control conventions to facilitate access to and accountability for controlled medicines.

This section covers four elements for achieving a balance between access for all people in need and safe use of controlled medicines:

- quantification, to estimate national requirements in order to meet medical and scientific needs on the basis of previous consumption of controlled medicines,
- procurement of controlled medicines to meet the national need,
- tracking of the distribution of controlled medicines and other supply chain measures to ensure equitable distribution and to prevent diversion and
- national production of controlled medicines.

7.1 Quantification of controlled medicines

Controlled medicines are quantified to estimate the amounts of specific formulations likely to be needed for legitimate medical and scientific purposes in a country. Of the many ways of quantifying essential medicines, including controlled medicines, the three most commonly used are from data on morbidity and mortality, on service availability and on past consumption *(52)*.

Quantification based on data on morbidity and mortality provides information on total need, on the assumption that all relevant cases are detected and treated, while estimates based on service availability provide an adjusted upper limit based on the capacity to treat. Both may be much higher than actual uptake. Estimates based on consumption are those most often used. This approach relies on data on past use, and it can perpetuate errors if relevant adjustments are not made to both demand and supply factors or if consumption was low due to lack of access. Reliance only on past data is therefore problematic, as it can perpetuate issues of access. Examples of demand-side adjustments include reserves for emergencies, seasonality and quantities reserved for periods of stock-out. Supply-side issues may include the impact of new or discontinued products and insufficient prescriptions due to poor training or misconceptions.

While the approaches for quantification of essential medicines and controlled medicines are similar, they also differ. Notably, the INCB requires that national quantification of controlled medicines used for legitimate medical and scientific purposes be reported *(52)*. Countries provide such reports to the INCB in advance, and production and imports are generally restricted to volumes consistent with the estimated demand.

The INCB requires governments to:

- submit statistical reports on narcotic drugs and psychotropic substances in accordance with the respective provisions of the international drug control conventions and relevant resolutions of the United Nations Economic and Social Council (2011 guideline 17) *(52)*;
- submit estimates and assessments of the quantities of controlled substances required for legitimate medical and scientific purposes (annually for narcotic drugs and for legitimate requirements for certain precursors and assessments at least every 3 years for psychotropic substances) (2013 guideline) *(52)*; and
- supplementary estimates or modified assessments to the INCB if it appears that the availability of controlled substances for medical and scientific purposes will fall short because of initial underestimation of regular demand, emergencies or exceptional demand (2011 guideline 16) *(52)*.

A ceiling on the production and importation of any product, including controlled medicines and the active ingredients for their manufacture, may render the supply chain less elastic or less responsive to a need for adjustment in a given supply period *(63)*. Larger increases in demand may become difficult to accommodate, particularly sudden changes such as product discontinuation or an emergency. Late delivery of previous years' supply to a country changes the approved demand and supply for the next year.

7.1.1 Recommendations and good practice statements

Strong recommendation

Governments should ensure that reporting of current consumption and the potential for need for controlled medicines for medical and scientific purposes, including ongoing adjusted estimates where necessary, are:

- accurate, timely and actively monitored and
- based on need that is estimated from the best available epidemiological data (including morbidity and mortality data), consumption data, clinical guidelines, service capacity and other relevant information.

Very low certainty evidence

Good practice statement

Governments should monitor the availability and affordability of controlled medicines and update estimates of need to ensure adequate supplies on an ongoing basis. If the national supply, demand or other areas of availability change significantly, updated estimates should be made and communicated to the INCB to allow for corresponding changes to manufacture, importation and distribution.

Remarks: In the absence of the results of rigorous research, the GDG discussed a compilation of national and individual experiences, with indirect evidence. Despite very low-certainty evidence for the impact of quantification policies for controlled medicines, the GDG made a strong recommendation, as accurate, timely, actively monitored quantification and reporting of current and potential requirements for controlled medicines by governments can prevent serious and life-threatening situations (e.g. uncontrolled severe pain and its consequences, substance and medication withdrawal syndromes, seizures, overdose) and save lives. The GDG noted that feasible methods exist for quantification of controlled medicines for medical and scientific purposes at national level. They include those specified in INCB guidelines and also extended guidance on management of medicine supply chains, although the Group commented that such methods might have to be adapted for countries other than those with high incomes. The GDG acknowledged that quantification based on past data on use in countries with known insufficient access can perpetuate problems of access. Therefore, the best available data, including epidemiological (both morbidity and mortality) and consumption data, clinical guidelines, service capacity and other relevant data should be used in quantification and relevant adjustments. Consumption trend analyses are critical to understanding the quantities delivered and dispensed, to confirm that an increase corresponds to a pragmatic increase in coverage and to eliminate the risk of diversion. Changes in supply chain management can have unintended consequences and should be accompanied by active monitoring to avoid harm. Governments are also encouraged to hold sufficient quantities of controlled substances as safety stocks and support use of stock management tools (paper and online) to ensure sufficient management of stocks of medicines. It noted that paediatric formulations should be considered in procurement and supply chain management. Conflict areas in which vulnerable populations have extensive medical need may have transition governments, and further consideration should be given to ensuring continued access to controlled medicines.

As quantification policies for supply chain operations and to meet INCB reporting requirements may differ, different national entities should address these aspects separately. For example, while INCB requirements require measurements to be reported in kilograms of the active ingredient, this may not be compatible with the units used logistically in medicines supply chain information systems. Therefore, accurate quantification for reporting to the INCB may not be translated into effective estimates for procurement or for the provision of appropriate pharmaceutical forms and dosages, particularly for meeting the needs of the paediatric population.

7.1.2 Overview of the rapid systematic review evidence

The rapid systematic review addressed the impact of quantification policies on controlled medicines. There was limited direct evidence, and the evidence was of very low certainty.

One primary study, not specific to controlled medicines, showed that, in an emergency context, WHO guidelines and standard operating procedures for quantification of consumption, morbidity data and forecasting of need improved supply chain management. Little wastage or expiration of medicines, no stock-outs and cost savings were reported *(64)*.

Qualitative evidence was used to support the conclusion that strict regulation could reduce access to medically necessary controlled medicines, particularly the ceiling on production, when the lead time for course corrections can be significant. The evidence also identified obstacles to improving national systems for quantification, such as political will, bureaucratic inefficiency, fragmentation of the health system, constraints in capacity, resources and infrastructure, particularly in LMICs.

Balance of health benefits and harms:	The rapid systematic review did not provide direct evidence for use by the GDG in their deliberations on this criterion. The GDG discussed a compilation of national and individual experiences that indicated that governments should ensure that quantification of controlled medicines and reporting of current and potential requirements are accurate, timely, actively monitored and updated. The GDG presented indirect evidence for medication classes other than controlled medicines, which showed that stock-outs occur and have negative consequences and that effective interventions can avoid them. The GDG presented indirect supporting evidence that substantiated the importance of basing quantification and reporting of controlled medicines on the best combinations of epidemiological (including morbidity and mortality) and consumption, clinical guidelines, service capacity and other data, including adjustments, as used in accepted principles of medicines quantification. The GDG recognized that, in countries that are known to provide insufficient access, adjustment of estimates to include the available service capacity, epidemiological data or other relevant data sources on demand and supply could better support the goals of ensuring adequate access and safe use of controlled medicines, as compared with exclusive use of estimates based on past consumption.
Human rights:	The GDG noted that national policies or initiatives to improve quantification of controlled medicines could help countries to fulfil their obligation to provide access to controlled medicines, which is a core minimum obligation of the right to health. Supporting recommendations were discussed, including the International Guidelines on Human Rights and Drug Policy, which states: in accordance with their right to health obligations, States should … take legal and administrative steps to ensure the adequate availability, accessibility, and affordability of controlled medicines …; and amend laws, policies, and regulations that unnecessarily restrict the availability and access to controlled medicines.
Socio-cultural acceptability:	The GDG recognized that improving access to controlled medicines, specifically opioids, may be viewed differently in different countries, depending on the national context. In some countries, governments and citizens may be resistant to extending the opioid supply because of concern about potential overuse, opioid-related harm and lack of capacity to manage the special requirements of controlled medicines. Such concerns can be addressed by education and promotion of the recommendations and good practice statements in this guideline. In countries in which stockouts and shortages have been reported, the health-care system may benefit from increased access to these medicines.
Health equity, equality and non-discrimination:	The GDG discussed current issues of equity in the estimates received by the INCB and, notably, differences in access among countries. They noted that improved quantification could reduce such disparities. The reports showed problems of data quality, timeliness and completeness of reporting by some countries, suggesting that they may be underrepresented in global estimates, thus reducing access.
Financial and economic considerations:	The GDG discussed national and individual experiences with respect to the cost-effectiveness of efficient quantification policies and how they can contribute to optimizing resource use and cost savings, despite initial costs.
Feasibility and health system considerations:	The GDG discussed the lack of capacity in some countries for inventory management and quantification. Weaknesses in other areas, such as epidemiological reporting, compound the problem.

7.1.3 Implementation considerations

Estimates of the demand for controlled medicines should be based on the best possible quantification method and the best available data, which depend on the national context. All patient groups should be considered in quantifications, including all ages and genders, displaced people and people affected by conditions in which use of controlled medicines is deemed to be medically appropriate. Governments should monitor the availability and affordability of controlled medicines and update estimates of need with the most appropriate method described in the WHO–INCB Guide on estimating requirements for substances under international control to ensure adequate, continuous supplies *(52)*.

Access may be problematic when the estimates provided to the INCB are lower than those required or when the need for controlled medicines changes rapidly, such as in a humanitarian crisis. Quantification of both needs and consumption may be more accurate in countries in which data are collected and available from several sources, such as national insurance programmes. Health system data, insurance and reimbursement information, importation and other records can also be used in quantification, although it should be assumed that the data may be imperfect and may require adjustment. Monitoring and regular evaluation of information for quantification can improve the usefulness of quantification, especially to avoid large over- or underestimates. Quantification of total need or other maximum levels can provide realistic indicators of unrelieved suffering. Use of controlled medicines requires trained health-care professionals, and purchases should be aligned not only with need but also with the availability of trained health-care staff.

Studies of supply chains for medicines generally support use of blended approaches, in which relevant data sources are combined to make annual estimates, including adjustments, checks and balances. Such approaches can be applied to controlled medicines, although the availability and quality of national data may be incomplete. If data are not collected routinely in logistic management information systems or health management information systems, they may be difficult to obtain for quantification. National infrastructure for Internet services can limit the reach of electronic systems in the health supply chain, making good-quality data more difficult to obtain in a timely manner. This is especially true in countries in which controlled medicines are available "unofficially" without a prescription.

A country might have several supply chains, such as national, subnational, public and private, which could result in heterogeneous data. Data aggregation approaches could improve quantification of consumption and need, especially in countries with limited reach of the logistic management information system.

Quantification differs widely in emergency situations, situations in which there is limited access and situations in which controlled medicines are over-prescribed. In emergency situations, a public health care target may be used as a guide to adjust estimates, such as for preparedness.

Countries in which there is no capacity to conduct inventory management and quantification may have lower regulatory maturity levels according to the WHO Global Benchmarking Tool for evaluation of national regulatory system of medical products.

7.2 Procurement guidelines, tools and mechanisms

Public procurement policy is usually applied to achieve and improve sustainable access to affordable medicines. Procurement guidelines, tools and mechanisms ensure that countries (or subnational systems) acquire sufficient quality-assured medicines to meet patient needs at the lowest sustainable price. In the context of controlled medicines, however, guidelines, systems and tools might have to be adapted. Restrictions on production, importation and distribution of controlled medicines are intended to avoid oversupply, which risks waste and public health harm through diversion and non-medical use. Such restrictions may also prevent or delay a rapid response in emergencies. Sustainable access to affordable, quality-assured controlled medicines may be complicated by restrictions on medicines under international control.

The availability and affordability of pharmaceutical products is affected by the efficiency, design and governance of procurement and supply chains. The total cost of a medicine includes the price to the procurer, delivery and related expenses, inventory holding costs and transactional costs. These mark-ups must be added to the factory price. Furthermore, the fairness of factory prices and mark-ups is often legitimately questioned, and governments should be (but often are not) able to question such prices. Transactional costs can be higher in certain types of procurement systems, such as those in which additional controls are added at several points in the supply chain.

Procurement may be suboptimal if there is inadequate management, underdeveloped policy or systems, lack of transparency, insufficient financing and not enough qualified procurement specialists. Additionally, inefficiency in public procurement and supply chain management of controlled medicines before their regulatory approval – in the context of scientific research or medical use in expanded access programmes -– can have significant repercussions on public health, failing to address the unmet needs that could be met by these medicines. A potential restriction of controlled medicines should be considered in the overall design and process of procurement systems, including longer, more costly procurement cycles due to the additional restrictions on importation. Restrictions on quantity can also increase the frequency of procurement cycles or the number of last-minute or emergency orders, both of which can increase procurement prices and related transactional costs. Regulators should be educated and trained in procurement.

