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ABBREVIATIONS AND ACRONYMS

ACT	acceptance and commitment therapy
CBT	cognitive behavioural therapy
CERQual	Confidence in the Evidence from Reviews of Qualitative research
ERG	External Review Group
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
GRC	WHO Guidelines Review Committee
LMIC	low- and middle-income country
NSAIDS	non-steroidal anti-inflammatory drugs
QALY	quality-adjusted life-year
PT	physical therapy or physiotherapy
RCT	randomized controlled trial
WHO	World Health Organization

GLOSSARY

Adjuvant: Medicines other than paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids that may help to relieve pain alone or in combination with paracetamol, NSAIDs or opioids. Typically, these adjuvant medicines are used for pain refractory to paracetamol, NSAIDs or opioids or when opioid therapy is contraindicated.

Adolescents: Young people between the ages of 10 and 19 years.

Biopsychosocial model of pain: The biopsychosocial model of pain recognizes pain as a complex multidimensional experience that is the result of the interaction of biological, psychological and social factors. This model provides a basis for the understanding and treatment of pain, taking into account the patient, their social context and the impact of illness on that individual from a societal perspective. Pain management thus requires a multimodal, interdisciplinary and integrated approach (adapted[1-3]).

Children: Persons aged 0 to 19 years of age.

End-of-life care: This is a type of palliative care for people in the final weeks or months of life. End-of-life care enables people to live as well as possible before death and to die with dignity. It includes social, psychological and spiritual support for the patient, family and caregivers.

Evidence-to-decision frameworks: These are tabular displays of relevant considerations which decision-makers use to make a decision or to formulate a recommendation.

GRADE: The 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.

GRADE evidence tables or profiles: These are tabular displays of summary measures of effect and GRADE certainty (quality) assessments of the body of evidence for a specific question (usually defined in population, intervention, comparator and outcome (PICO) format).

Life-limiting conditions: These are illnesses for which there is no cure and an early death is expected, but with which a person may continue to live for several more years.

Opioid: Substances produced in the body (endogenous opioids), derived from the opium poppy (semisynthetic opioids) or chemically synthesized (synthetic opioids) that act on opioid receptors in the central or peripheral nervous system and have the capacity to relieve pain or, in high doses, produce euphoria and respiratory depression.

Opioid stewardship: Opioid stewardship refers to a series of strategies and interventions involving the appropriate procurement, storage, prescribing and use of opioids, as well as the 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: meeting the needs of individuals who require pain control, while minimizing harms to the individual and to

other persons and populations. These harms include those that may arise from opioid overuse, misuse and diversion.

The essential practices of opioid stewardship in children are fourfold:

i. Opioids must only be used for appropriate indications and prescribed by trained providers, with careful assessments of the benefits and risks.

ii. The use of opioids by individuals, their impact on pain and their adverse effects must be continuously monitored and evaluated by trained providers.

iii. The prescribing provider must have a clear plan for the continuation, tapering or discontinuation of opioids according to the child's condition. The child and family must be apprised of the plan and its rationale.

iv. There must be due attention to procurement, storage and the disposal of unused opioids.

Palliative care: This is an approach to care for persons, families and caregivers who are facing a life-limiting illness or where a person is near the end of life. The goal of palliative care is to improve the quality of life of patients and their families. This approach focuses on the prevention and relief of suffering by means of early identification, assessment and treatment of pain as well as addressing the physical, psychosocial and spiritual needs of the individual and their family and caregivers.

Pain: An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage.[4]

Acute pain: Pain with a duration of less than 3 months.[4]

Chronic pain: Pain that persists or recurs for longer than 3 months. Chronic pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome. The 11th revision of the International Classification of Diseases (ICD-11) categorizes chronic pain as follows: 1) chronic primary pain; 2) chronic cancer-related pain; 3) chronic postsurgical or post-traumatic pain; 4) chronic secondary musculoskeletal pain; 5) chronic secondary visceral pain; 6) chronic neuropathic pain; 7) chronic secondary headache or orofacial pain; or 8) chronic pain, unspecified.[4]

Chronic primary pain: Chronic pain in one or more anatomical regions that is characterized by significant emotional distress (anxiety, anger/frustration or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles). Chronic primary pain is multifactorial: biological, psychological and social factors contribute to the pain syndrome. The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.[4]

EXECUTIVE SUMMARY

Chronic pain in children is a significant public health problem globally and a leading cause of morbidity in children, with a negative impact on their emotional, physical and social development and function. The lives of families and caregivers are also significantly impacted. Chronic pain, defined as pain that persists or recurs for longer than three months, can be primary (independent of any identified biological or psychological contributing factor) or secondary to a clear, underlying etiology. Pain in children differs from that in adults for a number of physiological, developmental and social reasons, and thus data and research on, and clinical experiences with, adults may not be directly applicable to children.

The management of chronic pain in children is complex and challenging, and there is a paucity of high-quality research studies on treatment interventions and management approaches. Pain management requires an approach that is tailored to each individual and context, and is multimodal and interdisciplinary, requiring trained healthcare providers and a coordinated, comprehensive, integrated response.

In these guidelines, the World Health Organization (WHO) provides evidence-informed recommendations for the management of chronic pain in children. The recommendations are based on the most current, high-quality scientific evidence, and were formulated following processes and using methods that meet the highest international standards for guideline development. The recommendations in this guideline are based on systematic reviews of the evidence on benefits, harms, acceptability and feasibility, as well as on equity and resource considerations. The recommendations were formulated by the Guideline Development Group, consisting of individuals with diverse expertise and experiences and with global representation.

The purpose of this guideline is to assist WHO Member States and their partners in developing and implementing national and local policies, regulations, pain management protocols and best practices. It will help countries balance concerns about ensuring access to appropriate therapies for pain relief with the harms arising from misuse of medications and other potential adverse effects of interventions for pain management.

These guidelines focus on physical, psychological and pharmacological interventions for the management of primary and secondary chronic pain in children 0 to 19 years of age.

GUIDING PRINCIPLES

The Guideline Development Group agreed that several key principles underpin the recommendations and best practice statements in these guidelines, and more importantly, guide all aspects of the care of children with chronic pain.

1. Access to pain management is a fundamental human right.
2. Children have the right to enjoyment of the highest attainable standard of health.
3. Member States and healthcare providers should ensure that children, and their families and caregivers, know their rights to self-determination, non-discrimination, accessible and appropriate health services, and confidentiality.

RECOMMENDATIONS

1. In children with chronic pain, physical therapies may be used, either alone or in combination with other treatments (*conditional recommendation, very low certainty evidence*).

2. a) In children with chronic pain, psychological management through cognitive behavioural therapy and related interventions (acceptance and commitment therapy, behavioural therapy and relaxation therapy) may be used (*conditional recommendation, moderate certainty evidence*).

   b) Psychological therapy may be delivered either face-to-face or remotely, or using a combined approach (*conditional recommendation, moderate certainty evidence*).

3. In children with chronic pain, appropriate pharmacological management tailored to specific indications and conditions may be used (*conditional recommendation, low certainty evidence*).

4. a) Appropriate pharmacological management tailored to specific indications may include the use of morphine under the principles of opioid stewardship, for end-of-life-care (*conditional recommendation, very low certainty evidence*).

   b) In children with chronic pain associated with life-limiting conditions, morphine may be given by appropriately trained healthcare providers, under the principles of opioid stewardship (*conditional recommendation, very low certainty evidence*).

BEST PRACTICES FOR THE CLINICAL MANAGEMENT OF CHRONIC PAIN IN CHILDREN

The Guideline Development Group also formulated several statements which represent best practice for the clinical management of chronic pain in children. These statements apply to all aspects of the clinical care of a child with chronic pain, including the planning, implementation and delivery of physical, psychological and pharmacological interventions.

1. Children with chronic pain and their families and caregivers must be cared for from a biopsychosocial perspective; pain should not be treated simply as a biomedical problem.

2. A comprehensive biopsychosocial assessment is essential to inform pain management and planning. As a component of this assessment, healthcare providers should use age-, context- and culturally appropriate tools to screen for, and monitor, pain intensity and its impact on the quality of life of the child and family.

3. Children with chronic pain must have a thorough evaluation of any underlying conditions and access to appropriate treatment for those conditions, in addition to appropriate interventions for the management of pain. Chronic pain in childhood often exists with comorbid conditions affecting the child's health, and social and emotional well-being, which require concurrent management.

4. Children presenting with chronic pain should be assessed by healthcare providers who are skilled and experienced in the evaluation, diagnosis and management of chronic pain.

5. Management, whether with physical therapies, psychological or pharmacological interventions, or combinations thereof, should be tailored to the child's health; underlying condition; developmental age; physical, language and cognitive abilities; and social and emotional needs.

6. Care of children with chronic pain should be child- and family-centred. That is, the child's care should:

    i. focus on, and be organized around, the health needs, preferences and expectations of the child, and their families and communities;

    ii. be tailored to the family's values, culture, preferences and resources; and

    iii. promote engagement and support children and their families to play an active role in care through informed and shared decision-making.

7. Families and caregivers must receive timely and accurate information. Shared decision-making and clear communication are essential to good clinical care. Communication with patients should correspond to their cognitive, development and language abilities. There must be adequate time in a comfortable space for discussions and questions regarding care management plans and progress.

