This scoping document is an updated and merged version of the scoping documents on chronic malignant pain and chronic non-malignant pain of 2008.

BACKGROUND

The initiative to develop these guidelines emerged from the findings of the Delphi study conducted in June 2007 (1) for the Access to Controlled Medications Programme. This study confirmed that experts and professional bodies related to pain are looking to the World Health Organization (WHO) to take a lead in guideline development. This document combines the scopes of the initial documents that were published by WHO in 2008 (2, 3). Initially, separate scoping documents were developed for malignant and non-malignant pain, but for feasibility reasons, it was decided shortly afterwards to develop a combined guidelines document for malignant and non-malignant pain in adults (including adolescents). Simultaneously, the opportunity was used to update its contents, using the experience of developing the WHO Guidelines on the Pharmacological Treatment of Persisting Pain in Children with Medical Illnesses. In particular, clinical questions are worded more concisely and accurately, several clinical and health systems questions have been added and the scope of the document is more clearly confined to pharmacological treatment.

Need for this guideline

The development of pain guidelines by WHO was initiated after WHA resolution 58.22 “On Cancer prevention and control” (2005) called on WHO to address access to opioid analgesics. Although the problem of insufficient access to controlled medicines did not receive much attention at the time of this resolution, over the years it became a topic of growing importance. At present, it has become a topic high on the agenda, e.g. the Union for International Cancer Control included it in its World Cancer Declaration and the International Association for the Study of Pain in the World Pain Declaration. Since, the UN Commission on Narcotic Drugs adopted several resolutions on access to controlled medicines. The issue of access to opioid analgesics is also one of the topics that is likely to be included in the United Nations action plan on non-communicable diseases (NCDs), e.g., it is likely that access to opioid analgesics will be one of the about 20 indicators that will be introduced to follow progress on NCD policies.

The Access to Controlled Medicines Programme (ACMP) that was established in 2007 as a result of WHO Resolution 58.22 studied the extent of the problem. One of the...
conclusions was that 5.5 billion people live in countries where there is no or low access to opioid analgesics (4). The programme also concluded that in these countries, each year tens of millions of pain patients are suffering without adequate treatment:

- 1 million end-stage HIV/AIDS patients
- 5.5 million terminal cancer patients
- 0.8 million patients suffering injuries, caused by accidents and violence
- Patients with chronic illnesses
- Patients recovering from surgery
- Women in labour (110 million births each year)
- Paediatric patients

When drafting the plans for the ACMP, it became clear that WHO has very limited guidance on how to treat pain. It was considered that this is a prerequisite to improve access to opioid analgesics: if WHO is not able to indicate when opioids should be used and when not, then it would be impossible to encourage that governments loosen their current strict policies that impede access to adequate pain management. Furthermore, there are many countries where health professionals have very limited or no experience with the use of opioid analgesics and this requires guidance. For these reasons, it was decided that guidelines should be developed that together cover all types of pain and that the guidelines should address both policy makers and health-care professionals.

After conducting a Delphi study among health-care workers around the world on what the topics of these guidelines should be, the WHO Steering Group on Pain Guidelines decided that there should be three guidelines:

- Chronic Pain in Adults (this scoping document; current working title: WHO Guidelines on the Pharmacological Treatment of Pain in Adults with Medical Illnesses) and
- Acute pain (regardless of age).

These three guidelines are developed by WHO's Access to Controlled Medicines Programme in the Medicines Access and Rational Use Unit (EMP/MAR) in collaboration with the Cancer Control Programme, the Management of Mental and Brain Disorders Unit, the Management of Substance Abuse Unit, the Clinical Procedures Unit, the Department of HIV and the Department of Child and Adolescent Health and Development. Recently, the Department of Ageing and Life Cycle joined.

In parallel to the treatment guidelines, the Framework of the ACMP also planned for policy guidelines and other tools and was partially able to develop these. Due to financial limitations, so far only the first treatment guidelines mentioned above have been developed. However, the programme was able to publish two other important tools: policy guidelines and a guide on estimating requirements for substances under control

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1 These guidelines replace the guidelines Cancer pain relief and palliative care in children.
Related WHO guidelines
The WHO Guidelines for the pharmacological treatment of persisting pain in adults overlap partially with other guidelines that are related to pain management are the IMAI guidelines developed by the department of HIV:
- Palliative Care: Symptom management and end of life care, Integrated Management of Adolescent and Adults Illness 2004;
- Palliative Care: Symptom management and end of life care, Integrated Management of Adolescent and Adults Illness 2003;
- General principles of good chronic Care, Integrated management of Adolescent and adult illness 2003.