The Operational principles for good pharmaceutical procurement introduces strategic objectives and operational principles for good pharmaceutical procurement, which can be reviewed and adapted by governments and public or private organizations to guide procurement of controlled medicines *(66)*. The strategies are based on the "six rights" of procurement practice: the right product, in the right quantity, in the right condition, in the right place, at the right time, for the right cost *(67, 68)*. Four strategic objectives of good pharmaceutical procurement are procuring the most cost-effective drugs in the right quantities, selecting reliable suppliers of high-quality products, ensuring timely delivery and achieving the lowest possible cost *(66)*.

Procurement policy includes value for money and the quality of medicines. Quality-assured medicines, including controlled medicines, are those that are duly registered by the national medicines regulatory authority in the country in which they will be distributed (imports and national manufacturing), and have been assessed by a recognized regulatory authority in a regulatory reliance scheme *(69)*. Establishment of regulatory control and monitoring are important parts of supply chain management for any medicine. Failure to establish appropriate regulatory oversight increases risk, including the risk of entry of substandard and falsified controlled medicines into the legitimate supply chain.

7.2.1 Good practice statements

Good practice statement

Governments should develop, implement and monitor good procurement policy to identify continually assessed and evaluated sources and achieve the best sustainable prices for quality-assured controlled medicines for medical and scientific needs.

Remarks: In the absence of rigorous research evidence, the GDG discussed a compilation of national and individual experiences and indirect evidence. The GDG deemed that there was insufficient evidence to develop a specific recommendation on procurement policies for controlled medicines.

7.2.2 Overview of the evidence from the rapid systematic review:

Little direct evidence on the procurement of controlled medicines was identified in the rapid systematic review. One primary study reported access-related drug management outcomes for quantification, procurement, supply and local production interventions during the medical response to the 2005 earthquake in Pakistan *(64)*. Little medicine wastage and expiries, no stock-outs and cost savings were reported.

7.2.3 Implementation considerations:

Considerations for implementing good procurement policies include:

- allowing competition among good-quality suppliers and other practices in line with WHO guidance on pharmaceutical pricing policies and the WHO model quality assurance system for procurement agencies. In some countries, restrictions on the number of companies or organizations permitted to import or sell controlled medicines can lead to local "oligopolies", which limit the benefits of broader competitive practices.
- establishing import regulations and guidance to streamline procedures for importation of controlled medicines. Procurement, regulatory and importation authorization should be aligned to ensure that products selected for procurement are appropriately registered and are included in importation control systems to avoid delays or rejection of products by customs authorities.
- ensuring resources and capacity to monitor the distribution of medicines and more detailed requirements for controlled medicines.

Fragile pharmaceutical systems will require support in implementing this good practice statement, which may involve stakeholder groups other than national governments.

Complementary guidance on assessing and optimizing procurement practice is also available for situations in which procurement may be constrained, such as restrictions on controlled medicines. For example, in the context of controlled medicines, when competition can be limited to a smaller group of suppliers, the options for evaluation of prices in procurement tenders may be extended to include external pricing reference or other means of ensuring fair pricing.

7.3 Supply chain management systems, tools and mechanisms

To improve access to controlled medicines, the INCB urges governments to:

> review national legislation and regulatory and administrative mechanisms, and design policies, to simplify processes and remove unduly restrictive regulations.

Controlled medicines must be quality-assured, and supply chains must be managed to maintain their quality, for instance, by ensuring appropriate transport conditions. Supply chain management systems, tools and mechanisms facilitate adherence to regulations on the safe management, transport, storage and elimination of controlled medicines throughout the supply chain, including safe disposal of medicines that have expired or cannot otherwise be used. Supply chain management can also ensure that substandard and falsified products do not enter the market.

All medicines, regardless of their control status, should be protected from diversion to ensure that they reach the populations who need them. As controlled medicines are used non-medically, countries often take additional measures to reduce the risk of the diversion of these products from the regulated supply chain.

Countries may decide which policies and regulations to apply, and it is important to ensure that implementation of these strategies does not impede access to controlled medicines. Common strategies used to prevent diversion include:

- importation only by central medical stores;
- distribution only by dedicated controlled medicine pharmacies, according to the characteristics of the primary health system;
- categorization of controlled medicines intended only for hospital use and which can be distributed only at hospital pharmacies as "hospital only";
- specialized (e.g. locked or guarded) transport or storage facilities;
- disposal of products that are no longer required or expired only by returning them to the medicine regulator; and
- track-and-trace mechanisms to ensure that stocks of controlled medicines can be identified and delivered only to authorized, designated locations.

7.3.1 Recommendations and good practice statements

Strong recommendation

Governments should use simple, appropriate technology and tools to:

- improve the traceability, efficiency and integrity of inventory management for controlled medicines;
- prevent waste and stock-outs;
- implement protocols for the prevention of diversion; and
- reduce the administrative burden for front-line staff handling controlled medicines.

Very low certainty evidence

Good practice statement

Governments should have supply chain and distribution plans for controlled medicines that ensure full geographical coverage, prevent waste or shortages and avoid inequity in access.

Good practice statement

Governments should ensure that local and regional productions hubs and supply chains are supported by adequate technologies, infrastructure, financial and human resources.

Remarks: In the absence of rigorous research evidence, the GDG used a compilation of national and individual experiences and indirect evidence. Despite very low-certainty evidence, the GDG made a strong recommendation, as they considered that use of technology and other tools to improve the efficiency and integrity of stock management prevents waste, stock-outs and diversion and reduces the administrative burden. Stock-outs and interrupted treatment can lead to significant harm and life-threatening situations, including pain crises, seizures and overdoses. The recommended intervention may therefore save lives, and the harms were considered to be immaterial.

7.3.2 Overview of the evidence from the rapid systematic review:

Little direct evidence was available on supply chain management systems and tools and mechanisms specifically for controlled medicines, despite both systematic and extensive open searching for the rapid systematic review. One primary study, not specific to controlled medicines, showed that, in an emergency, WHO guidelines and standard operating procedures improved supply chain management, resulting in less expiry and wastage and lower cost of medicines *(64)*.

Balance of health benefits and harms:	The GDG found no direct evidence in the rapid systematic review for consideration of this criterion. In the absence of rigorous research evidence, the GDG used a compilation of national and individual experience that indicated that governments should use simple, appropriate technology and tools to ensure that the right medicines are available to those who need them at the right time and place, including rational use of controlled medicine. The GDG also found indirect evidence, not specific to controlled medicines, that use of technology improves supply chain management.
Human rights:	The GDG concluded that national policies for use of simple technology and tools may help states to fulfil their obligation to provide access to controlled medicines, as a core minimum obligation of the right to health.
Socio-cultural acceptability:	The GDG considered that technology is likely to be widely accepted by stakeholders in all countries, particularly in comparison with manual supply chain management.
Health equity, equality and non-discrimination:	The GDG recognized that access to controlled medicines is a component of the right to health. The resolution of the United Nations General Assembly in 2016 is specifically relevant to quantification, estimates, procurement and supply chain.
Societal implications:	The GDG commented that patients would have access to medicines to which they would otherwise not have if the correct, simple, appropriate technology and tools are used to improve the efficiency and integrity of supply chain management. If governments fail to use such tools and technology, patients may live and die in needless suffering, with a negative societal impact.
Financial and economic considerations:	The GDG compared the cost of technology tracking systems with the cost of personnel working manually and the cost of no tracking, with the potential costs of medicine wastage and increased risks of illness.
Feasibility and health system considerations:	The GDG discussed national and individual experiences and evidence that use of simple technology and tools is feasible and can improve the efficiency and integrity of stock management, prevent waste, stock-outs and diversion, and reduce the administrative burden.

7.3.3 Implementation considerations:

Barriers to implementing supply chain initiatives, particularly in LMIC, include lack of human resources at all levels of the health system to implement, monitor and follow regulations and interventions, lack of training (especially of non-medical stakeholders), confusing and/or fragmented procurement and supply pathways and procedures, and poor material and infrastructural support for implementing programmes (e.g. no secure cupboards or drug record books). In most LMIC, opioids are not permitted to be stocked in primary care centres. Countries should, however, allow such centres to stock opioids so that they can be prescribed in primary care, while ensuring that safeguards such as double locks are in place. Education should be provided so that those who are allowed to prescribe opioids have up-to-date knowledge about assessing and treating pain and breathlessness.

Development of infrastructure and capacity throughout the supply chain is necessary for effective distribution of controlled medicines once they are in a country. The infrastructure includes local and regional production hubs, secured locations and processes for secure in-country transport to designated health facilities.

Limitations on prescribing authority, the level of a health-care facility and other restrictions can limit the number of sites at which controlled medicines can be distributed and dispensed, for example to specialized or upper-level hospitals and facilities. Such regulations may limit the access to medicines of all patients with legitimate needs.

Special measures to prevent the diversion of controlled medicines from the supply chain could increase costs for manufacturers, distributors, health facilities and community pharmacies. Adequate provision should be made to compensate for such costs, to ensure consistent access to these medicines.

Important barriers to nation-wide track-and-trace systems include access to technology and the cost of implementing the systems. More localized, smartphone-based electronic stock management approaches have been developed; however, cyber security must be considered.

Policies that require users of certain medicines to return used packaging and empty ampoules may be restrictive and onerous for patients and their families.

7.4 Production of controlled medicines

Ensuring access to medical products is complex, as governments are required to have relevant policies to make quality-assured medical products available to meet medical and public health needs with products that are acceptable and affordable. Most countries import at least a portion of their medicine supply; however, many LMIC in which local manufacture is not established are more dependent on an external supply, but at the same time have less purchasing power. This situation increases the risk of and inadequate supply or disruption. LMIC are increasingly developing local production of quality-assured medicines and health products to improve access to safe, quality-assured, affordable medical products. Such systems are, however, complex, and local producers often import the basic ingredients to produce the final formulations locally. Local production may help to ensure reliable supply chains, achieve universal health coverage, strengthen health security and achieve the health-related targets and broader Sustainable Development Goals.

Stipulations of the international conventions governing controlled medicines are applied to import and export transactions by customs officials, which may delay their arrival. The impact can be particularly great when there is an unanticipated increase in demand, such as during a humanitarian crisis, when the need for controlled medicines for trauma, surgery, pain management and mental health may be higher, while the resources to comply with complex regulations may be constrained. Local production of quality-assured controlled medicines can reduce the barriers associated with imported medicines in their finished form; however, the conventions also apply to the importation of active pharmaceutical ingredients used to manufacture the medicines locally. Local production of some of the ingredients may meet local needs, but locally manufactured products may be more expensive and, in most cases, the producers may have to secure a regional market to be sustainable.

7.4.1 Good practice statements

Good practice statement

Governments should systematically collect and analyse information on the potential health, financial and social benefits, as well as the risks and harms, of producing quality-assured controlled medicines within their countries to meet the health-care needs of their people.

7.4.2 Overview of evidence from the rapid systematic review:

No direct evidence about policies for local production of controlled medicines was identified. The good practice statement was informed by case studies of successful examples of local production.

7.4.3 Implementation considerations:

The cost of locally produced products as compared with imported products should be considered when deciding on policies for domestic production of controlled medicines. This includes the costs borne by governments for environmental and regulatory supervision and quality assurance. Local industrial production should ideally be regional and not national scope, as collecting and analysing information on the potential health, financial and social benefits and on the risks and harms of producing quality-assured medicines in a country will be more feasible in countries with a well-developed pharmaceutical production sector. A competent national regulatory agency will also be required, with processes to address substandard and falsified medicines and how best to form partnerships with industry.

Many locally produced medicines are made from imported active ingredients, which are themselves subject to international control, and thus import restrictions. This may reduce some of the potential benefits of local production in securing a sustainable supply, especially for emergencies. The duty that manufacturers and regulators must impose to comply with the provisions of the international conventions may also add to the cost.

Strengthening local production of controlled medicines to improve access requires a health workforce that is well trained in the use of controlled medicines for medical purposes. Otherwise, the increased availability of products cannot result in safe, effective treatment for patients and can lead to wastage. Countries should use information on the health, financial and social benefits of controlled medicines and also on the risks and harms of producing quality-assured controlled medicines in order to improve local production.

7.5 Links to other WHO documents

Quantification of controlled medicines

Although quantification of controlled medicines may present unique challenges, guidance from WHO and other organizations is relevant. This includes:

- WHO: Programme on substance abuse. Model guidelines for the international provision of controlled medicines for emergency medical care *(65)*.
- INCB and WHO. Guide on estimating requirements for substances under international control *(52)*.