8. The child and their family and caregivers should be treated in a comprehensive and integrated manner: all aspects of the child's development and well-being must be attended to, including their cognitive, emotional and physical health. Moreover, the child's educational, cultural and social needs and goals must be addressed as part of the care management plan.

9. In children with chronic pain, an interdisciplinary, multimodal approach should be adopted which is tailored to the needs and desires of the child, family and caregivers, and to available resources. The biopsychosocial model of pain supports the use of multiple modalities to address the management of chronic pain.

10. Policy-makers, programme managers and healthcare providers, as well as families and caregivers must attend to opioid stewardship to ensure the rational and cautious use of opioids. The essential practices of opioid stewardship in children include:

    i. Opioids must only be used for appropriate indications and prescribed by trained providers, with careful assessments of the benefits and risks. The use of opioids by individuals, their impact on pain and their adverse effects must be continuously monitored and evaluated by trained providers.

    ii. The prescribing provider must have a clear plan for the continuation, tapering or discontinuation of opioids according to the child's condition. The child and family must be apprised of the plan and its rationale.

    iii. There must be due attention to procurement, storage and the disposal of unused opioids.

1. INTRODUCTION

Chronic pain in children is a significant public health problem globally and a leading cause of morbidity in children.[5-7] Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage or described in terms of such damage.[4] Chronic pain is pain that persists or recurs for longer than three months. The 11th revision of the International Classification of Diseases (ICD-11) categorizes chronic pain as follows:[4]

- Chronic primary pain
- Chronic secondary pain
  - Chronic cancer-related pain
  - Chronic postsurgical or post traumatic pain
  - Chronic secondary musculoskeletal pain
  - Chronic secondary visceral pain
  - Chronic neuropathic pain
  - Chronic secondary headache or orofacial pain
  - Chronic pain, unspecified

Chronic primary pain is characterized by significant emotional or functional disability and is diagnosed independently of identified biological or psychological contributors. On the other hand, non-primary or secondary pain has a clear underlying etiology such as a disease, injury or lesion, or their treatment[4] (e.g. surgery, chemotherapy, radiotherapy). Pain is a common symptom of many long-term conditions, such as cancer, sickle-cell disease, diabetes and arthritic conditions.

It is difficult to determine the prevalence and burden of chronic pain in children, and estimates vary widely due to differences in study populations including age, sample size, the definition of pain used, and how pain is measured.6 In addition, data from low- and middle-income countries are scant.[8] Available studies suggest that chronic pain is experienced by about one-quarter to one-third of children,[5,9-11] with about 1 in 20 experiencing moderate to high levels of pain-related disability.10 Among adolescents, a systematic review reported significant variation in pain prevalence across studies, ranging from 8% to 83% for headache, 14% to 24% for back pain, 4% to 53% for abdominal pain; 4% to 40% for musculoskeletal pain and 4% to 49% for multi-site pain.[5] In a study set in a high-income country, 6% of children have chronic pain, with a higher prevalence among older children, children from low-income families, children using public insurance and children whose parents did not complete higher education.[12] Some studies indicate even higher rates, particularly among adolescents. Data from the WHO collaborative cross-national Health Behaviour in School-aged Children (HBSC) study based on nationally representative samples of adolescents, revealed that 44% of adolescents reported chronic weekly pain during the last six months.[6] Predictors of pain in adolescents included age and sex, with different demographic patterns and types of pain and locations across countries.[6]

Chronic pain negatively impacts the emotional, psychological, physical and social development and functioning of children and adolescents.[13] Typically, children with moderate and severe pain report high levels of physical disability;[14,15] emotional distress, anxiety and depression;[15,16] sleep problems[13] and poor academic performance[2,17,18] compared to peers without chronic pain. Socially, such children do not attend school as often and report higher levels of feelings of isolation.[18-20] Pain and the associated psychological distress and social consequences thus severely affect the quality of life of these children.[2,8]

Exposure to chronic pain in early life may have implications for the incidence, severity and duration of chronic pain, and may be associated with long-term, maladaptive neurological changes. Neuroimaging studies of children with acute pain and adults with chronic pain suggest that there are long-term changes in the structure, function and chemistry of the nervous system that correlate with subsequent cognitive, behavioural and somatosensory outcomes.[21] Chronic pain in childhood is associated with progression of pain into adulthood[2,22,23] and potentially predisposes these children to other chronic health problems in later life.[21] The negative impacts of chronic pain also extend to family members who report a higher burden of care[2,24] and a detrimental effect on family function.[25] As such, chronic pain during childhood has a very significant negative impact on the child over their life course as well as their wider family unit, making appropriate diagnosis and management essential.

The economic effects of chronic pain and its management in children are also significant. Much of the data on costs incurred by the treatment of chronic pain come from adult populations: this condition is one of the most costly medical conditions in Western society.[2,26] Data on children are extremely limited,[27,28] although available data suggest that the costs in children are substantial also. Estimates for the economic burden of chronic pain in adolescents in the United Kingdom extended to US$ 9.5 billion and in the United States to US$ 19.5 billion annually (2012 US dollars)[26-28]. Children with chronic pain have high rates of health care utilization[2,28,29] In addition, parents suffer significant financial consequences.[26,27]

Pain in children differs from that in adults for physiological, cognitive, developmental and social reasons,[18,21] The child's developmental processes lead to important and continuously changing differences in their perceptions, ability to express feelings and pain, as well as cognition and educational level.[21] These differences in the pain experience as the child ages also relate to their environmental, cultural and social context, including for example their relationship to parents, caregivers and healthcare providers.[21,25]

The management of chronic pain in children is complex and challenging for a number of reasons. First, despite important differences between adults and children, there is a paucity of high-quality research studies on the treatment of chronic pain in children and adolescents.[21] As a result, data from adults are inappropriately extrapolated to children. While there are some data on psychological therapy for pain in children and adolescents in high-income countries[30] there is much less on physical[31] and pharmacological therapies.[32] Second, given the multiplicity of pain etiologies, and individual responses across patients and their families and caregivers, pain management requires an approach that is tailored to each child and their context. Third, a multimodal, interdisciplinary approach is required, which entails trained healthcare providers and a coordinated response. Fourth, chronic pain in children and adolescents impacts all aspects of the child's and family's life, and interventions must therefore address this

broad context. Fifth, the diagnosis and optimal management of chronic pain in children may be adversely impacted by societal misperceptions and misinformation related to treatment modalities and their relative risks and benefits.

Finally, problems of inappropriate polypharmacy[33] and drug marketing, the misuse of analgesic medicines and drug addiction, particularly related to opioids, have led to significant challenges. Studies have shown an increasing prevalence of prescription opioid use and misuse among American adolescents and young adults,[34,35] which is associated with additional substance abuse.[36,37]

The United Nations Office of Drugs and Crime World Drug Report 2019[38] highlights the "global paradox of too much and not enough" and describes the difficulty of ensuring appropriate access to controlled substances for medical and scientific purposes while preventing their diversion and misuse. Every year almost 2.5 million children die with serious health-related suffering associated with the need for palliative care and pain relief, and more than 98% of these children are from developing regions.[39] It is estimated that 5.5 billion people, or over 75 percent of the global population, have low to nonexistent access to opioid analgesics.[40] Canada, Europe and the US contain approximately 17% of the world's population, yet consume about 89% of the world's supply of morphine (2013 data).[41]

There are a number of barriers to providing access to adequate pain management strategies including for vulnerable populations such as children, according to the Lancet Commission report of 2017 on palliative care and pain relief.[39] These barriers include the medical community and policy-makers' focus on extending life and productivity, opiophobia (prejudice and misinformation about the appropriate medical use of opioids), limited attention globally to non-communicable diseases, poor knowledge on the part of health professionals, and concerns about the nonmedical use of controlled substances. Very restrictive drug control regulations can interfere with appropriate therapeutic use of these medicines.[39,42,43] International drug control conventions aim to remove barriers that limit the availability of and access to controlled drugs for medical use. These conventions are based on legal and regulatory frameworks, as well as on clinical guidelines addressing rational prescription practices.

The management of pain requires a broad, multimodal and interdisciplinary approach that addresses its physical, psychosocial and social dimensions. Children, including adolescents, have the right to appropriate treatments (physical, psychological and pharmacological) for pain management, and policy-makers and providers need to ensure appropriate access to these management strategies, while minimizing the potential harms of inappropriate use in society. Human rights norms require that pain management be incorporated as part of the basic health package under universal health coverage schemes.[44]

1.1 PURPOSE

In these *Guidelines* the World Health Organization (WHO) provides evidence-informed recommendations for the management of chronic pain in children. These recommendations are based on the most current, high-quality scientific evidence, and were formulated following processes and using methods meeting the highest international standards for guideline development.[45]

The purpose of these guidelines is to assist WHO Member States and their partners in developing and implementing evidence-informed national and local policies, regulations, pain management protocols and best practices. It will help countries balance concerns about ensuring access to appropriate therapies for pain relief with the harms arising from misuse of medications and other potential adverse effects of interventions for pain management. These guidelines also can help to empower families and caregivers to advocate for services and research, and indicate key research gaps which can help to focus future studies.