However, these guidelines do not fully cover pain management in all its pharmacological aspects. Furthermore, the HIV Department will draw on the pain guidelines to develop for future updates of its guidelines.

Treatment of cancer pain is currently covered by the guidelines Cancer Pain Relief, 2nd Edition. This guideline was developed initially in 1986 and was updated in 1996. It is not an evidence based guideline and recommends several medicines that are now considered to be obsolete. It introduced the renown WHO Three-step Ladder of Cancer Pain Treatment, which is often applied outside the realm of cancer pain.

The guidelines to develop will also support the WHO policy publication Cancer control knowledge in action, Module 5: palliative care, that offers guidance on this aspect of cancer control planning and implementation.

In 2009, WHO published the Guidelines on the psychosocially assisted pharmacological treatment of opioid dependence.

Purpose of this Scoping document
In spite of its confinement to pharmacological treatment, the scope of the guidelines to develop on persisting pain in adults remains broad, addressing a wide range of conditions that have pain as a symptom. Therefore, where the evidence suggests, within the response to each clinical question, divergent approaches may be recommended for the treatment of different conditions with chronic pain if the evidence is found to support these. Similarly, where the evidence base supports it, divergent approaches should be recommended for the treatment of adolescents and adults, including the elderly.

This scoping document sets out:
- Overall objective of these guidelines;
- Types of patients to whom the guidelines apply;
- Outcomes that are sought;
- Proposed table of contents for the publication;
- Clinical and health-systems questions for which evidence needs to be sought and appraised so that evidence-based recommendations can be made.
The full guidelines should be developed in accordance with the principles for clinical guidelines laid down by the WHO Guideline Review Committee.

**OBJECTIVES AND PATIENT POPULATION**

The overall objective of these guidelines is to provide evidence-based recommendations that, if followed, will improve the pain experience for adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain in: pain related to cancer, Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), progressive life-threatening illnesses, various types of organ failure (e.g. renal or hepatic failure), or specific chronic non-malignant conditions. WHO statistics show a high level of disability related to these conditions (see tables 1 and 2). However, there are many more conditions which include or cause significant chronic non-malignant pain (e.g., chronic post-surgical pain, phantom limb pain).

The guidelines are intended to guide health-care professionals how to treat pain and in particular when to use opioid analgesics. They are also intended to clarify to policy makers (both in the government and in health-care institutions) when opioid analgesics are needed for treatment of persisting pain in adults.

Some therapies which contribute to the improvement of the pain experience are beyond the scope of this document. These include specific disease-modifying therapies (e.g., anti-cancer therapies, anti-retroviral therapies, anti-rheumatic therapies, joint replacement). These are addressed by other WHO guidelines and reference will be made to them as needed. These guidelines also will not cover non-pharmacological treatment of pain.

Patient population: These guidelines address adults (aged over 18 years) and adolescents (aged 10-18 years). The elderly (aged 60 years and over) will be addressed as a special subpopulation of the former. Since pharmacological treatment for adolescents is similar to that of adults, management of pain related to cancer, HIV/AIDS, and other life threatening illnesses in adolescents is included in these guidelines.

The critical outcomes that should be considered include: effectiveness of pain relief, maintenance of pain reduction and relief, cost effectiveness, speed at which pain reduction may be achieved, effect on quality of life, effect on an individual’s function, anxiety and mood, adverse effects (including risks), complications of treatments/interventions, and risk-benefit analysis of interventions for pain relief.