Procurement guidelines and tools

- Operational principles for good pharmaceutical procurement *(66)*;
- Quality assurance policy for the procurement of essential medicines and other health products *(70)*
- WHA72.8. Improving the transparency of markets for medicines, vaccines and other health products *(71)*
- Model quality assurance system *(68)*
- WHO guideline on country pharmaceutical pricing policies *(16)*

Supply chain systems

- Management Sciences for Health, World Health Organization Action Programme on Essential Drugs. 1997. Managing drug supply: the selection, procurement, distribution, and use of pharmaceuticals *(72)*.

Production of controlled medicines

- World Health Organization. 2021. WHA74.6 Strengthening local production of medicines and other health technologies to improve access *(73)*.
- World Health Organization. 2011. Guidelines for medicine donations, revised 2010 *(74)*.

7.6 Research gaps

Little direct evidence was available for making recommendations for the policies discussed above. Most of the evidence pertained to opioids, while one study also considered benzodiazepines *(75)*. The most common therapeutic settings were those for pain management and palliative care, and less evidence was available for other settings. The impact of quantification, procurement, supply chain and local production on the availability of controlled medicines for other indications requires further research.

Other evidence gaps include research on waste management and donations of controlled medicines, strategies to address substandard and falsified controlled medicines, and approaches to increasing the capacity for local production of controlled medicines, including economic assessments to determine feasibility and assessments of the impact of local products on medicine quality. A potential strategy to increase access to controlled medicines is development of regional hubs to produce controlled medicines for surrounding countries according to pooled need; however, little evidence is available.

Chapter 8

Regulation and control of medicines

Every country has statutory arrangements that provide a legal basis for ensuring that medicines are of assured quality, efficacy and safety and accessible to patients with clinical need and for scientific purposes. LMIC might face challenges in complex regulatory changes due to infrastructure or resource constraints.

The policies discussed in this chapter are those for prevention of inappropriate or unsafe use of controlled medicines. The policies should not be implemented in isolation but as part of a broader package designed to achieve an overall balance between access to and safety of controlled medicines.

This chapter addresses four broad areas of controlled medicine policy: product safety, possession and use, drug scheduling and imports and exports.

8.1 Safety of medicines

Before authorizing sale of a medicine in a country, the national regulatory authority evaluates the medicine to ensure that its quality, safety and efficacy have been demonstrated for use in humans and that the ratio of benefit to risk for the medicine is positive for the proposed indication, including for demographic or clinical sub-groups. The authority will review the packaging of the medicine and the information provided for health professionals and patients to ensure that they promote safe use for authorized indications only. Safety review policies apply to all medicines. For WHO recommendations on product safety, see WHO publications on strengthening regulatory systems *(50, 76)*.

Controlled medicines may be subject to more restrictions in the supply chain and more safety provisions than other medicines, as they are at increased risk of being diverted or used unsafely. The aim of many such additional safety provisions for controlled medicines is to reduce non-medical use, such as by modifying aspects of a medicine's formulation, packaging and/or labelling. These provisions are commonly used in countries in which controlled medicines are widely available, with a high risk of non-medical use.

Policies intended to reduce the risk of diversion or unsafe use of controlled medicines include a broad range of interventions, such as:

- warning labels to discourage clinically inappropriate prescription or use;
- packaging that makes it difficult for children and other vulnerable groups to unintentionally take the medicine (tamper-resistant packaging and changes in product volume in a package that is not tamper resistant); and
- packaging or formulations that make it difficult for people to deliberately use the medicine non-medically or at unsafe doses (sometimes referred to as misuse-deterrent or abuse-deterrent packaging or formulation), such as the buprenorphine–naloxone combination (Suboxone).

Some products are designed to prevent manipulation of the release rate of the controlled medicine by making it difficult to crush, chew or inject *(77)*, often referred to as "tamper-resistant" formulations.

The formulation of a controlled medicine may also impact the access of people who need the medicine, for example because it affects the cost of the product, the ease of handling or its use. Some formulations are changed to increase their use in situations in which their availability is limited or for sub-populations with specific clinical or access needs, including children, older people and those with limited access to health facilities. Paediatric formulation should always be available. An example of changes to formulations that can increase their affordability and access is oral morphine for pain management.

Policies intended to improve access to controlled medicines for people in need of treatment include formulations that:

- are physically easier for population groups to take, such as formulations that are more concentrated, so that a smaller volume is required, or are more easily stored;
- are more convenient or acceptable to take or administer; and
- have the same or greater therapeutic value at lower cost and of the same quality.

8.1.1 Good practice statements

Good practice statement

Governments should ensure that controlled medicines are available in formulations that are acceptable, affordable and accessible to those with clinical need.

Good practice statement

Governments should ensure that packaging of controlled medicines prevents accidental use by children and vulnerable adults. The additional cost of ensuring such safety features should not reduce access for patients with clinical need.

Good practice statement

Governments that are considering adoption of tamper-resistant formulations or packaging should weigh their potential safety benefits against their higher cost and the risk that they may limit access and/or increase harm.

Remarks: The data considered by the GDG were derived predominantly from studies in a few high-income countries and provided evidence that reformulation resulted in of both health benefits and harms. The GDG did not make a recommendation on reformulation of controlled medicines but issued three good practice statements on access to appropriate, affordable formulations and which encourage governments to determine the benefits and harms of tamper-resistant formulations and packaging of controlled medicines. Although these are essential requirements to ensure safe medicines, many LMIC and other countries might be unable to require them from manufacturers.

The GDG noted that the additional cost of such safety features could be significant but affirmed that this should not prevent implementation. Other measures, such as education, could also be used to increase safety and ensure access for patients with clinical need.

8.1.2 Overview of the evidence from the rapid systematic review:

The rapid systematic review provided some evidence that reformulation of opioid products reduces prescription rates and indicators of non-medical opioid use. Other studies provided contradictory evidence of substitution of non-reformulated products or large shifts to heroin use. Substantially higher health-care and prescription expenditure was observed after introduction of a tamper-resistant formulation of opioids. Evidence on outcomes related to opioid use disorder or overdose rates was inconsistent.

In two studies, warning labels led to reductions in the rates of prescription of codeine and oxycodone, and, in one study, unit-dose packaging reduced unintended paediatric poisoning by buprenorphine *(78, 79)*.

8.1.3 Implementation considerations:

The increased cost of tamper-resistant formulations and/or packaging may affect the affordability of medicines for those who need them, thereby limiting access. If policies requiring tamper-resistant formulations or packaging are introduced, the effects on health and health care use should be actively monitored, and strategies to minimize harm such as reduced access should be devised and implemented.

8.2 Possession and use of controlled medicines

Many countries have policies to regulate who is permitted to possess controlled medicines, in which situations and in what quantities. Regulations on possession apply to patients and other individuals, health-care providers, pharmacists, manufacturers, importers, procurement agencies and health facilities. Most laws on possession are national.

Policies intended to increase access to controlled medicines for people with clinical need include:

- extension of authorization to prescribe, dispense or handle controlled substances for medical use to personnel not previously allowed to handle these medicines (for example, nurse practitioners);
- extension of authorization to prescribe, dispense or handle controlled substances for medical use to non-health facility settings (for example, workers providing palliative care to patients at home); and
- other legal pathways to provide controlled medicines before regulatory approval under specific circumstances (for example, in Australia, Canada and Switzerland).

Policies intended to reduce diversion and non-medical use include legal penalties for:

- unauthorized people found in possession of or using controlled medicines;
- authorized people carrying or dispensing controlled medicines outside of authorized settings; and
- authorized people who have not complied with required registration, record-keeping or other restrictions on prescription or dispensing.

This last includes regulations for “pain clinics”, which may be required to register with the state, be owned by a physician, observe prescription regulations and keep patient records.

The main purpose of the policies is to reduce diversion, although they may result in reduced access to controlled medicines and also in stigmatization.

This chapter addresses only implementation of policies on possession and use relevant to medical use, including those on who is allowed to prescribe, dispense, handle, administer or use controlled medicines. Policies on prescribing practices, such as the quantities that may be prescribed, are covered in chapter 9. Policies on possession and use of controlled medicines outside the context of medical use are not covered in this guideline.

8.2.1 Good practice statements

Good practice statement

Governments should collaborate with health authorities, care providers, professional health organizations and patient advocacy groups to review laws and regulations on the possession and use of controlled medications. They should revise any laws that hinder access to these medicines for individuals with legitimate clinical needs.

Good practice statement

Governments, medicine regulatory agencies, health-care professional bodies and societies should ensure that permission to possess or handle controlled medicines is extended to all health professionals whose practice entails treating patients with a clinical need for controlled medicines.

Good practice statement

Governments should ensure that patients have adequate legal protection relating to the possession of prescribed controlled medicines for clinical need.

Remarks: The GDG considered that there was insufficient generalizable evidence for making a specific recommendation on policies for possession and use of controlled medicines. Good practice statements were made to encourage governments to review and refine policies for the possession and use of controlled medicines, as the GDG considered that they were relevant in the context of broader issues of access. It further noted that prescribers who make errors in prescriptions in good faith should not be prosecuted or penalized.

8.2.2 Overview of evidence from the rapid systematic review:

Studies on the impact of new laws, policies or regulations on possession and use of controlled medicines by health-care providers or patients covered two types of intervention: extending permission for prescribing controlled medicines (for physicians to prescribe buprenorphine) and laws governing pain clinics. The studies of extended permission found that the interventions increased access to buprenorphine treatment and reduced prescriptions of opioid analgesics. Systematic reviews and primary studies of pain clinics in the USA found that increased numbers of patients received methadone and buprenorphine after the introduction of pain clinic laws, reduced opioid prescribing and opioid diversion and fewer cases of paediatric poisoning. The impact on opioid overdosing was mixed, some studies finding fewer deaths from opioid overdose and others reporting increased numbers of heroin-related overdoses. In one review, increased policing of people on methadone in China led to substantial reductions in the rate of patients treated with methadone *(80)*.

8.2.3 Implementation considerations:

Legitimate clinical needs are considered to be conditions in which the use of controlled medicines is deemed medically appropriate according to evidence-based guidelines.

Health professionals who treat patients with clinical need require the right to possess and handle controlled medicines without fear of legal or professional jeopardy or prosecution. It is important that prescribing and non-prescribing health professionals who distribute controlled medicines, such as nurses working in home care or the community, can handle controlled medicines for patients without fear of legal or professional jeopardy or prosecution. In some countries, nurses who take controlled medicines to patients at home fear prosecution, although this is often the only way of delivering the medicines to patients. This is also a challenge for the relatives of patients who are too unwell to travel and pick up and transport their controlled medicines. Lack of the right to possess and handle controlled medicines can also be a challenge for health professionals and patients in emergency and humanitarian settings.

Legal protection of the right to possess prescribed controlled medicines for clinical use must include clear definition of the period of validity of prescriptions of controlled substances. It should specify the type of prescription, which may be written, electronic or verbal. It should also include the maximum quantity or dosage permissible under current legal regulations. For instance, a patient may legally be prescribed up to a 90-day supply of controlled medications, to ensure adequate management of their condition, while adhering to guidelines set by regulatory authorities. Provision of this information ensures that both health-care providers and patients understand the legal framework for controlled medications.

8.3 Drug scheduling

Drug scheduling comprises classification of active ingredients in medicines into categories according to their potential therapeutic benefit and risk of harm. The 1961 Single Convention on Narcotic Drugs and the 1971 Convention on Psychotropic Substances classify controlled substances, including medicines, into one of four "schedules". The complete texts of the conventions, the latest versions of the schedules of the substances they cover and information on the control measures applicable to the schedules can be freely downloaded from the website of the United Nations Commission on Narcotic Drugs *(81)*. The WHO Expert Committee on Drug Dependence makes recommendations to the United Nations Secretary-General and the United Nations Commission on Narcotic Drugs on the appropriate level of international control required to prevent harm to health while ensuring that medicines are accessible for clinical use when necessary. The conventions require countries to place these substances under national control and to report their production, manufacture and trade to the INCB.

Scheduling is intended to provide flexibility in the regulation of controlled medicines, so that access to psychoactive medicines for medical and scientific purposes can be assured while guarding against non-medical use. Although scheduling is mandated by the conventions, countries may classify medicines differently on their national lists and may also add medicines that are not included in the conventions. Policies related to drug scheduling should balance reducing non-medical use with ensuring access for medical and scientific use. Optimization of public health should be the priority, for which many factors must be taken into consideration, such as unmet clinical needs, stagnated innovation due to insufficient commercial interest, harm reduction and other risks and benefits associated with drug scheduling, including the potential risk of overly restrictive scheduling and disproportionate harms to vulnerable communities.