1.2 SCOPE AND TARGET AUDIENCE

These guidelines address the management of primary and secondary chronic pain in children 0 to 19 years of age, with a focus on physical, psychological and pharmacological interventions for pain relief. Relevant considerations were examined in population sub-groups where possible.

Not all potential therapies for chronic pain in children and adolescents are included in this edition of these guidelines. For example, interventional procedures for pain were not included as these interventions are less commonly delivered to children. In addition, while there may be possible roles for traditional and complementary medicine and practices in chronic pain management, these interventions were not included in the scope of these guidelines. The evidence base regarding their effectiveness and safety, as well as the quality assurance of interventions are being strengthened.[46]

These guidelines are intended for use by a wide range of audiences, including national and local policy-makers and their expert advisers, as well as technical and programme staff at organizations involved in the assessment, management, monitoring and education of children with chronic pain and their families. These guidelines may also be used by healthcare providers and their professional societies, and by researchers who are interested in addressing gaps in the evidence. Importantly, families and caregivers of patients with chronic pain can use these guidelines as a tool to better understand the management of this condition and the scientific evidence underlying the various interventions.

The audience for Guidelines for the management of chronic pain in children is a global one: it is intended for a wide range of settings with varied perspectives and resources. These guidelines are relevant to all Member States, including low-, middle- and high-income countries.

2. METHODS

Guidelines on chronic pain in children was developed according to WHO's guidance for guidelines as set out in the *WHO handbook for guideline development* (2nd edition, 2014)[45] and meets international standards for evidence-informed guidelines. The main steps for the development of WHO guidelines include: 1) identification of contributors to the guideline process; 2) establishment of the general scope of the guideline and development of the key questions; 3) performance of systematic reviews of the evidence to address the key questions; 4) assessment of the certainty (quality) of the body of evidence for important and critical outcomes; 5) formulation of recommendations; 6) drafting of the guideline document for review and approval by the Guideline Development Group (GDG) and for peer review; 7) review and approval by WHO's quality assurance body; and 8) publication and dissemination. A brief overview of the processes and methods used is found below; more detailed information is found in web Annex A.

A broad range of contributors participated in the development of these guidelines, including individuals with diverse experiences, expertise and perspectives. Each type of contributor had a well-defined role and was subject to specific WHO policies and procedures: this approach helps to ensure the effectiveness of all contributors and transparency of the process.

The WHO Steering Group comprised members from relevant technical units at WHO headquarters, and regional offices were invited to join. This group provided technical guidance and support throughout the development process, as well as project management and administrative support. The GDG was responsible for finalizing the scope and key questions and for developing the recommendations. Members of the GDG came from all WHO regions and from a wide variety of settings. They had a broad range of expertise, perspectives and experiences related to the management of chronic pain in children, including human rights law, bioethics, social policy, care in humanitarian settings and lived experience with chronic pain. The guideline methodologist supported the WHO Steering Group and the GDG throughout the development process. Systematic review teams, selected through an open competition, were contracted to provide reviews of the evidence. The External Review Group (ERG) attended the recommendation-formulation meeting and provided input into the final content and presentation of the guideline. This group was composed of individuals with diverse expertise in the topic and/or in implementation of policies or programmes related to pain management in children.

WHO requires that all internal and external contributors to the Organization's guidelines are thoroughly assessed for conflicts of interest before they participate in the development process. All available information on potential contributors was reviewed by the WHO responsible technical officers and a WHO ethics officer. Only after it was determined that no significant conflicts of interest existed, were individuals formally invited to join the GDG or the ERG. External contracts were issued only to individuals and groups with no conflicts of interest.

In response to Member States' needs and with stakeholder consultation, the GDG determined the scope of the guidelines, key questions for the systematic reviews and prioritized potentially relevant outcomes. WHO then commissioned a systematic review of the quantitative evidence on the benefits and harms of physical, psychological and pharmacological interventions for chronic pain in children. A second review examined qualitative evidence on patient, family, caregiver and healthcare provider experiences with, and perceptions of, the benefits, harms and sociocultural acceptability of those interventions. Data on barriers and facilitators for implementation of these interventions were also examined.

While the scope of these guidelines includes children of all ages, children's cognitive, social and functional abilities continuously evolve as they grow and develop. Thus, the benefits and harms of interventions and other relevant considerations were examined in population sub-groups wherever possible. In addition, data suggest that substance abuse disorders including opioid addiction are most prevalent in adolescents aged 15 to [19,35,47] further supporting the need for stratified data and tailored recommendations to the extent possible

The commissioned systematic reviews adhered to Cochrane methods and standards.[48] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system[49] was used to assess the certainty (quality) of the body of quantitative evidence for each critical and important outcome. GRADE-CERQual (Confidence in the Evidence from Reviews of Qualitative research)[50] was used to assess confidence in the findings of qualitative evidence. The specific approaches and methods used are summarized in web Annex B and described in detail in each review.[51,52]

A systematic review of data on costs, cost-effectiveness and other economic measures was also performed in order to further inform the recommendations in these guidelines. Web Annex I provides a summary of the methods used; details are available in the full review.[53]

The GDG formulated recommendations at a series of virtual meetings which were held on 15-19 September 2020. Facilitated by the guideline methodologist, the GDG used a structured evidence-to-decision framework[54] to ensure a transparent process and comprehensive discussions of relevant considerations. Recommendations were based on evidence of benefits, harms, the relative value placed on the outcomes of the intervention, acceptability, feasibility, resource considerations and the effect of the interventions on equity across population groups.

Each recommendation could be for or against a specific intervention, and either strong or conditional. Strong recommendations mean that most patients, caregivers or providers would select the intervention, or the recommendation would be adopted as policy in most situations. On the other hand, conditional recommendations mean that most individuals would want the suggested course of action, but many might not and shared decision-making may be needed. At a policy level, there may be a need for substantial debate among stakeholders prior to uptake into policy.[45]

The GDG discussed and agreed upon the recommendations by consensus, meaning that all members agreed to the final wording. When consensus could not be reached, anonymized voting occurred via email, organized and tabulated by WHO staff. A decision threshold of 80% was predetermined for approval of any recommendation requiring a vote.

In addition to recommendations on interventions for the management of chronic pain in children, these guidelines present a set of guiding principles. These principles, composed and approved by the GDG, underpin all aspects of the management of chronic pain in children. They are principles based on human rights and ethics and, as such, their formulation does not require a systematic review of research evidence on benefits and harms.

Another type of statement contained in these guidelines is referred to as best practice statements. These statements provide general and overarching guidance for the clinical care of children with chronic pain. Like guiding principles, they do not require a systematic review of the benefits and harms of an intervention; rather, they are based on good clinical practice, healthcare provider experience and the principles of good clinical care (for example, shared and informed decision-making). Best practice statements are generally uncontested because not carrying out the best practice would be illogical.

These guidelines also contain a list of research gaps related to the management of chronic pain in children. This list was generated from the systematic reviews and discussions of the GDG.

Following the formulation of recommendations by the GDG, the writer drafted the guidelines for review and approval by the GDG, and for peer review by the ERG. Once finalized in the light of the comments received, these guidelines underwent a review process by the Guidelines Review Committee (GRC), WHO's quality assurance body for guidelines. Finally, the guidelines were prepared for publication and dissemination.

3. SUMMARY OF THE EVIDENCE

WHO commissioned three systematic reviews to provide the evidence upon which the GDG would base its decisions and recommendations. One review focused on quantitative data on the effectiveness (benefits and harms) of physical, psychological and pharmacological interventions for chronic pain in children. The second review focused on qualitative and mixed methods evidence examining the acceptability and feasibility of interventions for the management of chronic pain in children from the perspective of patients, family members, caregivers and healthcare providers. The third review examined economic evaluations and the cost of interventions.

The findings of these reviews are briefly outlined below, including the outcomes which the GDG agreed were critical and important. Two time-periods were examined for the quantitative review: post-treatment and follow-up. Post-treatment outcomes were measured immediately after the study intervention was completed. Outcomes at follow-up were measured at the most distal interval after the end of the intervention period, up to 12 months from the end of treatment. More details are provided in the web annexes to these guidelines and in the full publication of the reviews.[51-53]

3.1 BENEFITS AND HARMS

3.1.1 PHYSICAL INTERVENTIONS

The systematic review of quantitative outcomes[51] included 25 studies with relevant results: 24 published studies and one in a trial registry. This was the smallest of the three bodies of evidence, with a total of 1470 study participants. Twenty-four of the studies were randomized controlled trials (RCTs) and one was a non-randomized comparative study. The interventions examined in these studies covered a broad range of physical therapies (PT): exercise, aerobics, yoga, stretching, strengthening and hydrotherapy. Twelve of the 25 studies were RCTs comparing one type of PT to another and 11 RCTs compared PT to standard care, an active (non-PT) intervention or to a wait-listed control. In addition, one RCT compared two PT interventions with two control arms. Finally, one non-randomized study compared two PT interventions. There were no low-income countries represented in these studies. A summary of study characteristics is found in web Annex C.