The risk of use of opioid medicines will be addressed through both clinical questions and health-systems questions, including how to balance the potential harms against the potential benefits of pain management with these medicines.
Table 1 Disability-adjusted Life Years (DALYs) for a few pain conditions in 2002
Source: www.who.int

<table>
<thead>
<tr>
<th>Conditions</th>
<th>2002 (x 1000 DALYs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low back pain</td>
<td>2320</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>14,861</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>4866</td>
</tr>
</tbody>
</table>

Table 2 Disability-adjusted Life Years (DALYs) in 2002 and projections to 2030
Source: Matthers & Loncar 2006 (6)

<table>
<thead>
<tr>
<th>Diseases</th>
<th>2002 (x 1000 DALYs)</th>
<th>2030 (baseline projection)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant neoplasms</td>
<td>75,336</td>
<td>105,001</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>82,380</td>
<td>185,923</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>148,985</td>
<td>176,999</td>
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<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>28,049</td>
<td>48,369</td>
</tr>
<tr>
<td>Diabetes</td>
<td>16,165</td>
<td>29,715</td>
</tr>
<tr>
<td>Alzheimer and other dementias</td>
<td>10,392</td>
<td>18,394</td>
</tr>
</tbody>
</table>

PROPOSED CONTENTS

A. Executive summary

The objective of these guidelines, the patients to whom they apply, the target audience and key recommendations should be stated. It will also contain a reading guide.

B. Introduction

This should include:
- A clear statement on the overall objective of these guidelines and the patients to whom these guidelines are meant to apply;
- A statement on the target audience: Who will use these guidelines? Those involved in the pharmacological pain treatment in adults: physicians (both general practitioners and specialists), nurses, physician assistants and pharmacists. The guidelines are also aimed at policy makers and programme managers, who may not be directly providing care, but play an important role in ensuring care of patients;
- A clear statement on what is beyond the scope of this document;
- A clear statement, that whatsoever treatment is selected, moderate and severe pain need always to be addressed;
• Recognition that much of pain management can be carried out in primary care and the community, with only a relatively small percentage of patients requiring specialist pain management;
• A description of the biopsychosocial context in which these guidelines are contained, including the wider context of palliative care, the importance of holistic care of patients and their families and the recognition of pain as only one of many symptoms and areas of concern for patients with these diseases;
• A discussion how to balance the risk of use of opioid medicines against the potential benefits of opioid pain management.
• The concept of total pain based on International Association for the Study of Pain (IASP) and WHO definitions including the psychological, emotional, cultural and social sequelae of living with chronic pain over prolonged periods of time;
• The limited availability of high quality clinical trials of medicines and other therapies in chronic pain over prolonged periods of time and the realization that many recommendations will be based on clinical experience and best opinion;
• The effectiveness of a coordinated team approach, in its broadest sense, i.e. depending on the resources available and the setting in which pain is being managed, teams may vary in composition (different disciplines, professions and combinations of professionals and non-professionals), complexity and size.

C. Causes and classification of pain

This should be a section to state
• A definition and clinical features of pain according to the pathophysiological mechanism:
  o Neuropathic pain (central or peripheral);
  o Nociceptive pain (somatic or visceral)
  o Mixed pain (nociceptive and neuropathic components);
• Other classifications, such as:
  o Malignant vs. non-malignant pain;
  o Acute vs. chronic or persisting pain;
  o Breakthrough or episodic pain;
  o Pain at rest and pain on movement.
• Key investigations or clinical procedures/actors which maybe helpful in distinguishing between different causes/types of pain;
• Specific medical conditions associated with chronic pain in adults;
• Recognition that there might be more than one cause of pain in patients with cancer and other life limiting illness and the importance of being able to identify them.
A model for this chapter can be found in the corresponding WHO Guidelines for the treatment of persisting pain in children.

D. Evaluation of persisting pain

This should include:
• The importance of systematic evaluation using validated tools, chosen depending on the type of patient, and the need for frequent reassessment;

• Recommendation about the steps which should be taken in a holistic assessment and documentation of pain, including assessment of cause, type, severity, activity and sleep disturbance, mood (anxiety, depression etc) and social impact;
• Recognition that there is a need to evaluate measure and monitor pain and pain control and that a variety of pain scales are available though not one has been shown to be superior to others across all settings;
• Recognition of the importance of diagnosing of underlying conditions and symptomatic nature of pain management.
• Description of the evidence underpinning a selection of frequently used validated pain scales and the settings in which each has been validated for use (these pain scales to appear in annex);
• Recognition that patients often do not report pain – for a variety of reasons including religion, finance, fear and culture;
• The need to enquire if patients are suffering pain, even if they are being attended for other clinical conditions. Recognition that health workers often underestimate and under treat a patients’ pain and the key role of health workers with skills in communication, both verbal and non verbal.