Scheduling to reduce non-medical use may be warranted when new data suggest that the risk of harm associated with a medicine is greater than previously considered or when a country becomes aware of evidence of a local problem of non-medical use. This can be addressed by increasing the risk category of a medicine in the national schedule ("up-scheduling") or adding a medicine that is not under international control to the national schedule.

Scheduling to increase access for patients in need may be warranted when new data suggest that a scheduled medicine or substance has therapeutic uses that were not previously recognized or when evidence is found that the risk of non-medical use has been overestimated. Examples include decreasing the risk category of a medicine in the national schedule ("down-scheduling") and removing a medicine that is not under international control from the national schedule.

8.3.1 Good practice statements

Good practice statement

Governments should ensure that changes to the scheduling of controlled medicines are based on robust scientific evidence relevant to the context of use, to achieve balance between ensuring access and preventing public health harm.

Good practice statement

Discussions on drug scheduling should include input from health authorities, associations of health professionals, patients, families and all relevant stakeholders. When reviewing drug scheduling, optimizing health outcomes should be the priority, balancing access for clinical need with preventing harm.

Good practice statement

Governments and relevant authorities should ensure that medicine scheduling does not impede access to controlled substances for use in ethically approved clinical research.

Remarks: The GDG considered that the evidence on the effects of drug scheduling pertains largely to safety in high-access contexts in which stricter prescription practices have been enforced. There was limited evidence of the impact of scheduling on access and on human health. The GDG agreed that a recommendation to tighten regulations, even in specific settings, could limit access to controlled medicines. The GDG also expressed concern about the potential negative impact of increased control of controlled medicines in settings in which there is already limited access. Therefore, no recommendations were made with regards to drug scheduling.

8.3.2 Overview of the evidence from the rapid systematic review:

No studies were identified on access-related outcomes resulting from drug scheduling policies. One systematic review that addressed up-scheduling of hydrocodone in the USA found mixed results, with a reduction in the prescription of hydrocodone and increased prescribing of other opioids. Some of the studies found reduced non-medical use of hydrocodone but increased non-medical use of other opioids. Primary studies provided evidence that reduced prescribing of opioids and benzodiazepines reduced non-medical use and poisoning after up-scheduling of the individual opioids or benzodiazepines studied.

8.3.3 Implementation considerations:

In countries in which non-medical use of controlled medicines is considered a serious public health problem, governments may re-schedule certain controlled medicines on the basis of robust scientific evidence, if adequate safeguards are in place to ensure access to the (re)scheduled medicine by patients with clinical need. Such decisions should be made independently and by an evidence-based mechanisms, such as a health technology assessment. Another approach is down-scheduling with the provision of adequate safeguards to prevent unsafe use. Overly strict scheduling has been reported to be a significant obstacle to clinical research and thus to eventual access to potential clinically useful medicines.

8.4 Regulatory procedures for import and export

The international conventions require countries to report the volumes of opioids and other controlled medicines that are imported and exported. Except in emergency situations, imports of controlled medicines must be approved by the relevant authorities. Other regulatory procedures that govern cross-border trade in controlled medicines differ by jurisdiction but often include special licenses and other forms of clearance, such as permits for registration of each batch of controlled medicines traded.

The aim of special measures is to minimize the diversion of controlled medicines to non-medical uses; they also facilitate the reporting required by INCB as well as quantification (chapter 7). Such requirements, however, increase bureaucracy and thus processing time. Their effect may therefore be especially evident when previously unplanned imports or exports are required, for example, in a natural disaster or other humanitarian or health emergency, including pandemics. The requirements also have a negative impact on quantification, as some countries find it difficult to justify why increased quantities are required, as compared with previous data.

In all countries, if medicines are not diverted to non-medical use, their consumption in medical settings should equal local production plus imports, net of exports and retained stock. Policies to help maintain a level of supply that meets the country's medical needs without exceeding it can reduce diversion.

Governments and the INCB, which oversees implementation of the international conventions, register and track imports and exports of medicines controlled under the 1961 convention (and sometimes other medicines) and compare them with other data to identify signs of possible diversion. The aim of such measures is to minimize diversion of controlled medicines to non-medical uses while ensuring medical needs.

Import and export policies for controlled medicines may include:

- reporting of exports by destination and imports by source (mandatory for medicines controlled under the 1961 convention);
- approval of import (and sometimes export) permits by international or national authorities;
- restriction of trade to designated or registered wholesalers, distributors or handling agents;
- batch registration; and
- waivers for emergencies *(65)*.

8.4.1 Good practice statements

Good practice statement

Governments and relevant authorities should review their requirements and procedures governing trade of controlled medicines to ensure that they are proportionate, do not obstruct the flow of medicines necessary to treat people with clinical need and competently minimize diversion.

Good practice statement

Governments should encourage universal use of electronic authorization and reporting in implementing trade regulations for controlled medicines.

Good practice statement

Governments and relevant authorities should ensure that controlled medicines can be exported or imported rapidly for use by humanitarian response organizations that are duly authorized by relevant national authorities

Remarks: The GDG considered that there was insufficient evidence for a specific recommendation on regulatory procedures or policies for importing and exporting controlled medicines. It noted that the requirements and procedures governing the trade of controlled medicines should not obstruct access to psychoactive substances for medical and scientific research purposes, including for early access programmes before regulatory approval.

8.4.2 Overview of the evidence from the rapid systematic review:

No studies were identified on access to or the safety of interventions related to import or export regulation.

Two qualitative studies in countries with poor access to controlled medicines reported the perspectives and experiences of health-care providers and government officials. The interviewees highlighted the barriers and administrative burden associated with legal importation of controlled medicines and their negative effect on access to pain treatment.

8.4.3 Implementation considerations:

Regulatory capacity for importation and exportation of controlled medicines should be responsive to changes in demand. Governments that are considering regulation of the import and export of controlled medicines should include the cost and availability of the necessary technology, staff training and other processes in the regulatory system in order to avoid unnecessary barriers to access while minimizing the risk of diversion. Use of dedicated, secure online platforms, such as the International Import and Export Authorization System developed by the INCB, may help governments to encourage use of electronic authorizations and standardized reporting in adhering to trade regulations for controlled medicines.

Enforcement of the guidelines for access to controlled medicines in humanitarian crises has sometimes resulted in blockage of supplies that include controlled medicines, blocking not

only controlled medicines, but also other emergency supplies. The WHO Model guidelines for the international provision of controlled medicines for emergency medical care and the Sphere handbook: Humanitarian charter and minimum standards in humanitarian response provide guidance on implementing regulatory procedures or policies for the import and export of controlled medicines *(65, 82)*.

There is no credential that specifically permits a "humanitarian responder" agency to import or export medicines. Licensing permits for importers, exporters and national distributors are issued by the national medicines regulatory authority and/or the national customs authority. They may also provide temporary or time-restricted authorization for certain entities in emergency situations.

8.5 Links to other WHO documents:

Safety of medicines

- World Health Assembly WHA67.20. Regulatory system strengthening for medical products *(76)*.

Regulatory procedures for import and export

- World Health Organization (2020). Maintaining essential health services: operational guidance for the COVID-19 context: interim guidance, 1 June 2020 *(83)*.

8.6 Research gaps

Although there is considerable evidence on the safety of up-scheduling controlled medicines, predominantly for opioids, there is limited information about the impacts of up-scheduling access to controlled medicines. Additional research is therefore required, as is research on the effectiveness of policy to down-schedule medicines. Research should also be conducted on the feasibility and acceptability of electronic authorizations for controlled medicines internationally and of the clinical and societal outcomes.

Chapter 9

Prescribing, dispensing and administration

This chapter describes national policies on prescribing, dispensing and administering controlled medicines by health service providers. Such policies are designed to ensure safe access to controlled medicines for medical use while minimizing harmful use. Policies exist in four areas:

- development, dissemination and implementation of clinical practice guidelines;
- regulations or policies governing prescription, dispensing and administration;
- systems for tracking prescribing and use patterns and for monitoring patient health outcomes; and
- policies for the management of pharmaceutical industry relations with health-care systems, health-care professionals and the public.

9.1 Clinical practice guidelines

A WHO guideline is a document containing recommendations for clinical practice or public health policy. The Institute of Medicine in the USA defines clinical practice guidelines as statements containing recommendations that are intended to optimize patient care *(84)*. Clinical practice guidelines are developed by various organizations to guide clinicians and other health-care providers in treating patients according to the best available evidence. They usually provide advice on the optimal regimens of effective, safe, cost-effective medicines for specific medical conditions and patients. Some guidelines provide advice on when a medicine is not indicated because of an unfavourable balance of benefits to harms.

WHO provides model clinical practice guidelines in therapeutic areas in which controlled medicines are most frequently used. This chapter addresses broader policies on the availability and use of clinical practice guidelines for health conditions in which use of controlled medicines is deemed to be clinically appropriate. They include conditions that cause acute and chronic pain; anaesthesia during procedural, pre- and post-surgical care; palliative care; mental, neurological and substance use disorders; humanitarian and other health emergencies; and clinical research on emerging medical applications of controlled substances. Controlled medicines may also be used in specific patient populations, including pregnant women, specific age groups (e.g. infants, children, adolescents, older people) and individuals with current or past substance use disorders.

Clinical practice guidelines that provide recommendations on prescribing, dispensing and administering controlled medicines are important, because they:

- provide objective, standardized, reliable, measurable clinical criteria for deciding whether to prescribe a controlled medicine;
- address the likelihood of dependence and harmful use, which could indicate treatments that are less likely to cause harm while maximizing benefit;
- include information on continuity of care and best practice in settings in which controlled medicines may be required, such as the provision of OAT for people with opioid dependence who are in prison or the choice of medicines that can be used most feasibly in trauma surgery in field hospitals during humanitarian crises;

- provide information to guide care for patients with special needs, including children, adolescents, pregnant women, older people, those living in rural or remote locations, those with limited financial resources, people who use other medications and substances and people in contact with the criminal justice system; dosing of children requires paediatric formulations; and
- may address attitudinal barriers among health-care workers that hinder the access of some patients; and
- increase the confidence of health-care professionals in prescribing, dispensing and administering controlled medicines.

When clinical guidelines for controlled medicines are used into practice, some adaption may be necessary according to local epidemiology, conditions or resources.

9.1.1 Good practice statements

Good practice statement

Governments and relevant authorities should ensure that clinical guidelines that include controlled medicines are:

- developed or revised by independent experts according to a scientific process based on the best available evidence;
- designed to optimize access to controlled medicines that are safe, effective and appropriate for all patients with clinical need;
- are non-discriminatory and address the needs of specific and vulnerable populations; and
- are designed to protect the population from harm.

Remarks: The GDG considered evidence on the impact of policies governing the development, dissemination and implementation of clinical practice guidelines for controlled medicines. No evidence was available on the impact of such policies on access to controlled medicines, and the evidence on safety was limited to a few high-access contexts. The GDG therefore did not make a recommendation for policy interventions on clinical practice guidelines for controlled medicines.

9.1.2 Overview of evidence from the rapid systematic review:

No evidence was found on the impact of clinical practice guidelines on access to controlled medicines. Studies on safety-related outcomes indicated that use of clinical guidelines in a health system reduced the prescription rates and quantities of controlled medicines. The studies were conducted in contexts in which access to controlled medicines is high (predominantly Canada and the USA). The potential harm or unintended consequences of clinical guidelines were not assessed routinely; however, no evidence was found of an increase in under-managed pain, readmission or requests for refills of controlled medications. The few studies of patient outcomes gave mixed results. In some studies, reduced prescribing in accordance with guidelines resulted in fewer emergency visits, opioid poisonings and deaths or a transition to chronic use of controlled medicines among new users, whereas others showed no change.

9.1.3 Implementation considerations:

Specific and vulnerable populations whose needs should be considered in the development of guidelines on controlled medicines are identified in the good practice statement. Meaningful engagement of relevant populations in development if guidelines is recommended to ensure that they meet the needs of those populations.

National clinical practice guidelines should be aligned with national EMLs, relevant WHO guidelines and World Health Assembly resolutions and should be updated regularly to reflect the latest global norms and standards. The recommendations in national guidelines should be reflected in operational protocols for local implementation.

Clinical practice guidelines should be feasible to implement in the context in which they are to be applied. Many factors influence the willingness or ability of providers to implement clinical guidelines, including gaps in knowledge, skills and self-efficacy; lack of interprofessional support; stigmatization of the use of controlled medicines; anxiety about changes in regulatory frameworks and prescription practices; resistance to policies that are perceived to reduce clinical autonomy and individually tailored treatment; patient–provider dynamics; and a bias towards pharmaceutical treatments. Governments should consider mechanisms to overcome such barriers to use of guidelines, such as providing local tools, personnel and resources, reinforced by appropriate communication among ministries of health, public health officials and practising clinicians as well as in undergraduate, postgraduate and continued professional education and training of health-care professionals (see chapter 10).