When compared to standard care or an active (non-PT) control (n=12 RCTs), PT had beneficial effects on pain intensity and functional disability immediately post-treatment (both very low certainty evidence), although no benefits were noted at longer-term follow-up for these outcomes (very low certainty). No difference was found between treatment and control groups for health-related quality of life, role-functioning or emotional functioning (depression or anxiety), either post-treatment or at follow-up (all very low certainty). Activity participation and patient global impression of change improved post-treatment in the treatment group (very low certainty). No studies reported data on 30% or 50% pain reduction, sleep, global satisfaction with treatment or fatigue.

Only four of these 12 RCTs reported data on treatment-related adverse events (total of 161 study participants). Two studies reported no adverse events; one study reported events unrelated to the intervention; and one study reported one adverse event in the treatment group and none in the control group. In one study children reported muscle soreness associated with learning new exercises, which generally resolved within several days.

These studies of PT interventions included few participants and had serious limitations (risk of bias) in study design and execution. The body of evidence for all outcomes was therefore assessed as very low certainty, both immediately post-intervention and at longer-term follow-up (web Annex D; detailed forest plots and certainty of evidence assessments are found in the systematic review[51]).

3.1.2 PSYCHOLOGICAL INTERVENTIONS

The systematic review included a large body of evidence on psychological interventions for chronic pain in children with 63 published RCTs comprising 5025 participants (see web Annex C). Of the 63 trials, 13 included multiple arms. The intervention arms included cognitive behavioural therapy (CBT) (43 arms), relaxation training (15 arms), behavioural therapy (7 arms), as well as arms for hypnosis, problem-solving therapy and acceptance commitment therapy (ACT). The comparison arms included active controls (36 arms), standard or usual care (16 arms) and 17 wait-listed control arms. All of the studies except two were situated in high-income countries, including 34 in the US or Canada and 25 in Western Europe. The types of chronic pain included migraine or tension-type headache (23 studies), primary visceral pain (12 studies), mixed pain conditions (15 studies), among others. A summary of the outcomes reported in the included studies is found in web Annex E; additional details are found in the systematic review.[51]

When psychological therapies were examined as a group, they provided small benefits compared to any control for the outcomes of reducing pain intensity (low certainty evidence), 50% pain reduction (low certainty) and functional disability (low certainty) post-treatment. At follow-up, a small benefit was demonstrated for the outcomes of 50% pain reduction (very low certainty) and functional disability (moderate certainty). Global judgement of satisfaction post-treatment (moderate certainty) and at follow-up (very low certainty), and patient global impression of change were also improved post-treatment and at follow-up (very low certainty).

No beneficial effects were demonstrated for the outcomes of 30% pain reduction, health-related quality of life, emotional functioning (both depression and anxiety), role functioning and sleep quality post-treatment and at follow-up (range, high to very low certainty).

CBT, behavioural therapy, ACT and relaxation training are distinct approaches, although they are closely related and may have similar goals: increased functioning and improved ability to effectively manage pain and distress such that they do not interfere with daily life. A pooled analysis of these four interventions was thus performed with findings similar to the analyses of all psychological therapy combined (see web Annex E).

For the subset of studies which examined CBT, ACT, behavioural or relaxation therapies versus any control, studies where the intervention was delivered in a face-to-face format

were compared to those delivered via a remote format (using the internet, smartphone, CD-ROM or manuals). In these studies, face-to-face therapies reduced pain intensity post-treatment, pain by 50% or more post-treatment and at follow-up, disability post-treatment and at follow-up, activity participation post-treatment, and satisfaction at follow-up. Remote therapies reduced pain intensity post-treatment and had beneficial effects on 50% pain reduction, satisfaction, and impression of change post-treatment and at follow-up. No benefits were reported for other outcomes. (See web Annex E; full data are provided in the systematic review.[51])

Few studies reported adverse events of any kind. From the data that were reported, participants in the psychological therapy groups did not report adverse events; however, poor reporting of adverse events has been noted previously in psychological trials.[55]

3.1.3 PHARMACOLOGICAL INTERVENTIONS

The systematic review of quantitative data on benefits and harms included 29 RCTs and five comparative, non-randomized studies that delivered a pharmacological intervention to 4091 children with chronic pain. The identified studies examined paracetamol (acetaminophen), anticonvulsants, antidepressants, leukotriene receptor antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), progestin and a triptan. No eligible studies were identified which examined ketamine, opioids or other types of analgesics. Fifteen of the 34 studies included a comparator which was either a placebo or an intervention not involving a pharmaceutical agent (behavioural intervention, acupressure or fennel extract). Eighteen studies compared one pharmaceutical agent to another; one additional study included both an active drug and a placebo arm. Most studies were from high-income countries, with only one study from a lower middle-income country (Pakistan) and no studies from low-income countries. A summary of study characteristics is found in web Annex C and more detailed information in the systematic review.[51]

Overall, there were very few studies for each drug class (see web Annex F for a summary of the results and the systematic review for full details[51]).

One study compared the effects of an anticonvulsant (pregabalin) to placebo, and reported a beneficial effect on pain intensity and patient global impression of change, both post-treatment (both very low certainty evidence), but no significant effects on 30% or 50% pain reduction, or sleep post-treatment (all very low certainty evidence).

A total of six studies compared antidepressants to placebo. There was no significant difference in the pooled outcome of pain intensity post-treatment (three studies, low certainty evidence) or at follow-up (two studies, very low certainty). A single study reported benefits for 30% and 50% pain reduction post-intervention (both very low certainty). Another small study reported improvements in health-related quality of life post-treatment and at follow-up with antidepressants (very low certainty). Studies reported no effects on functional disability post-treatment (very low certainty), anxiety and depression (both low certainty post-treatment and very low certainty at follow-up), activity participation post-treatment (very low certainty) and patient satisfaction post-treatment (low certainty) and at follow-up (very low certainty) compared to placebo.

A single study compared NSAIDs to acupressure and found no difference in pain intensity post-treatment (very low certainty evidence).

Few adverse events were reported in the RCTs included in this review. Of the available data, more events were related to treatment groups than controls, although the differences were not statistically significant except for a comparison of an antidepressant (duloxetine) to placebo where there were significantly more treatment-related adverse effects in the treatment group (very low certainty evidence). Note, however, that the included RCTs were generally small and may not have had sufficient power to detect statistically significant differences in the incidence of less common adverse events.

3.2 ACCEPTABILITY AND FEASIBILITY

Seventy-four studies met the inclusion criteria, of which 33 were selected for detailed assessment as they were set in low- or middle-income countries. (See web Annex G for a summary of the study characteristics and the systematic review for more details.[52]) Of these studies, 18 focused on specific interventions included in the scope of these guidelines, including 12 which were linked to trials included in the effectiveness systematic review. All 18 studies were set in high-income countries and encompassed physical therapy (n=5), psychological interventions (n=9) and mixed interventions (n=4). No studies examined pharmacological therapies. Few studies focused on children less than eight years of age. In view of the lack of qualitative evidence on included interventions in low- or middle-income settings, 15 additional studies in these settings were identified from the cohort of 74. These studies did not examine a specific intervention for pain, but rather provided data more generally on attitudes and barriers to pain management in children. Overall, the majority of the 33 studies had significant methodological limitations. The main findings of this review are presented in web Annex H; detailed findings are found in the systematic review.[52]

This analysis identified a range of perceived benefits and harms of physical and psychological therapies. For physical therapies, benefits included increased physical activity, lower perceived pain intensity and increased energy. Harms included increased pain during and after exercise, increased family distress, conflict and child non-adherence, child exhaustion, and time spent in therapy which impinged on parental time with other children and paid work. For psychological therapies, perceived benefits included improved sleep, mood, quality of life and family communication, and decreased anxiety. Sometimes a group format was supportive and helped to "normalize" pain for children. On the other hand, a group format could be unsuitable for mixed-severity chronic pain conditions and relies on skilled facilitation to avoid alienating some children.

Feasibility of the interventions was related to ease of access, mode of delivery, family resources, parental support and the burden of the intervention. Barriers and facilitators were noted in relation to these interventions. Barriers included boring intervention content, an unappealing group format, children's reluctance to practice new skills in front of peers, and a mismatch between the intended intervention outcomes and those desired by parents or children. Facilitators included perceived personal relevance, individual tailoring or choice of intervention content, and the child's personal experience with an effective intervention.

The review identified a number of barriers to optimal pain management in children more generally. These include poverty, difficulties accessing care, sociocultural norms regarding the expression of pain, lack of access for healthcare professionals to expertise

and training in paediatric pain assessment and management, and lack of paediatric healthcare services.

3.3 ECONOMIC REVIEW

WHO commissioned a systematic review of economic evaluations of the physical, psychological and pharmacological interventions considered in these guidelines.[53] This review yielded only three studies,[56-58] all set in high-income countries and all focused on CBT, with varying intensity. One study presented a cost-utility analysis comparing the cost per additional quality-adjusted life-year (QALY) between two interventions;[57] the second was a cost-effectiveness analysis presenting cost per unit reduction in pain score;[56] and the third study compared costs only.[58] The cost-effectiveness analysis by Evans and colleagues[56] examined an intensive programme of interdisciplinary pain rehabilitation consisting of therapy, group exercise, recreational and art therapy, and parent psychoeducation duriGng a two-week inpatient and one-week day-hospital stay. The study found an improvement in pain after the intervention, with cost savings (US$ 27 119) compared to the prior year, primarily due to decreased healthcare utilization.