9.2 Regulations and policies governing prescription, dispensing and administration

The international conventions require countries to have policies that require medical prescriptions for the supply or dispensation of medicines to individuals, limiting their provision to medical and scientific purposes. These regulations supplement those covered by the laws on possession and use described in chapter 8, which determine who is allowed to handle specific medicines. This chapter covers policies that address prescription itself, i.e. the quantities that can be prescribed at any one time, restrictions on where medicines may be taken, the frequency and means by which prescriptions may be refilled and similar issues. Governments may also have broader policies on prescription and dispensing that are common to all medicines, such as requiring prescription by the name of the active ingredient rather than the brand name and incentivizing generic substitution by pharmacists. These aspects are covered in other WHO guidance and are not repeated here.

Most policies on prescribing and dispensing controlled medicines promote optimal use of controlled medicines to safeguard patients and reduce the risk of substance use disorders after initiation of prescription medicine. Policies to limit the volumes of medicines prescribed may also reduce the risk of diversion of medicines for non-medical use. Such policies should be based on therapeutic guidelines for specific conditions. Some policies are also designed to improve access or to facilitate continued treatment by reducing regulatory barriers to ensure continued adherence to clinically recommended regimens. In some countries, policies on controlled medicines for indications such as OAT for opioid use disorder limit access to these essential medicines.

Policies to reduce the risk to patients of over-prescription or other inappropriate prescribing or dispensing include:

- restricting the quantity or duration of medicines that may be prescribed or dispensed at any one time;
- restricting the frequency or mode for filling repeat prescriptions;
- requiring verification of patient identity and markers of safe use (such as urine testing);
- rules intended to reduce prescription forgery, such as a requirement that prescriptions be hand-written, or, if available, directly transmitted by the prescriber to the pharmacy;
- requiring supervised or verified administration;

- encouraging compliance with restrictions on prescription, including through audit, feedback and professional support; and
- use of technical solutions such as automated dispensing cabinets.

Policies must have a balanced approach to both reducing risk to patients and preventing access for patients in need. Policies to increasing access by people with clinical need include:

- an increase in the volumes that may be prescribed or dispensed to people with clinical need whose access to services is physically or socially constrained;
- extension of prescription and dispensing services to new contexts or new models of delivery; and
- reduction or elimination of supervised or verified administration, for example by dispensing "take-home" doses.

9.2.1 Recommendations and good practice statements

Strong recommendation

Governments should develop and implement policies to ensure that prescription, dispensing and administration of opioid agonist treatment are available for people with opioid dependence in all settings where there is clinical need and ensure continued access throughout transitions of care. The settings include communities, prisons and other closed settings.

Low certainty evidence

Good practice statement

In settings where there is high prevalence of non-medical use of certain controlled medicines, with associated harm, policies for prescribing, dispensing and administration of controlled medicines should be implemented to limit diversion to non-medical use without reducing access for those with clinical need or for the purpose of scientific research.

Good practice statement

Governments and relevant authorities should ensure that regulations and guidelines on prescription, dispensing and administration of controlled medicines be formulated to optimize safe, effective, equitable, convenient access for those with clinical need, while maintaining proportionate safeguards against potential harm.

Good practice statement

Governments and relevant authorities should ensure that regulations enable health professionals to prescribe, dispense and administer controlled medicines without undue barriers, allowing them to work to their full scope of practice, to ensure that controlled medicines are accessible to patients with clinical need.

Remarks: Despite low-certainty evidence, the GDG made a strong recommendation on policies governing OAT, as the Group considered that failure by governments to make OAT available in all types of settings, including the community, prisons and other closed settings, could lead to serious or life-threatening situations, including medication withdrawal syndromes, recidivism, blood-borne infections, criminality and overdose. The recommended intervention may therefore improve public safety and well-being and save lives. The potential harm of implementing the recommendation was deemed to be immaterial.

Evidence from the review indicated the effectiveness of the intervention in prison populations, including reductions in mortality rates and in the incidence of hepatitis C. The GDG discussed the evidence for consistent support of OAT in many settings, including evidence from the rapid systematic review that showed reduced mortality rates in all populations and settings. Highly restrictive rules for prescribing or dispensing may deny services to incarcerated, homeless and other marginalized populations, violating their right to health. In view of the favourable outcomes and consideration of human rights and equity, a strong recommendation was made.

Although the evidence considered by the GDG was specific to OAT and opioid dependence, the Group noted that access to other types of controlled medicines should be ensured in all settings in which there is a clinical need, including continued access during transitions of care (such as access to benzodiazepines for individuals with epilepsy).

The GDG agreed that it would make no other recommendation on prescription practices. Most of the evidence was related to increasing access or reducing harm, and few studies addressed the impact of harm-reducing activities on access and vice versa. The GDG considered that it could not make recommendations, even for specific settings, as they might reduce access or increase harm.

9.2.2 Overview of the evidence from the rapid systematic review:

Prescription practices: A single study showed that laws to limit prescribing of opioid analgesics increased the number of people who started OAT.

Primary studies on interventions to regulate provider prescription practices showed inconclusive effects on prescription rates and quantities; however, a systematic review found consistent improvement in prescription practices and no change in other outcomes. Inconsistent evidence was found on the effect of interventions to regulate provider prescription practices on patient practices (e.g. use of multiple prescriptions and prescribers, refill requests, appropriate disposal). Evidence from the systematic review showed consistent positive effects of interventions to regulate provider prescription practices on pain relief and withdrawal symptoms.

All the evidence for safety-related outcomes of prescription practices was derived from studies in high-access contexts. Few studies addressed harm resulting from these interventions, and most showed no change rather than a worsening of outcomes.

Prescription governance: No evidence was found on the effect of governance of prescriptions on access. The rapid systematic review showed consistent reductions in prescription rates or quantities, errors and non-adherence to prescription best practices after adherence to prescription governance. Two reviews of large care coordination interventions found large reductions in emergency department visits, and one review of medication management technology found fewer adverse events or errors after implementation of the intervention. All the evidence on safety-related outcomes of prescription governance was derived in high-access contexts.

New service models: Two systematic reviews provided consistent, generalizable evidence that extending OAT in prison settings to people with opioid dependence reduced opioid use and mortality. One primary study on the development of a "hub-and-spoke" system, in which OAT was centrally prescribed by specialists and care was supported in the community by non-specialists, increased the number of physicians who provided buprenorphine and the number of people on OAT, while decreasing overall health-care costs *(86)*.

No evidence on the safety outcomes of new service models was identified in the review.

Balance of health benefits and harms:	The GDG discussed the consistent evidence of a decrease in the mortality rate of individuals with access to OAT in prison, with additional health benefits after release.
Human rights:	The evidence considered by the GDG included that from the report of the Special Rapporteur on Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment *(49)*, which states: drug dependence should be treated like any other health-care condition. Consequently…denial of medical treatment and/or absence of access to medical care in custodial situations may constitute cruel, inhuman or degrading treatment or punishment and is therefore prohibited under international human rights law *(87)*.
Socio-cultural acceptability:	The GDG noted that, in some countries and settings, OAT is not acceptable for many reasons, including the absence of political will, financing, infrastructure, logistics and capacity. Additionally, the GDG considered that opioid use disorders and use of medicines for treatment may be stigmatized. Fear of being unable to control or of contributing to diversion of opioid agonist medicines to illicit use may be barriers to implementation of OAT in some countries. The GDG discussed WHO guidance that includes evidence that OAT programmes have positive effects on criminal recidivism and re-incarceration.
Health equity, equality and non-discrimination:	The GDG discussed consideration of equity in access to treatment between people living in correctional facilities and people in the community. The principle of equivalence of care should be considered in all types of health-care settings. The GDG discussed whether governments should pay additional attention to women's prisons, as members of Group reported that access to OAT is currently less often available at present than in men's prisons. The principle of equivalence of care should also be considered in settings in which access to controlled medicines is particularly limited, such as in LMIC and rural and remote settings.
Societal implications:	The GDG discussed the lack of access to controlled medicines in many countries, particularly in the global South, which has led to serious suffering. The Group discussed evidence from the systematic review that OAT reduces mortality among incarcerated populations, which has important societal implications.
Financial and economic considerations:	In the WHO Evidence for Action series, Effectiveness of interventions to address HIV in prisons, published in 2007, OAT (referred to as opioid substitution therapy in that publication) was shown to be cost-effective due to its impact on various outcomes, including crime and HIV infection.
Feasibility and health system considerations:	The GDG considered that the following should be ensured: • continuity of treatment during transitions of care between the community and prisons; • training and capacity-building for delivery of the intervention; • health systems for controlled medicines – monitoring, supervision, licensing; and • comparison of methadone and buprenorphine in terms of feasibility of delivery and monitoring.

9.2.3 Implementation considerations:

For changes in prescription practices, prescription governance or new models of care to be successful and sustainable, there should perhaps also be significant changes in the organization and delivery of care as well as access to interprofessional and specialist support and effective care coordination. New initiatives to regulate access to controlled medicines should perhaps be balanced by initiatives to reduce anxiety in both patients and providers that the new regulations will be punitive and/or reduce access to medically necessary care. Extension of treatment for stigmatized conditions, such as OAT, may require dedicated work to increase provider capacity and motivation to provide such treatments. Only extending permission, without addressing other barriers to implementation, might be insufficient to improve access throughout the health system.

Policies for the availability of OAT in prisons for people with opioid dependence should maximize access, whether or not a person was prescribed OAT before their entry to prison. Policies to regulate eligibility for OAT should not include use of illegal drugs while under treatment.

Inability to travel to dispensing sites may be a significant barrier to treatment with controlled medicines. Activities to overcome this barrier include changing dispensing regulations to allow take-home (unsupervised) doses of OAT. In some settings, long-acting formulations of medications for treatment of opioid use disorder (e.g. buprenorphine) are available to reduce the number of take-home doses of medications for treatment of opioid use disorder in unsupervised settings.

Stigmatization can undermine willingness to be treated for substance use disorder. Attitudes and other social factors should be considered to maximize access to treatment. Education and evidence-based interventions to reduce stigmatization should be used to remove barriers to evidence-based treatment.

Providers often lack the skill, knowledge and self-efficacy for prescribing opioids, for minimizing potentially inappropriate prescription of opioids and benzodiazepines or for offering OAT. Such gaps are often related to a perception that prescribing opioids or offering OAT is more appropriate for specialists than a general practitioner or in primary care. Increasing access may require dedicated capacity-building in primary care.

Extending permission to prescribe, dispense and administer controlled medicines to other health professionals who treat patients in situations in which controlled medicines are clinically appropriate, such as nurses, may increase access to controlled medicines for those in need when the current prescribing workforce is insufficient to meet clinical need. Experience and evidence of nurse prescribing, in both high- and low-income countries, indicates the feasibility of extending permission to prescribe to nurses and other appropriate health professionals after appropriate training.

Extending support to regulation of pharmacies that dispense prescribed controlled medicines might also increase access to controlled medicines. Some countries require extensive, expensive safeguards, which discourage pharmacies from stocking controlled substances; these include armed guards, alarms connected to police stations and expensive safes for storage. The safeguards should be reasonable and proportionate, not excessive.

It should be recognized that primary health facilities often have requirements for controlled medications that are different from those of secondary and tertiary health facilities. Primary facilities often deal with more basic health needs and may not require access to the range of controlled substances necessary for the complex cases managed at secondary and tertiary facilities. Recognizing such distinctions will strengthen the regulatory framework, particularly in regions where health systems are less regulated. The approach will not only increase the safety and efficacy of use of controlled substances but will also significantly reduce the administrative burden on regulatory authorities, so that they can focus on critical oversight functions.

9.3 Prescription monitoring programmes and pharmacovigilance systems

Prescription drug monitoring programmes (PDMPs) are designed to collect information on prescription and dispensing of controlled medicines to identify over-prescription, patients who see multiple prescribers and other practices that may indicate diversion of controlled medicines. The programmes are also used to identify people who may be at risk of other harm, such as substance use disorder or overdose. The purpose of these systems sometimes depends on the setting and who has access to the system and its information. When health-care professionals have access, the goal may be to provide information for clinical decisions. For law enforcement agencies that have access to the information, the goal may be to detect inappropriate prescribing that could contribute to harm, such as diversion. Aggregated data from these programmes are used to identify areas of low use, signalling constrained access or unmet need; however, such use of data is uncommon in practice. It may be dangerous when law enforcement agencies use the data to identify areas of high use and assume non-medical use. This may lead to increased policing and prosecution, even if the use is for OAT or if there is a higher rate of patients requiring palliative care.