The other two studies examined internet-based CBT interventions. Lalouni et al.[57] compared the intervention to standard care for children with functional abdominal pain, and reported that the intervention cost US$ 186, leading to cost savings of US$ 974 and an increase in QALYs of 0.0187.

Finally, Law and co-authors58 compared internet-based CBT to an internet education programme in children with chronic pain due to a range of etiologies. The authors reported that costs decreased for both intervention groups compared to the prior year, with no significant difference between groups.

This review also included a search for comparative cost analyses and studies reporting resource use if they examined at least two of the physical, psychological or pharmacological interventions of interest. No studies were identified, however. In addition, the review included estimated costings for interventions or groups of interventions identified in the effectiveness reviews as well as interventions where evidence was not identified but where costing might assist the GDG in making recommendations. Only costs of the intervention or medicine and its delivery were included; downstream or other effects of the interventions such as reduced health services utilization or work leave for parents and caregivers were not included. Costings are presented in Tables 3, 4 and 5 of the economic analysis report.[53]

4. GUIDING PRINCIPLES

The GDG agreed that several key principles underpin the recommendations and best practice statements in these guidelines. More importantly, these *guiding principles* underlie all aspects of the care of children with chronic pain. These principles are based on human rights conventions and ethics considerations.

1. Access to pain management is a fundamental human right

Fundamental human rights recognized in international human rights instruments[59-61] include the right to be free from torture, and from cruel, inhuman or degrading treatment or punishment. States therefore have an obligation to protect persons from torture and maltreatment and this right is threatened if persons do not have access to essential medicines for pain relief. The Special Rapporteur on torture and other cruel, inhuman or degrading treatment or punishment noted in his third report to the Human Rights Council of the United Nations on 14 January 2009[62] (paragraph 72): "…the Special Rapporteur is of the opinion that the de facto denial of access to pain relief, if it causes severe pain and suffering, constitutes cruel, inhuman or degrading treatment or punishment." The recommendations continue (paragraph 74e): "Given that lack of access to pain treatment and opioid analgesics for patients in need might amount to cruel, inhuman and degrading treatment, all measures should be taken to ensure full access and to overcome current regulatory, educational and attitudinal obstacles to ensure full access to palliative care."

A further report of the Special Rapporteur on 1 February 2013[63] (paragraph 56) reaffirms: "… 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. Governments must guarantee essential medicines which include, among others, opioid analgesics 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."

Various governmental and inter-governmental bodies have articulated the dual obligation of ensuring adequate availability of opiates for medical and scientific purposes, while at the same time preventing illicit production and trafficking of these drugs.[64-66] The Preamble to the 1961 Single Convention on Narcotic Drugs[67] 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", while also noting the potential for misuse of these medicines and the need to prevent and combat misuse with effective measures.

2. Children have the right to enjoyment of the highest attainable standard of health

The United Nations Convention on the Rights of the Child (CRC)[68] presents several Articles relevant to the child with chronic pain.

Article 3, paragraph 1:

"In all actions concerning children, whether undertaken by public or private social welfare institutions, courts of law, administrative authorities or legislative bodies, the best interests of the child shall be a primary consideration."

Article 23, paragraph 1:

"States Parties recognize that a mentally or physically disabled child should enjoy a full and decent life, in conditions which ensure dignity, promote self-reliance and facilitate the child's active participation in the community."

Article 24, paragraph 1:

"States Parties recognize the right of the child to the enjoyment of the highest attainable standard of health and to facilities for the treatment of illness and rehabilitation of health. States Parties shall strive to ensure that no child is deprived of his or her right of access to such health care services."

3. Member States and healthcare providers should ensure that children, and their families and caregivers know their rights

Member States and healthcare providers should ensure that children, and their families and caregivers know their rights to self-determination, non-discrimination, accessible and appropriate health services, and confidentiality. This enables families to advocate for their child and for themselves, and to seek the support to which they are entitled.

5. BEST PRACTICES FOR THE CLINICAL MANAGEMENT OF CHRONIC PAIN

The GDG formulated several statements that represent best practice for the clinical management of chronic pain in children. These statements apply to all aspects of the clinical care of a child with chronic pain, including the planning, implementation and delivery of physical, psychological and pharmacological interventions.

1. Children with chronic pain and their families and caregivers must be cared for from a biopsychosocial perspective; pain should not be treated simply as a biomedical problem.

2. The biopsychosocial model of pain recognizes pain as a complex multidimensional experience that is the result of interaction among biological, psychological and social factors. This model provides a basis for understanding the effects of pain on an individual and their family and caregivers, and the diagnosis and treatment of pain. It takes into account the patient, their family and social context, and the impact of illness on that individual from a societal perspective. Pain management thus requires a multimodal, interdisciplinary and integrated approach.1-3

3. A comprehensive biopsychosocial assessment is essential to inform pain management and planning. As a component of this assessment, healthcare providers should use age-, context- and culturally appropriate tools to screen for, and monitor, pain intensity and its impact on the quality of life of the child and family.

4. Children with chronic pain must have a thorough evaluation of any underlying conditions and access to appropriate treatment for those conditions, in addition to appropriate interventions for the management of pain. Chronic pain in childhood often exists with comorbid conditions affecting the child's health, and social and emotional well-being, which require concurrent management.

5. Children presenting with chronic pain should be assessed by healthcare providers who are skilled and experienced in the evaluation, diagnosis and management of chronic pain.

6. Management, whether with physical therapies, psychological or pharmacological interventions, or combinations thereof, should be tailored to the child's health; underlying condition; developmental age; physical, language and cognitive abilities; and social and emotional needs.

7. Care of children with chronic pain should be child- and family-centred. That is, the child's care should:

    i. focus on, and be organized around, the health needs, preferences and expectations of the child, and their families and communities;

    ii. be tailored to the family's values, culture, preferences and resources; and

    iii. promote engagement and support children and their families to play an active role in care through informed and shared decision-making.

8. Families and caregivers must receive timely and accurate information. Shared decision-making and clear communication are essential to good clinical care. Communication with patients should correspond to their cognitive, development, and language abilities. There must be adequate time in a comfortable space for discussions and questions regarding care management plans and progress.

9. The child and their family and caregivers should be treated in a comprehensive and integrated manner: all aspects of the child's development and well-being must be attended to, including their cognitive, emotional and physical health. Moreover, the child's educational, cultural and social needs and goals must be addressed as part of the care management plan.

10. In children with chronic pain, an interdisciplinary, multimodal approach should be adopted which is tailored to the needs and desires of the child, family and caregivers, and to available resources. The biopsychosocial model of pain supports the use of multiple modalities to address the management of chronic pain.

Policy-makers, programme managers, and healthcare providers, as well as parents and caregivers must attend to opioid stewardship to ensure the rational and cautious use of opioids. The essential practices of opioid stewardship in children include:

i. Opioids must only be used for appropriate indications and prescribed by trained providers, with careful assessments of the benefits and risks.

ii. The use of opioids by individuals, their impact on pain and their adverse effects must be continuously monitored and evaluated by trained providers.

iii. The prescribing provider must have a clear plan for the continuation, tapering or discontinuation of opioids according to the child's condition. The child and family must be apprised of the plan and its rationale.

iv. There must be due attention to procurement, storage and the disposal of unused opioids.

6. RECOMMENDATIONS

The Guideline Development Group (GDG) formulated recommendations based on the systematic reviews of the evidence on benefits, harms, acceptability, feasibility and economic evaluations, and on other considerations as outlined in Chapter 2 (Methods) and in more detail in web Annex A.

6.1 RECOMMENDATION 1

In children with chronic pain, physical therapies may be used, either alone or in combination with other treatments (conditional recommendation, very low certainty evidence).

6.1.1 REMARKS

This recommendation was achieved by consensus among the GDG members.

6.1.2 RATIONALE

The GDG based this recommendation on the following evidence and other considerations:

- When compared to non-physical therapy interventions or to wait-listed controls, physical therapy interventions for children with chronic pain due to various etiologies had a moderate effect on pain intensity post-treatment (very low certainty evidence). Benefits were not demonstrated at longer-term follow-up however, in the small number of available studies (very low certainty evidence).
- Functional disability and activity participation were improved post-treatment when used in the management of chronic pain of varying etiologies (very low certainty evidence).
- Adverse events were poorly reported in the studies examined; however, the events that were reported were generally minor or of short duration and did not require treatment.
- While physical therapy interventions were generally considered feasible and acceptable to children, parents and caregivers, views were mixed. Children reported concerns with these interventions, including boredom with exercises and reluctance to practice new skills in front of peers.
- The costs of physical therapy interventions are likely to vary across countries and specific settings, although the potential costs of not appropriately managing chronic pain could be high. Although analysis of these potential benefits compared to costs was not systematically reviewed across a range of settings, it was the GDG's opinion that these costs could be substantial, including in terms of healthcare utilization (in- and outpatient medical and mental health services) and the costs to parents of lost work time.

6.2 RECOMMENDATION 2

Recommendation 2a. In children with chronic pain, psychological management through cognitive behavioural therapy and related interventions (acceptance and commitment therapy, behavioural therapy and relaxation therapy) may be used (conditional recommendation, moderate certainty evidence).

Recommendation 2b. Psychological therapy may be delivered either face-to-face or remotely, or using a combined approach (conditional recommendation, moderate certainty evidence).

6.2.1 REMARKS

This recommendation was reached by consensus among the GDG members. The GDG decided to not make a recommendation regarding hypnosis: only three studies examined hypnosis, providing data on only three of the critical or important outcomes (mixed results, all very low certainty evidence).

6.2.2 RATIONALE

The GDG considered the following factors when formulating this recommendation.

- Of the intervention arms in the 63 included psychological trials, all but five arms (three on hypnosis and two on problem-solving) examined cognitive behavioural therapy, acceptance and commitment therapy, behavioural therapy or relaxation therapy. The GDG agreed that these four types of therapies have shared features in terms of their purpose, mechanism and delivery. They therefore felt that they could be combined to examine outcomes and support a recommendation.
- The systematic review reported a reduction in pain intensity, and a beneficial effect on 50% pain reduction and functional disability from cognitive behavioural therapy, acceptance and commitment therapy, behavioural therapy and relaxation training immediately post-treatment when these interventions were examined as a group (all low certainty evidence). At longer-term follow-up, there were beneficial effects on 50% pain reduction (very low certainty) and functional disability (moderate certainty).
- These effects did not differ between patients who had face-to-face therapy and those who were remote from the therapist.
- The systematic review of qualitative evidence reported that children had mixed views about the acceptability of psychological therapies. Children and parents perceived benefits (improved sleep, mood, quality of life and family communication, and less anxiety). The group format could be supportive and normalize pain for children. On the other hand, children expressed concerns regarding these interventions, including boring content, perception of a lack of relevance to themselves and reluctance to practice new skills in front of peers, and the group format could be unsuitable for groups of children with mixed conditions or mixed severity of pain. Parents and children noted the burden of travel time to attend face-to-face sessions and concerns regarding a mismatch between the intended intervention outcomes and those desired by parents or children. The effects of these concerns on the effectiveness of psychological interventions is unknown, however.

- Various facilitators for effectiveness of these interventions were also noted: perceived applicability to the child, individual tailoring or choice of intervention content, and the child's personal positive experiences with the intervention. The effects of these facilitators on effectiveness are unknown.
- Economic analyses from two high-income countries showed that psychological interventions were either less costly or had a similar cost than standard care, an educational intervention without cognitive behavioural therapy or care prior to the intervention. The required resources in low- and middle-income countries would probably vary, particularly in areas where there is less access to health services or few trained therapists.
- The costs of psychological therapy interventions are likely to vary across countries and specific settings, although the potential costs of not appropriately managing chronic pain could be high. Although analysis of these potential benefits compared to costs was not systematically reviewed across a range of settings, it was the GDG's opinion that these costs could be substantial, including healthcare utilization (in- and outpatient medical and mental health services) and the costs to parents of lost work time.

6.3 RECOMMENDATION 3

In children with chronic pain, appropriate pharmacological management, tailored to specific indications and conditions, may be used (*conditional recommendation, low certainty evidence*).

6.3.1 REMARKS

This recommendation was achieved by consensus among the GDG members. In view of the paucity of evidence on specific drug classes and medicines, the GDG decided to make this general recommendation for pharmacological therapy. The reader is referred to the Summary of the evidence section 3.1.3, Web Annex F and the systematic reviews for more detailed results.

6.3.2 RATIONALE

The GDG considered the following factors when formulating this recommendation:

- The systematic review of the evidence reported small reductions in several pain measures post-treatment with several pharmacotherapies when used for the management of chronic pain of various etiologies in children.
- The small number of studies, the lack of inclusion of longer-term observational or population-based studies and the low rates of adverse events reported within included studies made it difficult to determine the risk of adverse events for specific drugs or classes of drugs.
- Although the balance of benefits and harms was difficult to determine based on the available evidence in children, particularly for specific drugs and indications, the GDG felt that pharmacotherapy has potential benefit for children with chronic pain, following individualized risk assessment.

- The costs of pharmacological therapy interventions are likely to vary across countries and specific settings, although the potential costs of not appropriately managing chronic pain could be high. Although analysis of these potential benefits compared to costs was not systematically reviewed across a range of settings, it was the GDG's opinion that these costs could be substantial, including healthcare utilization (in- and outpatient medical and mental health services) and the costs to parents of lost work time.

6.4 RECOMMENDATION 4

Recommendation 4a: Appropriate pharmacological management tailored to specific indications may include the use of morphine under the principles of opioid stewardship, for end-of-life-care (conditional recommendation, very low certainty evidence).

Recommendation 4b. In children with chronic pain associated with life-limiting conditions*, morphine may be given by appropriately trained healthcare providers, under the principles of opioid stewardship (conditional recommendation, very low certainty evidence).

(*) Life-limiting conditions are illnesses for which there is no cure and an early death is expected, but with which a person may continue to live for several more years.

6.4.1 REMARKS

This recommendation was reached by consensus among the GDG members.

6.4.2 RATIONALE

The GDG considered the following factors when formulating this recommendation.

- There were no comparative studies identified in the systematic review of the evidence on the use of morphine or other opioids in children with chronic pain.
- There was moderate confidence that parents' attitude towards the use of morphine for their children with chronic pain due to cancer was positive and accepting, though some healthcare providers were reluctant to give opioids due to fear of their addictiveness (low confidence evidence). Some healthcare providers believed pain went untreated because of this fear, and that children needed better pain management.
- The cost of morphine preparations varies widely across countries.
- Overall, the GDG felt that access to morphine for children in end-of-life care, and in specific and limited situations for children with life-limiting conditions, was essential for adequate management of their pain.

6.4.3 CONSIDERATIONS

When children are prescribed morphine in the context of end-of-life care or in very specific situations for life-limiting conditions, there are a number of important considerations.

- The use of morphine is never a stand-alone treatment: opioids are always prescribed in the context of the biopsychosocial model of care, considering the balance of benefits and harms for the individual.
- The prescription of morphine must be undertaken by an appropriately trained and experienced healthcare provider, who takes responsibility for the regular follow-up care of the child, monitoring and dose adjustment, and other principles of opioid stewardship.
- The pharmacokinetics of morphine in children are not well studied, and there is variability in children's individual sensitivity to morphine and their pain perceptions. It is therefore essential that all healthcare providers involved in the management of children receiving morphine are trained in the assessment and monitoring of these children.
- Children and their families should be given information about physiological dependence, tolerance, side-effects and how to manage them. Appropriate interventions to prevent, minimize and manage side-effects should be instituted.
- Healthcare providers who prescribe opioids must work to mitigate the risks that extend beyond the child. Such efforts include, for example, safe transport, storage and disposal of opioids.
- Children who are appropriately prescribed morphine for chronic pain in the context of end-of-life care or in children with life-limiting conditions, may require morphine for the management of intercurrent, acute or breakthrough severe pain (e.g. sickle cell crisis). Time-limited use of morphine in these contexts should be at the lowest appropriate dose and duration possible and must be regularly reviewed in order to ensure the fewest possible adverse events. Healthcare providers and caregivers need to perform frequent and repeated reassessments of pain and other symptoms, and the principles and relevant guidelines for acute pain management should be followed, including having an opioid stopping plan and adhering to other aspects of opioid stewardship.

7. RESEARCH GAPS

During the guideline development process, the GDG identified a number of key gaps in the knowledge base and in research evidence on the treatment of chronic pain in children. Articulating these gaps may benefit researchers, funders and other stakeholders with an interest in the management of chronic pain in children. Importantly, research which addresses these gaps will facilitate evidence-informed guidelines as well as decision-making in Member States and at the local level. The gaps presented here are not prioritized and are not intended to be fully comprehensive.

7.1 GAPS IN RESEARCH DESIGN AND EXECUTION

The GDG noted that existing research was often suboptimal in terms of quality of design, execution and reporting. The GDG suggested that future research could be improved by addressing the following key issues.

a) Large, multicentre trials are needed which examine individual and multimodal therapies across a range of settings, including hospitals, hospices, the home and the community.

b) Individual-level analyses (such as single-case experimental design) can complement group-based studies such as RCTs. Such designs allow for more detailed analyses at the individual level, including examination of how children respond to interventions across different phases of an illness and its treatment.

c) The reporting of study population characteristics should be improved in future research, particularly descriptions of medical conditions and mechanisms of underlying pain.

d) Work is needed to catalogue, evaluate and validate tools for the assessment and re-assessment of pain due to specific conditions, in specific settings and for children of various age-ranges and abilities.

e) Standardized sets of patient- and family-centred outcomes, as well as culturally sensitive outcomes, need to be developed and routinely measured in future research studies. This will facilitate comparisons of outcomes across studies and populations.

f) Analyses of outcomes by age strata and sex are needed to better understand behaviours and outcomes for population subgroups.

g) Studies of all types need to include long-term follow-up, particularly for adverse events.

h) Comprehensive collection of observational data on outcomes including adverse events is needed with tools such as registries.