Electronic PDMPs can reduce barriers to access to controlled medicines for therapeutic use by overcoming logistical barriers such as paper-based reports. They may also facilitate information-sharing among health-care professionals, retrieving patients' histories, identifying contraindications and determining pharmacological need. Prescribers who are uncertain of a patient's medication history may become more confident in prescribing when these data are readily available. PDMPs may have a more limited role in promoting access to medicines for people with clinical need but no current access, unless they are used to address concern about early detection of possible diversion or inappropriate use and thus increase the confidence of prescribers and governments.

Pharmacovigilance systems record adverse events associated with the use of any medicine used in the health system for rapid follow-up by regulatory authorities and the health system. Pharmacovigilance systems also provide system-generated signals of unsafe products, including those associated with non-medical or other unsafe use. Reports of harm to individual patients are aggregated by manufacturer, hospital safety board, medicine regulator and other responsible authorities. For controlled medicines, the patterns seen in aggregated data may provide signals that the medicines are causing dependence or are being used non-medically or to quantify other known or emerging harms. When such signals are detected, regulators can act, for example, by withdrawing the market authorization of a harmful product or by applying other policies to reduce harm, such as those described in this document.

Pharmacovigilance and PDMPs do not provide direct information on non-medical use of controlled medicines; however, they allow timely monitoring, which may indicate diversion or other public health harms or difficulties in accessing prescription medicines due to lack of prescribing. Both approaches may therefore ensure the safe use of and more appropriate access to controlled medicines.

Prescription monitoring programmes include mandatory or voluntary use of electronic systems to record prescriptions, which permit easy auditing of the types, volumes and duration of prescriptions by individual physicians to individual patients.

Pharmacovigilance systems may include:

- voluntary or mandatory reporting to the medicine regulator and local health authorities of adverse events witnessed by or reported to health service providers;
- voluntary or mandatory reporting to the medicine regulator and local health authorities of adverse events recorded by or reported to market authorization holders of medicines;
- voluntary reporting to the medicine regulator and local health authorities of adverse events experienced by medicine users; and
- proactive analysis of reported adverse events by the medicine regulator, industry or health authorities, with follow-up action to reduce harms.

9.3.1 Good practice statements

Good practice statement

Governments should ensure robust nationwide systems that allow monitoring of prescriptions for controlled medicines, with specific attention to the protection of patient privacy, to optimize access to and safe use of controlled medicines. Where feasible and affordable, electronic systems should be prioritized. The absence of these systems should not be a barrier to accessing clinically necessary controlled medicines.

Good practice statement

Governments should ensure that systems for monitoring prescriptions of controlled medicines are not used to expose caregivers, patients or prescribers to unwarranted scrutiny in the delivery or receipt of clinically indicated health care.

Good practice statement

Governments should ensure active monitoring of the safety of controlled medicines, including new formulations, through a robust pharmacovigilance programme.

Remarks: The GDG did not make a recommendation on prescription drug monitoring or pharmacovigilance policy. The Group noted that evidence in the rapid systematic review was from studies in high-access countries and therefore pertained only to the safety outcomes of PDMPs. While there was some evidence that PDMPs may reduce "doctor shopping", non-medical use of controlled medicines and the total number of controlled medicines prescriptions, the GDG was unclear about the resulting health outcomes and the impact of these interventions on access to controlled medicines in other contexts. The GDG did not make a recommendation about PDMP policies because of concern that their implementation might create a barrier to accessing controlled medicines. Similarly, the GDG noted that countries may find implementation of these programmes prohibitively expensive. Furthermore, if the policies are not implemented robustly, they may put patients or providers at personal, legal or professional risk because of breaches of privacy.

While noting the advantages of prioritizing electronic PDMPs, it was further noted that most countries (especially LMIC) still do not have effective PDMPs and use paper-based systems. Good practice for non-electronic systems and hybrid approaches to facilitate access and to reduce bureaucracy could be further explored.

9.3.2 Overview of the evidence from the rapid systematic review:

No studies of the effects of pharmacovigilance were identified in the rapid systematic review, and no evidence was found of the effect of PDMP interventions on access.

The evidence on safety outcomes for PDMPs was mixed. The strongest effect was seen in provider prescription practice. Most studies showed decreases in prescription rates and in the quantities of controlled medicines prescribed, although many studies found little or no effect on these outcomes. The few studies in which mandatory PDMPs were studied found a greater reduction in the number of prescriptions. Patient practice outcomes (e.g. non-medical use, diversion, "doctor shopping") were similarly mixed, some studies showing meaningful improvements and others showing little or no change. A small number of studies showed increased heroin use after PDMP.

Health outcomes were also mixed, with use of mandatory PDMPs resulting in more consistent, substantial improvements in health outcomes (e.g. health-care engagement related to non-medical use and rates of opioid use disorder). All the evidence of the safety outcomes of PDMP interventions was from studies in high-access contexts.

9.3.3 Implementation considerations:

Lack of fully functioning pharmacovigilance and prescription monitoring systems should reduce work to increase access to controlled medicines in countries with high unmet need. In high-access contexts, PDMPs may reduce unsafe prescription practices but may also reduce access to medically indicated treatment because of prescriber anxiety or stigmatization or by increasing patient reluctance to seek help or initiate treatment with controlled medicines. Alternatively, PDMP could help providers to identify potential non-medical use and related concerns, provide more effective, patient-centred care and improve access to treatment for substance use disorders.

Installing and running prescription monitoring systems may be expensive, which may discourage implementation and maintenance of these systems. The value of both PDMPs and pharmacovigilance systems in monitoring unsafe use of medicines depends largely on their completeness and active, timely analysis of the data generated. Many countries are using systems such as the WHO Global Antimicrobial Resistance and Use Surveillance System to monitor antibiotic prescription and use in addressing the threat of antimicrobial resistance. It would be both feasible and cost-effective to integrate monitoring of controlled medicines into these systems. While additional investment in establishing or strengthening PDMP and pharmacovigilance systems could deliver benefits beyond controlled medicines, systems take considerable time to reach maturity. These considerations can be used in deciding whether to invest in costly electronic systems in resource-constrained environments, as paper-based systems may be more feasible and sufficiently robust in certain countries.

Appropriate training of health-care providers and regulators in use of prescription monitoring systems could reduce any negative effects such, as stigmatizing responses resulting from incorrect interpretation of data. Concern that data will be shared for non-health purposes may limit use of these systems, which rely for their effectiveness on complete reporting. Even with appropriate training, monitoring systems and documentation add considerably to the work of health-care professionals, which may make them reluctant to prescribe opioids or other controlled medicines. These tasks also require additional resources (e.g. work time, staff) if they are not be an additional barrier to opioid prescribing.

Pharmacovigilance systems rely largely on spontaneous reporting of adverse events by health-care providers, patients, caregivers and pharmaceutical companies to national medicine regulators or other health authorities. As they do not provide information on use in non-medical settings, they are likely to miss signals of non-medical use that are identified in approaches specifically designed to capture local patterns of non-medical use of controlled drugs and the related harm.

Many countries, particularly LMIC, use manual reporting systems. Implementation of a centralized electronic prescription monitoring system would enable officials to monitor the consumption of controlled medicines in various jurisdictions and help to establish a robust framework that would allow regulatory bodies to access comprehensive data on the consumption and prescribing patterns of controlled medicines. Such a system would not only enhance transparency but also improve the ability of health authorities to identify trends, track potential non-medical use and ensure that prescribed medications are used appropriately. It could also improve data-sharing among stakeholders, including health-care providers and insurance companies, thus improving public health outcomes and regulatory oversight.

9.4 Relations with the pharmaceutical industry

In 1988, WHO published WHO ethical criteria for medicinal promotion *(91)*, which states that medicines should be available to all those who need them, with guidance to ensure appropriate use. Most medicines are made by companies that wish to make a profit for their shareholders. Profits can be maximized by marketing new products, by increasing price or sale volume or both and by cutting the costs of production and distribution and in other areas. Policies governing the relations between the pharmaceutical industry, health systems and the wider public determine the ways in which companies can enter markets, increase their market share or influence prices. Harmful marketing of medicines include reducing thresholds for diagnosing disease, relying on surrogate endpoints, exaggerating claims of safety and efficacy, inventing new diseases and encouraging unapproved uses *(92)*.

For-profit pharmaceutical companies interact with health systems through marketing, funding of research, participation in clinical guideline development and other activities. The best interests of company executives and shareholders are not, however, always aligned with the best interests of clinicians and patients. Many countries therefore impose restrictions on pharmaceutical marketing. Only very few countries permit medicine manufacturers to advertise prescription medicines directly to patients, and many prohibit the payment of incentives to public health officials, doctors, health workers or health facilities to encourage use of a specific medicine or brand. In some countries, however, especially those with largely profit-driven health services, health institutions and personnel derive significant income or other benefits from selling medicines directly to patients or by providing incentives to doctors to prescribe a particular brand. Such incentives may contribute to over-prescription and use of medicines, even when they do not represent the best therapeutic option for patients. WHO and Health Action International have published a practical guide to understanding and responding to the commercial promotion of pharmaceutical products *(93)*.

Governance includes effective prevention and management of conflicts of interest that could compromise the integrity of decisions in the public pharmaceutical sector. The primary objective of policies and strategies on conflicts of interest is to safeguard the integrity of decision-making. Conflicts of interest related to pharmaceuticals are common in health-care systems in high- and low-income countries alike. They are, however, often not well understood, and there is limited information on how conflicts of interest are managed in public pharmaceutical decision-making, particularly in LMIC.

A recent 10-country study by WHO identified common gaps, including lack of organized practices for preventing and managing conflicts of interest *(94)*.In response, WHO developed a manual to improve understanding of conflicts of interest in public pharmaceutical decision-making and provide guidance on preventing and managing such conflicts, as identified in the WHO study and in the WHO Good Governance for Medicines programme *(94)*.

9.4.1 Good practice statements

Good practice statement

Governments should implement national regulations to ban misleading or unethical marketing of controlled medicines to patients, health-care providers and other stakeholders involved in medicine purchase or supply.

Good practice statement

Governments, professional societies and international organizations should implement robust, transparent policies to prevent and manage conflicts of interest in the training, education of and promotion of products to health professionals and in the development of clinical guidelines. This includes both direct and indirect commercial influence via patient groups or other stakeholders.

Good practice statement

Governments should implement policies to address undue influence, including preventing and managing conflicts of interest of legislators, regulators and other government officials who may formulate or vote on legislation or rules for controlled medicines.

Remarks: The GDG did not make a recommendation on regulation of industry marketing or policies on conflicts of interest, as there was insufficient evidence to determine the impact of such interventions on access to controlled medicines. Introducing measures to identify and manage potential conflicts of interest was considered to be good practice. The GDG therefore made three good practice statements encouraging policies to prevent misleading or unethical marketing of controlled medicines to relevant stakeholders and minimizing undue influence from the pharmaceutical industry on guideline development and decisions.

9.4.2 Overview of the evidence from the rapid systematic review:

No evidence was found on the impact of regulation of industry marketing on access to controlled medicines. The qualitative evidence indicated that the pharmaceutical industry attempts to increase access to controlled medicines (specifically opioids) and described the associated risks, including preconceived, potentially inaccurate or incomplete understanding of patients about controlled medicines, increasing provider anxiety about balancing effective treatment and avoiding unintended harm. One study of the relation between conflict of interest policies and the volumes of opioid prescription in academic medical centres in a high-access context showed that policies that require disclosure or restriction of promotion reduced the volume of prescriptions of name brand opioids *(95)*.

9.4.3 Implementation considerations:

Regulation of industry marketing to both providers and the public may be difficult. Monitoring of pharmaceutical industry relations and activities may be resource intensive, and many countries do not have the necessary resources. Governments should be able to monitor the marketing strategies of pharmaceutical companies to prevent misleading and unethical marketing.

Adequate funding for evidence-based non-pharmacological therapies for conditions in which controlled medicines are used (e.g. for the management of chronic pain and treatment of some mental health disorders) will probably reduce the demand for medicines and therefore reduce the danger posed by marketing practices that favour over-use of medication. The relations of countries with industry and the financial viability of the industry to provide access to controlled medicines in various regions should also be considered.

9.5 Links with other WHO documents:

Clinical practice guidelines

- World Health Organization. 2014. WHO handbook for guideline development, 2nd Edition *(18)*.
- World Health Organization. 2019. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents *(85)*.
- World Health Organization. 2023. WHO Model Lists of Essential Medicines *(20, 21)*.