7.2 RESEARCH GAPS RELEVANT TO SEVERAL INTERVENTION TYPES

There are a number of research gaps which are relevant to more than one type of intervention.

a) Studies need to be conducted in real-world settings, where comorbidities, adherence to treatments and other common variations among study participants are taken into account.

b) Studies of the effectiveness, safety and feasibility of interventions in a range of low- and middle-income countries are needed. As well, research is needed on intervention effectiveness and feasibility in humanitarian, low-resource and other diverse settings.

c) Studies of the effectiveness of diverse models for the delivery of physical and psychological interventions are needed, including the use of digital technology such as telemedicine and mobile phone applications to support patients and families in pain management programmes.

d) Studies on interdisciplinary and multimodal treatments of different types of conditions resulting in chronic pain in children are needed.

e) Qualitative and mixed-method studies will help programme managers, providers, and patients and their families understand how and why interventions are effective, the predictors and facilitators for, and barriers to effectiveness, and predict successful outcomes.

f) Once effectiveness of an intervention is demonstrated in high-quality studies, cost-effectiveness should be examined in a variety of settings, particularly in low- and middle-income countries.

g) Studies are needed which explore ways to strengthen training and expand human resource capacity to deliver pain interventions in low- and middle-income countries, and in low-resource settings such as humanitarian programmes.

7.3 POPULATIONS IN WHICH FURTHER STUDY IS NEEDED

There are inadequate data on interventions for chronic pain in children across all age groups and a wide range of subpopulations. Several research gaps are particularly notable.

a) While research is needed across all age groups, from 0 to 19 years of age, systematic reviews of effectiveness did not identify any studies in children less than 10 years of age. This younger age group therefore merits particular attention.

b) Research is needed for children with specific conditions, including:

i. vulnerable children such as those with developmental or intellectual disabilities, exposed to trauma or challenging life experiences, living in humanitarian settings, and with comorbid mental health conditions;

ii. children with chronic cancer-related pain during or following cancer treatment; and

iii. children with life-limiting conditions or those requiring end-of-life pain management both in inpatient settings and in the community.

c) Several population groups need particular attention including indigenous populations, and family members including siblings and caregivers of children with chronic pain.

7.4 RESEARCH GAPS RELATED TO SPECIFIC INTERVENTIONS

There are significant research gaps for all three of the main intervention types examined in these guidelines.

7.4.1 PHYSICAL THERAPY

Given the paucity of evidence and the low quality of existing studies, a wide range of studies is needed which examine the effectiveness and safety of physical therapy interventions for chronic pain in children. In particular, large multicentre trials are needed, along with studies examining tailored interventions and interventions which integrate activity-based therapies within daily life.

7.4.2 PSYCHOLOGICAL INTERVENTIONS

Although more studies were identified on psychological therapy than on physical or pharmacological therapies, much additional research is needed to optimally inform treatment and care management recommendations, particularly in low- and middle-income countries. Large, well-designed trials are needed. Importantly, intervention definitions and descriptions should be improved. For example, studies need to report the number and length of sessions, the duration of work performed outside of therapy sessions, and the specific role and tasks for parents, children, or both. The core or active components of successful treatments need to be determined as this augments the efficient delivery of the intervention and its cost-effectiveness.

Specifically, the following areas merit attention from researchers and funders:

a) studies of tailored interventions, based on age, level of function and disability;

b) research to address active mechanisms and mediators, including predictors and moderators of the treatment response, since knowledge of these factors is crucial for developing tailored interventions;

c) studies examining different modes of delivery, for example,internet-, workbook- or phone-based interventions, in low-, middle- and high-income countries; and

d) interventions for families, caregivers and youth that can be delivered without psychologists, such asby community health workers, school teachers or peer support groups.

7.4.3 PHARMACOLOGICAL INTERVENTIONS

As highlighted by the systematic reviews underpinning these guidelines, there are significant research gaps related to the effectiveness and safety of pharmacological interventions for chronic pain in children.

a) There are few pharmacokinetic studies of medicines in children with chronic pain. Studies are needed which examine the effects of different medicines in specific conditions, including varying dosages and treatment regimes.

b) Adherence to different medicines and treatment programmes needs to be examined, particularly in adolescents.

c) Safety data are needed on the range of medicines of potential use in children with chronic pain, both from trials and from long-term, longitudinal cohort studies. These data should include both serious and other adverse events.

d) Evidence of the effectiveness and safety of opioids is completely lacking in children. Some key research gaps include:

   i. The effectiveness and safety of opioids including morphine in end-of-life care and in life-limiting conditions, including longer-term use in the latter condition.

   ii. The effectiveness and safety of longer-acting opioids and subcutaneous infusions of morphine in children needing end-of-life care.

   iii. Population-level surveillance for adverse events including overdose and misuse.

   iv. Studies of societal attitudes towards the appropriate use of opioids for chronic pain in children, as well as overdose, misuse and addiction.

8. UPTAKE AND IMPLEMENTATION

When planning to implement the recommendations in these guidelines, Member States and other end-users need to ensure that the necessary policies, regulations, infrastructure and personnel are in place to provide accessible, high-quality health services for children with chronic pain. In addition, there are a number of important considerations for end-users as they implement these recommendations.

8.1 NATIONAL HEALTH POLICIES TO ENSURE ACCESS TO A RANGE OF TREATMENT OPTIONS

It is important that Member States' national policies and regulations ensure wide and equitable access to appropriate and high-quality services for children with chronic pain. Treatment costs and bureaucratic processes must not preclude or discourage equitable access to appropriate therapies. Health services for chronic pain are an essential part of universal health coverage (UHC) for children. National packages of essential services must be accompanied by an appropriate budget allocation and include the range of therapies recommended in these guidelines, as well as access to specialist providers and referral services, when indicated. It is not sufficient to include only some of the treatment modalities under UHC, for instance, pharmacological interventions, as this may lead to unintended consequences such as a singular focus on medicines which could place children and families at risk of overreliance and problematic use. In addition, pharmacological therapy is likely to be less effective without appropriate attention to physical and psychological therapies as part of the biopsychosocial model of care. Finally, families may seek other treatments which are not evidence-based: this has economic consequences for the family and carries the potential for adverse events.

The WHO Model Lists of Essential Medicines and the WHO Essential Medicines List for Children include an appropriate range of medicines for treating pain in children. The United Nations Committee on Economic, Social and Cultural Rights considers that the right to health requires countries to ensure access to medicines included on the WHO model list.[69] As a central part of national medicines policies, the WHO model lists can be adapted by countries and serve as a guide for national lists[70] to ensure access to quality medicines and their rational use. A core strategy for rational use of medicines is the education and training of healthcare providers on key policies that affect quality, supply, use and disposal of medicines. Healthcare providers should have adequate protection and support such that they can discharge their duties related to the handling of controlled medicines including opioids.

8.2 CAPACITY STRENGTHENING

In order to achieve optimal access to effective and cost-effective services for children with chronic pain and their families, significant strengthening of capacity may be needed, particularly in low- and middle-income countries. Capacity is needed both in terms of healthcare providers and in health systems capable of delivering high-quality,

recommended services. Training of healthcare providers in chronic pain management in children may need to be augmented. This includes education and training at the undergraduate and post-

graduate levels, and in continuing education curricula, and applies across the range of providers involved in caring for these children. Such training should encompass a broad range of topics, including the assessment of pain, other symptoms and treatment responses; tools used for these assessments; treatment modalities; screening for and treatment of the adverse effects of interventions; and communication and support strategies for children and their families.

In order to effectively deliver care for chronic pain in children, healthcare workers must fully understand the biopsychosocial model of pain management to a level commensurate with the provider's role and responsibilities in children's care. In some settings, this may require a significant change in the culture and attitudes of providers, as well as additional training.

Given the importance of clear, accurate and comprehensive communication among the various healthcare providers involved in a child's care, providers must be trained and continuously work to improve their communication skills with the child, and their family and caregivers. Providers must be comfortable with shared decision-making and approaches to support and empower patients and their families. This may require additional training and support networks to ensure these skills.

In view of the multimodal and multidisciplinary approaches to chronic pain management, providers must be aware of the range of management options available, and have a level of knowledge tailored to their specific role. Providers must have basic knowledge of physical and psychological therapies, how to optimally monitor progress and adverse effects, and when treatments require modification or discontinuation. Likewise, providers need to have an understanding of the medicines used for the management of pain in children, their appropriate use, potential adverse effects and monitoring thereof, and the principles of opioid stewardship, including when and how to discontinue these medicines. In addition, providers need to know when children might benefit from referral to specialist or other services.

Specialized referral services and networks may need to be established to ensure that interdisciplinary, multimodal, integrated therapies are delivered as indicated. Novel models may be needed, such as task-shifting and virtual consultations with providers and care teams.

8.3 OPTIMIZING INTERVENTIONS FOR CHRONIC PAIN

There are a number of important considerations with regards to the implementation of interventions for chronic pain in children in order to optimize care, outcomes and the use of resources.

An early step in the management of chronic pain should involve education of the patient, family and caregivers about the biopsychosocial nature of pain. Explanations should be tailored to the concerns and questions of the child and family. Communication aids such as metaphors, booklets and web resources should be selected to match the learning style and preferences of children and their caregivers.

The management of chronic pain should also include the establishment of goals, set collaboratively and according to their abilities by the child, family, caregivers and the relevant healthcare providers. Setting goals helps the child to achieve the highest obtainable quality of life and promote their ability to do and be what they value or have reason to value.