Regulations and policies governing prescribing, dispensing, and administering

- World Health Organization. 2023. Left behind in pain: Extent and causes of global variations in access to morphine for medical use and actions to improve safe access *(26)*
- International Narcotics Control Board. 2023. No patient left behind: Progress in ensuring adequate access to internationally controlled substances for medical and scientific purposes: supplement to the annual report of the Board for 2022 on the availability of internationally controlled substances *(28)*.
- World Health Organization. 2009. Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence *(88)*.
- World Health Organization. 2019. WHO guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents *(85)*.
- World Health Organization. 2020. Consolidated guidelines on HIV, viral hepatitis and STI prevention, diagnosis, treatment and care for key populations *(57)*.
- World Health Organization, United Nations Office of Drugs and Crime. 2022. Establishing and delivering evidence-based, high-quality opioid agonist therapy services an operational tool for low- and middle-income countries *(89)*.
- World Health Organization, United Nations Office on Drugs and Crime. 2020. International standards for the treatment of drug use disorders: revised edition incorporating results of field-testing *(90)*.

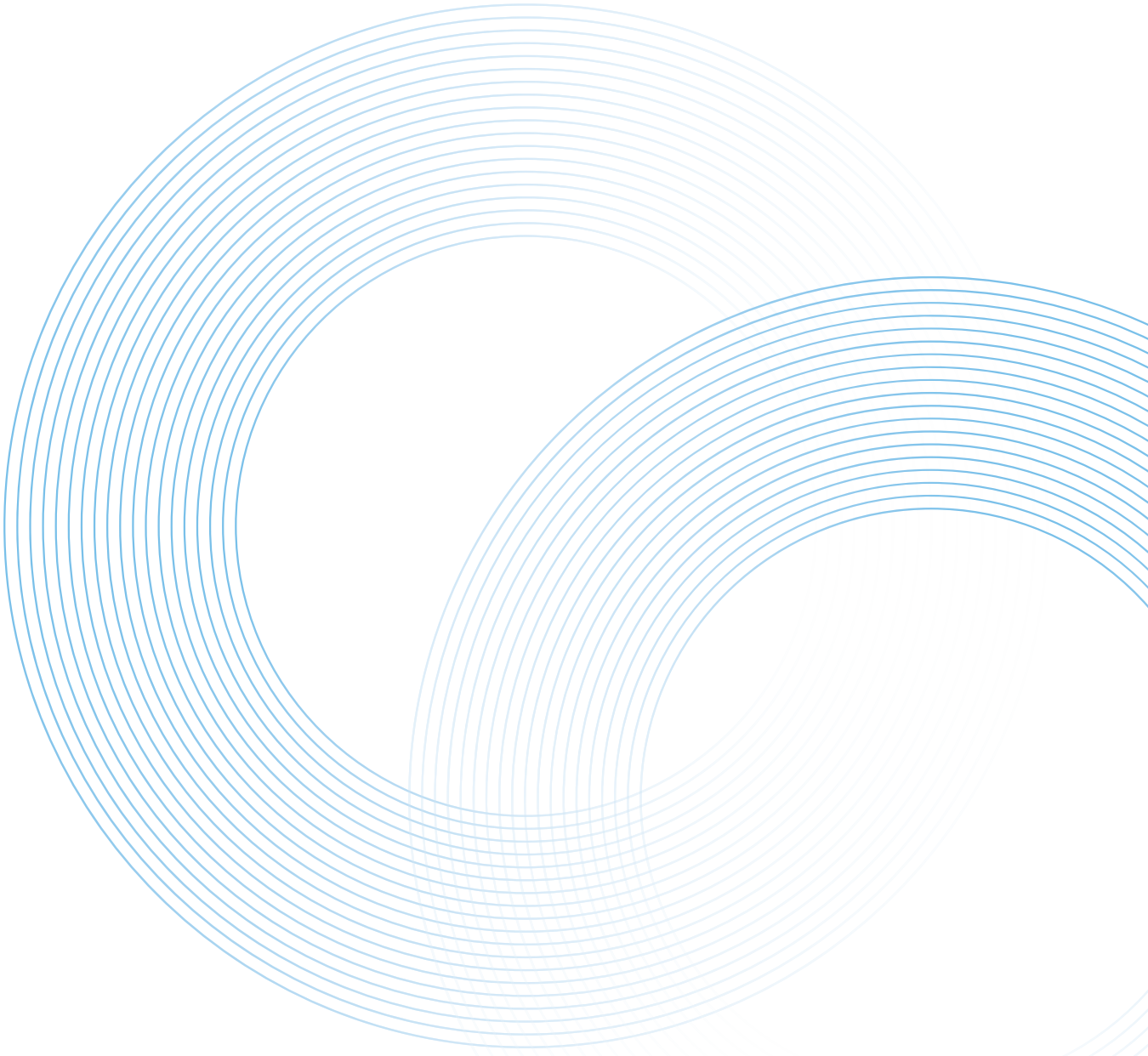
Pharmaceutical industry relations

- World Health Organization. 1988. Ethical criteria for medicinal drug promotion *(91)*.
- World Health Organization, and Health Action International. 2010. Understanding and responding to pharmaceutical promotion: a practical guide *(93)*.
- World Health Organization. 2022. Managing conflicts of interest, a how-to guide for public pharmaceutical-sector committees in low- and middle-income countries *(94)*.
- World Health Organization. 2017. Responding to industry initiatives to increase access to medicines and other health technologies in countries *(96)*.

9.6 Research gaps

The evidence for this chapter was predominantly of low certainty, was derived from studies in contexts in which there is high access to controlled medicines and in specific treatment settings. Most of the studies addressed use of opioids and, secondarily, benzodiazepines. Pain management and mental health were the most common therapeutic reasons, although several studies did not specify a therapeutic area. Future research should address:

- the incentives used internationally to encourage use of guidelines and how effective they are in changing prescribing, dispensing, administration or use of controlled medicines in clinical practice;
- whether policy initiatives can improve access to and the benefits and harms of controlled medicines;
- the amount of financial and in-kind donations received from the pharmaceutical industry by government officials in various countries; and
- the proportion of industry funds used in marketing.



Chapter 10

Education, knowledge and attitudes

This chapter addresses policies for programmes to increase the knowledge and understanding of health-care professionals, patients and the public about controlled medicines. The chapter covers policies for increasing:

- knowledge, skills, confidence and competence and changing the attitudes of health-care professionals towards appropriate, safe use of controlled medicines;
- knowledge, understanding and competence and changing the attitudes of other stakeholders, including legislators, bureaucrats, regulators and health-care managers, towards balanced access to and the safety of controlled medicines; and
- knowledge and changing the attitudes of patients, their families, other affected groups and the general public about the value of controlled medicines and the importance of appropriate, safe use.

10.1 Training and education of health-care professionals

National and local policies govern the settings in which training for health professionals is provided, including who can, or must, receive specialized training in controlled medicines, and the content of training materials. Health professionals may have concerns about risks relatied to the prescription, dispensing or administration of controlled medicines. Similarly, the use of psychoactive medications may be socially stigmatized. These concerns may be a barrier to patient access to controlled medicines. Conversely, health professionals may overestimate the safety or underestimate the risks associated with the use of controlled medicines, leading to unsafe or inappropriate use.

The aim of policies that govern training for health professionals is to ensure accurate understanding of the benefits and potential risks associated with controlled medicines. They may also include information to help health-care professionals to prevent, identify and respond to unsafe or inappropriate use. Education and training are expected to encourage authorized health-care professionals to provide comprehensive evidence-based care, including that which requires controlled medicines, confidently and safely to people with clinical need. The policies are also intended to increase the understanding of health-care workers of the conditions that may require treatment with controlled medicines, including for workers who do not directly prescribe, dispense or administer controlled medicines, but are in a position to reduce barriers to safe, appropriate access.

Better knowledge and skills of health professionals and practitioners in direct contact with patients may increase referral to appropriate health-care providers in areas that are neglected in some health systems, such as mental health or substance use disorders, palliative care and treatment of pain. Well-informed health professionals and front-line workers may also recognize and respond to signs and symptoms of unsafe use of controlled medicines.

Training policies may include:

- appropriate training in the curricula of relevant health-care disciplines (medicine, pharmacy and nursing) in recognizing the symptoms of the conditions for which controlled medicines are used;
- appropriate training in the curricula of relevant health-care disciplines (medicine, pharmacy and nursing) in the therapeutic value, safe use and potential harm of controlled medicines in different patient populations (including children, older people, pregnant women, people with substance use disorders and others with special needs);
- appropriate training in the curricula of relevant health-care disciplines (medicine, pharmacy and nursing) in policies or laws that regulate controlled medicines (including policy changes);
- continued professional education in the areas cited above for people authorized to procure, prescribe, dispense or administer controlled medicines;
- continued professional education in the areas cited above for front-line health workers who may be in contact with people in need of controlled medicines; and
- ongoing professional mentoring and support for health professionals who provide health care to people with a clinical need for controlled medicines.

10.1.1 Recommendations

Strong recommendation

Governments, academic institutions and other responsible bodies should promote comprehensive training in adequate access and safe use of controlled medicines, according to clinical guidelines, in core curricula and continuing professional education programmes of relevant health-care disciplines.

Very low certainty evidence

Remarks: Although the evidence was of very low certainty, the GDG made a strong recommendation for integrating comprehensive training on access to and safe use of controlled medicines, according to clinical guidelines, into the core curricula and continuing professional education programmes of schools for relevant health-care disciplines. The GDG considered that implementation of this recommendation was associated with a very limited risk of harm and a very significant potential benefit of training to increase access to and the safety of controlled medicines.

10.1.2 Overview of the evidence from the rapid systematic review:

Consistent, positive effects of education and training of health-care professionals in controlled medicines were identified, resulting in meaningful improvements in their knowledge, attitudes, intention and/or self-efficacy, particularly in improving pain management and access to opioid agonist treatment. No evidence of unintended harm was observed.

Provider education improved various safety measures and increased adherence of health-care professionals to local best-practice or treatment standards.

Balance of health benefits and harms:	The GDG recognized the consistent, positive effects of education and training in controlled medicines for health-care professionals in improving access to and safe use of controlled medicines. The GDG found no evidence of harm resulting from educating or training health-care professionals.
Human rights:	The GDG noted that training of health-care professionals recognizes human rights, whereas insufficient education of health-care professionals and workers in the conditions for which controlled medicines are used, such as palliative care and substance use disorders, can result in suboptimal management and subsequent patient harm.
Socio-cultural acceptability:	The GDG noted that training and education of health-care professionals has been shown to reduce stigmatization.
Societal implications:	The GDG discussed the potential unintended harms of replacing other topics in curricula with training in care related to controlled medicines. Information on controlled medicines and their safe, equitable use should not replace other content but should be added.
Financial and economic considerations:	The GDG recognized that training and education of health-care professionals produces skilled, competent professionals and may thus result in better care. It may also reduce use of health care and the costs and burdens due to absence from work.
Feasibility and health system considerations:	The GDG noted the differences in the availability of technology and infrastructure among countries and recognized that this might limit training and education of all health professionals. Qualitative evidence indicated that many providers have significant gaps in skills, knowledge and self-efficacy with respect to controlled medicines. Barriers such as limited time for training, inadequate training materials and infrastructure, especially in LMIC, may impact delivery and outcomes. Online training can reduce training costs and increase access to training and education.

10.1.3 Implementation considerations:

Training and education to improve access to controlled medicines and prevent harm should be tailored to the priorities of each country. For instance, countries with excellent access to controlled medicines and a high prevalence of non-medical use might choose to invest in education and training in harm reduction, while countries with limited access to controlled medicines might focus on training and education in improving access and measures to prevent inappropriate use. Training in the use of controlled medicines should be integrated into training in specific conditions to ensure that controlled medicines are considered at the same time as other medicines and approaches (including non-pharmacological options).

Cultural factors can create barriers to education about controlled medicines in some countries, and targeted strategies might be necessary to address moral concerns and cultural stigmatization, which limit access to these medicines and affect the success of training programmes. Socio-economic factors, such as inadequate training materials, skilled trainers and training infrastructure, are also significant. Often, locally relevant materials must be developed, as those created in the

global North might not adequately reflect the diverse cultural, moral and professional contexts of providers in the global South, nor the available resources and services. Health-care professionals may not be fluent in English or may prefer to use material in their native language, which can be challenging in countries that have several national languages. Implementation challenges in humanitarian settings should also be considering when developing materials. Any of the above can significantly limit the applicability, acceptability and effectiveness of educational materials. When local infrastructure allows, use of virtual training may increase access, and interprofessional education of health-care professionals and mentoring systems may promote continuing education (e.g. peer-to-peer help and training the trainer).

Rapid training, certification or accreditation in prescribing controlled medicines may be critical in humanitarian emergencies or other major disruptions because of unavailability or regulatory restrictions.