The feasibility of delivering any intervention for chronic pain management in children may vary across settings. Feasibility is generally related to ease of access, mode of delivery, family resources, degree of parental support and the burden (time, inconvenience and cost). Healthcare providers must consider all these aspects of feasibility as they work with the child and family.

The social and educational context of children with chronic pain is critically important as interventions are planned and implemented. Support for families and children can be based in the home and community, and engage not only health professionals, but school and social services. Care should be delivered as close to home as possible, and in the child and family's preferred location. As far as feasible, care pathways should revolve around the child's and family's schedules and education timetables. This will help to avoid taking the child away from routine physical and social environments, which would otherwise increase the burden placed on them and their family.

As a chronic condition, attention must be given to the maintenance and sustainability of the intervention, and its long-term outcomes. Although research evidence is lacking, healthcare providers and other persons involved in the care of these children should be continually seeking approaches which sustain and augment care and positive outcomes. These include reassessing disease status and pain control using validated tools appropriate to the child's age, developmental status, mode of communication and culture. "Booster sessions" for effective interventions can be used to enhance outcomes over the long term.

As children age and their capabilities, decision-making capacity, views, interests and activities change, care teams must ensure that appropriately tailored services evolve to meet the child's needs. The adolescent's care team must facilitate a smooth transition from child to adult services.

9. DISSEMINATION AND UPDATING

The current guideline will be posted on the WHO website. In addition, it will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations.

As this is a global guideline, Member States are expected to adapt the recommendation to their own setting, taking into feasibility, resource availability and other considerations at the national and subnational level. WHO regional and country offices can assist with the adaptation processes.

Monitoring and evaluation will be built into the dissemination and implementation process to provide data and information on uptake, implementation and impact. WHO plans to collaborate with national authorities to include questions about the new recommendations, and healthcare workers' experiences when implementing them—in relevant routine national training assessments and other evaluations.

The WHO Steering Group will continue to follow research developments in the management of chronic pain in children, particularly for interventions in which the certainty of the evidence was found to be low or very low. If these guidelines merit an update, or if there are concerns about their validity, WHO will coordinate the guideline update, following the procedures and methods of the WHO guideline development process.

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ANNEX. GUIDELINE CONTRIBUTORS

The following individuals contributed to development of the *Guideline on chronic pain management in children.* Persons who contribute to WHO guidelines do so in an individual capacity: they do not represent any Member State or government, or any organization or entity with which they may be affiliated.

WHO seeks to ensure that all contributors to its guidelines are free of any interests that might conflict with Member States' interests. The WHO Steering Group, the Director of the WHO Department of Maternal, Child and Adolescent Health and a representative from the WHO Office of Compliance, Risk Management and Ethics assessed disclosures of interests, curriculum vitae and other information provided by the contributors and determined that there were no conflicts of interest among the individuals contributing to this guideline.

GUIDELINE DEVELOPMENT GROUP

TABLE 1. MEMBERS OF THE GUIDELINE DEVELOPMENT GROUP

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African Region				
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Region of the Americas				
Bustamante Tuchez, Linda Marisol	Unidad Nacional de Oncología Pediatrica, Guatemala City, Guatemala	F	Paediatric palliative care, paediatric oncology	None declared
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Kolodny, Andrew	Brandeis University, Heller School of Social Policy and Management Massachusetts, United States of America	M	Access and regulation of access to medicines	President of Physicians for Responsible Opioid Prescribing (PROP) (2011 to 2013). Director of PROP (2014 to present) (both are unpaid roles). PROP does not accept funding from commercial entities. PROP has taken positions favouring increased US. government regulation of pharmaceutical companies.
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Eastern Mediterranean Region				
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Joslin, Rhiannon	Western Sussex Hospitals NHS Foundation Trust Southampton, United Kingdom of Great Britain and Northern Ireland	F	Physiotherapy, chronic pain experience of children	None declared
Toebes, Bridgit	University of Groningen, Faculty of Law Haren, Netherlands	F	Human rights laws, right to health	None declared
Yael, Ben Gal	Schneider Children's Medical Center of Israel, Clalit Health Organization Tel Aviv, Israel	F	Oncology nurse, policy advocacy	None declared
South East Asia Region				
Palat, Gayatri	MNJ Institute of Oncology and Regional Cancer Centre Hyderabad, India	F	Palliative medicine	None declared
Rajagopal, M R	Trivandrum Institute of Palliative Sciences Kerala, India	M	Palliative medicine, anaesthesiology	None declared
Western Pacific Region				
Dans, Leonila*	University of the Philippines – Manila Quezon City, Philippines	F	Paediatric Rheumatology, clinical epidemiology	None declared
Lord, Susan	John Hunter Children's Hospital, Hunter Medical Research Institute, University of Newcastle Newcastle, Australia	F	Anaesthesia and pain medicine	None declared
Voo, Teck Chuan	Centre for Biomedical Ethics, National University of Singapore, Yong Loo Lin School of Medicine Singapore, Singapore	M	Biomedical ethics, public health ethics	None declared
Yotani, Nobuyuki	National Center for Child Health and Development Tokyo, Japan	M	Paediatric palliative care	None declared

(*) Co-chairs

EXTERNAL REVIEW GROUP

TABLE 2. MEMBERS OF THE EXTERNAL REVIEW GROUP

Name	Affiliation	Region	Gender	Expertise	Declaration of interests
Bhandari, Rashmi	Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University Medical Center, USA	AMR	F	Clinical psychologist, paediatric pain management, academic	None declared
Foster, Helen	Newcastle University, Newcastle, United Kingdom of Great Britain and Northern Ireland	EUR	F	Paediatric rheumatology, clinical management of pain	None declared
Hagemann, Tracy	University of Tennessee, College of Pharmacy, Nashville, USA	AMR	F	Paediatric pharmacist, Paediatric pain management, academic	Paid speaker for professional body conferences between 2006–2014
Nakawesi, Jane	Mildmay Hospital Kampala, Uganda	AFR	F	Paediatrician, clinical management of pain in children, rehabilitation and palliative care	None declared
Pate Joshua	University of Technology Sydney Sydney, Australia	WPR	M	Physiotherapist, experience with paediatric pain. academic	None declared
Wicksell, Rikard	Associate professor Karolinska Institute Stockholm, Sweden	EUR	M	Clinical psychologist, paediatric chronic pain	Research grant from AFA Insurance (2015–2018, €340k) for the development and evaluation of a digital behavioural intervention for chronic pain.

Abbreviations: AFR, African Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; F, female; M, male; SEA, South-East Asia Region; WPR, Western Pacific Region

WHO STEERING GROUP

TABLE 3. MEMBERS OF THE STEERING GROUP

Department	Director	Focal persons
Maternal, newborn, child, adolescent health and ageing	BANERJEE, Anshu	Pura Rayco-Solon* (MCA/CHD) Ayesha de Costa* (MCA/CHD) Bernadette Daelmans (MCA/CHD) Zeea Han (MCA/AAH) Yuka Sumi (MCA/AAH)
Noncommunicable diseases	KRUG, Etienne	Cherian Varghese (NCD/ODN)
Mental health and substance abuse	KESTEL, Devora Lillia	Dilkushi Poovendran (MHP/HPS), Vladimir Poznyak (MSD/ADA Tarun Dua (MSD/BRH),
Access to Medicines and Health Products	SIMÃO, Mariângela	Gilles Fortè (MPH/MHA)
Integrated health services	KELLEY, Edward Talbot	Marie-Charlotte Bouesseau (UHL/IHS)
African Region	ZAWAIRA, Felicitas	Neema Rusibamayila Kimambo (AFR/CAH)

(*) Responsible technical officers

Guideline Development Group meeting observers

Jo Wilmshurst, President, International Child Neurology Association

Guideline methodologist

Dr Nandi Siegfried, Consultant, Cape Town, South Africa.

Systematic review teams

The Cochrane Pain, Palliative and Supportive Care (PaPas) group, Cochrane Qualitative Implementation methods Group (QIMG) and the Cochrane Response team performed systematic reviews of the evidence. The review of quantitative evidence was led by Dr Emma Fisher and the qualitative evidence review by Dr Emma France.

Economist

Dr James Hawkins, The National Guideline Alliance, the Education, Quality and Projects Directorate of the Royal College of Obstetricians and Gynaecologists (RCOG), United Kingdom of Great Britain and Northern Ireland.

Writer

Dr Susan L Norris, Consultant, Portland, OR, USA

Editor

Iain Bamforth

Layout

Jean Claude Fattier

WEB ANNEXES

https://apps.who.int/iris/bitstream/handle/10665/337644/9789240017894-eng.pdf

Web Annex A. Processes and methods for guideline development

Web Annex B Systematic review of effectiveness and qualitative evidence: summary of the methods

Web Annex C. Systematic review of effectiveness: characteristics of the evidence

Web Annex D. Systematic review of effectiveness: results, physical therapy

Web Annex E. Systematic review of effectiveness: results, psychological therapy

Web Annex F. Systematic review of effectiveness: results, pharmacological therapy

Web Annex G. Systematic review of qualitative evidence: study characteristics

Web Annex H. Summary of the key findings of the systematic review of qualitative research

Web Annex I. Systematic review of economic studies: methods

Web Annex J. Systematic review of economic evaluation studies: study characteristics

Web Annex K. Evidence-to-decision tables


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