10.2 Education of patients and the public

The aim of patient and public education programmes is to provide comprehensive information about the clinical use of controlled medicines, including their safety and efficacy and the risks associated with non-medical use. Such programmes are designed to encourage those in need to seek treatment while discouraging inappropriate use, including primary prevention of non-medical use.

Policies on the provision of information about controlled medicines to patients and the public may encourage or mandate information campaigns for specific groups or circumstances. They may also govern the content or financing of such information.

The public, including those who are ill, may have a negative view of controlled medicines (e.g. use of illicit drugs and other stigmatized behaviour). Such views may generate fear or reduce support for programmes that provide controlled medicines. Concern about the risks associated with controlled medicines may also discourage people from seeking care. Conversely, the risk may be increased if the potential harm associated with controlled medicines is not understood. Public education may address these issues and build social support for approaches to controlled medicines that prioritize public health, including harm reduction and appropriate safeguarding.

A more knowledgeable public that is better informed about the benefits of controlled medicines for clinical use and also about the harm associated with inappropriate use may be less likely to exert pressure on physicians to prescribe or dispense inappropriately.

The policies addressed in this chapter and the associated interventions can be categorized as:

- patient and family education for people already receiving controlled medicines, such as:
  - provision of information on safe storage and use and the risks of non-medical use and
  - provision of information and training to reduce overdose and other risks associated with unsafe use; and

- public information campaigns to provide accurate, balanced knowledge about the therapeutic uses of controlled medicines and the associated potential benefits and risks, including:
  - mass media campaigns;
  - information campaigns in targeted settings, such as schools; and
  - information on the availability of and access to services.

10.2.1 Recommendations

Strong recommendation

Governments should ensure, through appropriate authorities and institutions, the delivery of balanced, accurate information about controlled medicines to patients, families, caregivers and the public. Information should be provided about the potential benefits and risks of therapeutic use and also of the potentially serious risks associated with non-medical use.

Low certainty evidence

Remarks: The GDG made a strong, evidence-based recommendation for policies to ensure accurate, balanced information for patients, families, caregivers and the public about controlled medicines. The Group noted that there was consistent evidence of positive safety outcomes resulting from educational interventions and that patients, families and the public required awareness-raising and information to promote safe use. Evidence of the impact of patient and public information interventions on access was limited. The GDG made a strong recommendation, as the evidence from the systematic review showed a net benefit of awareness promotion among patients and the public, with no appreciable risk of harm. Furthermore, educational activities were considered to be adaptable to Member States' resources and priorities.

10.2.2 Overview of the evidence from the rapid systematic review:

Patient education: Education of patients to encourage appropriate, effective use of controlled medicines for cancer pain generally improved patients' knowledge, attitude and pain scores, with mixed results for quality of life.

Patient education to discourage inappropriate or unsafe use of controlled medicines consistently improved various aspects of patient knowledge, attitudes and practice, including knowledge of appropriate use and potential risks, intention to use controlled medicines appropriately, reports of appropriate use and/or reduced non-medical use and appropriate disposal of unused medicines.

Public education: No evidence on the effect of public education on access outcomes was identified.

Public education to discourage inappropriate or unsafe use of controlled medicines improved public knowledge, attitude and intention for appropriate use, and no studies showed worsening of these outcomes. An improvement in reduced use of opioids or benzodiazepines was found, with evidence of fewer deaths due to overdoses, although limited results were available on large-scale public education interventions or health outcomes.

Evidence for the effects of patient and public education on safety and access outcomes was limited to high-access contexts and to cancer pain control settings. Categorization of a wide variety of interventions as patient education precluded conclusions about any one approach.

Balance of benefits and harms:	The GDG discussed the positive effects of educating patients and the public on controlled medicines. While the GDG was certain about the evidence for safety-related outcomes, and positive effects were seen for access-related patient knowledge outcomes, the evidence was less certain for access and health-related outcomes.
Human rights:	The GDG, noting that special United Nations human rights procedures recognize the impact of prejudice on access to controlled medicines, recommended that greater awareness and information be provided to patients, families, caregivers and the public.
Socio-cultural acceptability:	The GDG considered that educational interventions are likely to be socially and culturally acceptable; however, consideration should be given to language and the provision of information according to the local context, cultural aspects and health literacy.
Health equity, equality and non-discrimination:	The GDG noted that some patient or public education may provide information about a medicine that is not widely available or accessible, thus creating an issue of access. The GDG discussed considerations of differences in access to information that depend on whether individuals or groups can access the Internet, their health literacy and access to and interpretation of information in a specific language or format.
Societal implications:	The GDG noted that public information may address both treatment and prevention (e.g. reducing non-medical use of controlled medicines). Patient or public education may increase access to treatment for substance use disorder by reducing stigmatization.
Financial and economic considerations:	The GDG discussed the costs of delivering patient and public education and raised concern that public education is expensive. An informed public may, however, be more likely to seek or accept treatment, which may optimize management of conditions and reduce the incidence of undertreated conditions, which may have positive economic implications.
Feasibility and health system considerations:	The GDG raised concern about the feasibility of training and education in practice, noting that the mode of delivery will impact feasibility. Integration of education on controlled drugs into existing means for disseminating information to patients and the public was considered to be a lesser financial burden for health systems.

10.2.3 Implementation considerations:

To develop and deliver relevant public education, governments will require information about the benefits and potential harms related to access to and the safety of controlled medicines in their context, in order to target education appropriately. For example, information developed for contexts with good access to controlled medicines and established patterns of non-medical use may not be useful in increasing access in contexts with little or no access.

Education of patients and the public about controlled medicines may include barriers to access and safe use of controlled medicines, such as anxiety, incorrect or incomplete knowledge and stigmatization, and health system barriers. Education is more likely to overcome these barriers when it is part of a longer-term communication strategy, is addressed not only to patients and includes shared decision-making. Governments might have to consider who is best placed to deliver education. This might be health professionals at the time of prescribing or supply. Education of patients and the public may also include prescription and dispensing of controlled medicines.

Education after medication initiation of family members in addition to the patient may maximize safe use of controlled medicines. People who are already receiving controlled medicines for treatment are likely to be concerned about potential changes to their treatment, particularly if they have been stabilized on a treatment without harm or if any changes are discussed in a way that reflects stigmatization of their condition or the treatments they are receiving. Public education can address these barriers by explaining why changes are made in the patients' best interests and in approaches that allow shared decision-making. Public education may also be more impactful if delivered over the long-term rather than once, and includes not only current or potential patients but community members and leaders, lawmakers, regulators and others who play a role in public knowledge, attitudes and practices related to controlled medicines.

When public education is included in other delivery systems, the accuracy and consistency of messaging in several modes and to various audiences may maximize its effectiveness. These include use of technology (e.g. online) and various modes of messaging (e.g. radio broadcasting, public awareness campaigns on multiple platforms including mass media, and education delivered by health-care professionals to patients, families and carers, community groups and peer distribution of information). Information should be tailored to populations in accordance with their health literacy and language. All messages in public education campaigns should have detailed input from experts in health care, including those with relevant lived experience.

Concern about diversion, unintended harm and addiction can affect patients and providers. Misinformation and stigmatizing beliefs and attitudes are barriers to evidence-based treatment for opioid use disorder, particularly for patients who have developed prescription opioid use disorder. Consideration of how to educate the public and providers to address this effectively may increase acceptance of first-line evidence-based treatments such as OAT.

10.3 Links with other WHO documents:

Training and education of healthcare professionals

- World Health Organization. 2013. Transforming and scaling up health professionals' education and training *(56)*.

Education of patients and the public

- World Health Organization. 2023. Therapeutic patient education: an introductory guide *(97)*.
- World Health Organization, UNESCO. 2021. WHO guideline on school health services *(98)*.

10.4 Research gaps

Most of the evidence on access and safety outcomes of education and training of health-care professional was from high-access contexts (predominantly Canada and the USA). There is no evidence that the effects of education or training programmes would be substantially different in low-access contexts. Some qualitative evidence from low-access settings suggests, however, that providers in these contexts may face similar (and in many cases more intense) moral and cultural concern about increasing access to controlled medicines. Health system and regulatory barriers are also likely to be greater. Research is therefore required on the impact of education and training of health-care professionals in countries with low access to controlled medicines.

The overall certainty of the evidence in this chapter was judged to be low or very low. Most of the studies included in the rapid review were observational, and most were of a pre–post designs, often with no control group. Follow-up times were often too short to judge whether changes in outcomes were sustained. Additional high-certainty evidence is required.

Most of the evidence from the rapid systematic review addressed controlled medicines used for pain management and substance use disorders. Some of the qualitative evidence suggested that providers working in pre- and post-operative care, mental health and/or seizure disorders are confronted with moral and cultural concerns about access to controlled medicines and also health system barriers. Such concerns and barriers may differ by cultural context. Further research is required into the effects of policies and educational interventions in various therapeutic and cultural contexts.

Other research gaps are on:

- the long-term outcomes of education and training and the effect of booster training (as most of the studies were of short-term interventions);
- potential harms of provider education;
- public education material that is effective in changing attitudes, knowledge and behaviour with respect to controlled medicines;
- the influence of social media on safe use of controlled medicines and optimization of public education on controlled medicines on social media platforms; and
- understanding how public education campaigns are effectively translated into actionable knowledge and behaviour change and to identify the most impactful platforms for reaching target audiences.

Chapter 11

Monitoring, evaluation and research

Published scientific literature was lacking for several policy areas addressed in this guideline. This gap may have several explanations, including the inherent difficulty in designing studies to test national policies, especially when those policies are shaped by international law, which limits experimental opportunities. Additionally, it is difficult to assess and quantify the extent of unmet clinical need for conditions treated with controlled medicines. As non-medical use of controlled medicines is often illegal, it is difficult to track and compare the desired result of policies designed to decrease both unmet need and non-medical use.

Research on some outcomes of policies intended to increase access to controlled medicines did not include assessment or reporting of the impact of such policies on safety. Furthermore, most studies of policy interventions to reduce the harm of controlled medicines did not address their impact on access.

Studies in LMIC were under-represented in the academic literature. This may be due partly to structural biases associated with language and research funding, but also coincides with more limited access to controlled medicines in those regions. In the past, problems of overuse and oversupply of controlled medicines were largely limited to high-income countries, which cannot be generalized to countries with low access.

Recognizing these research gaps, the GDG members used their knowledge and experience in interpreting evidence to formulate recommendations and good practice statements.

Significant gaps were found in research in all four intervention areas included in this guideline.

Procurement and supply chain management:

- Certainty and context
  - There is little direct evidence on procurement and supply chain management.
  - Most of the available research addressed opioids.

- Areas for future research
  - Further research should be conducted on the impact of quantification, procurement, supply chain and local production on use of controlled medicines for other indications.
  - Research should be conducted on waste management of controlled medicines, donations, strategies to address substandard and falsified medicines and approaches to local production.
  - Little evidence is available on potential strategies to increase access by establishment of regional hubs for production of controlled medicines according to pooled need.

Medicines regulation and control:

- Certainty and context
  - There is considerable evidence on the safety outcomes of up-scheduling controlled medicines.

  - Limited information is available about the impacts of up-scheduling on access to controlled medicines.
  - Most studies on the safety of opioids were conducted in high-access settings.

- Areas for future research are on:
  - the impacts of up-scheduling and down-scheduling on access to controlled medicines and the potential safety outcomes; and
  - the feasibility and acceptability of use of electronic authorization for controlled medicines internationally and the clinical and societal outcomes.

Prescribing, dispensing and administration:

- Certainty and context
  - The evidence is predominantly of low certainty and is from countries with high access and in specific treatment settings.
  - Most of the studies were of the use of opioids and benzodiazepines, primarily for pain management and mental ill health.

- Areas for future research
  - international incentives for use of the guideline and their effectiveness in changing behaviour with respect to controlled medicines;
  - impact of policy initiatives on access to and the benefits and harms of controlled medicines;
  - financial and in-kind donations from the pharmaceutical industry to government officials; and
  - the proportion of industry funds used for marketing.

Education, knowledge and attitudes:

- Certainty and context
  - The overall evidence is of low quality.
  - Many of the studies are observational, with short follow-up times; higher-quality research with longer follow-ups should be conducted.
  - Most of the evidence is on pain management and substance use disorders.
  - Most of the evidence is from studies in countries with good access (Canada, USA).

- Areas for future research
  - the effects of policies and educational interventions in various therapeutic and cultural contexts, including moral and cultural concerns and health system barriers, which differ by context;
  - the impact of education and training in low-access countries;
  - long-term outcomes of education and training and booster interventions;
  - potential harm of provider education;
  - effective public education materials and their impact on attitudes and behaviour;
  - influence of social media on safe use of controlled medicines; and
  - the effectiveness of public education campaigns and identification of the platforms with the greatest impact.

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