Several parts of this chapter can be drafted in analogy of the WHO guidelines on persisting pain in children.

E. Pharmacological treatment strategy

This should include a statement of the principles of treatment:
• Underlying cause of pain should be treated whenever possible;
• The need to use a systematic approach consisting of;
  o a two or three step strategy;
  o oral administration as a key component of pain management in most patients with persistent medical illness;
  o regular administration of analgesics ("by the clock") combined with a rescue strategy for breakthrough and intermittent pain;
  o individualised therapy;
• The necessity to monitor and evaluate for therapeutic and adverse effects;
• The need to prevent unwanted effects;

This section should focus on medicinal therapy: non-opioid medicines, opioid analgesics, co-analgesics and adjuvant medicines, rescue doses, routes of administration, efficacy, safety (including risks), cost effectiveness, limitations, benefits, side effects and their prevention.

F. Specific opioid issues

There are a number of topics that are specific for opioids, including:
• When to start opioids? When to try stopping or reducing them? When to try to introduce an alternative?
• How to find the right dosage of opioids?
• When the times comes to discontinue opioid use, how to taper dosing to avoid opioid withdrawal?
• How to switch between opioids in a clinical setting?
• How to identify patients who have become tolerant to opioid treatment?
• If appropriate, how to organize a “medicines holiday” as a strategy to treat tolerance phenomena?
• How to supervise opioid treatment?
• How to recognize opioid hyperalgesia?

Chronic use of opioids might result in opioid dependence syndrome. Therefore, how to prescribe opioids in such a way as to minimize problems including;
• How to identify patients at risk of abusing opioids prior to the commencement of treatment?
• How to identify patients at risk of opioid dependence prior to the commencement of treatment?
• How to identify patients who have developed opioid dependence syndrome while using prescribed pain medicines chronically? How to treat pain in patients who have developed opioid dependence syndrome or who have a history of opioid dependence syndrome.

G. System issues

The content of this section should flow from the evidence-based recommendations in the treatment section, as well as evidence sought and appraised in response to the systems questions 23-26 (see below).

This section should include:
• A specific recommendation (which flows from the treatment recommendations) listing the key medicines which should be available for pain relief at primary, secondary and tertiary levels;
• Guidance on cost-analysis of the health system inputs that are required in order to achieve the critical outcomes for this patient population;
• A recommendation on the skills required to prescribe and dispense treatment to adults with chronic pain related to cancer, HIV/AIDS, other life threatening illnesses and non-malignant conditions;
• A statement about the safeguards that are useful to enable opioids to be safely and reliably administered to those who require them for effective pain control;
• How health systems should balance the availability of prescription opioids for pain while preventing opioid dependence and diversion.
• Key policy, legislative and regulatory issues that ensure opioid availability across all levels of care, including:
  o a statement that recognizes the need to ensure opioids availability for medical and research purposes;
  o the facts and myths associated with opioid tolerance and dependence, including the barriers imposed by inappropriate use of terminology, e.g. opioid dependence, opioid tolerance;
o how to establish determinants for increased risk that a patient could divert controlled medicines;
o what safeguards exist for minimizing the risk of diversion of controlled medicines.

All recommendations should be based on evidence sought and appraised in response to clinical questions 1–25 (see below).

I. Annexes

- Selection of frequently used pain scales measuring pain intensity and pain relief, including those which are particularly suitable for specific groups, e.g. patients with dementia, learning disability, adolescences etc;
- Opioid analgesic conversion table;
- Oral-parenteral conversion table;
- Opioid analgesic half-life table;
- Pharmacological profiles for selected medicines (opioid analgesics, non-opioid analgesics and optionally adjuvant medicines and opioid antagonists);
- Background to the clinical recommendations;
- Background to the health system recommendations;
- Evidence tables (GRADE) for treatment and other background materials;
- Research agenda;
- Opioid analgesics and the international conventions;
- List of contributors, including external partners, provisional list of members of the WHO steering group, list of the Guidelines Development Group, list of members of the External Review Group.

R. Other elements to include

- Summary of principles and recommendations;
- Acknowledgment of contributors and donors;
- References;
- Additional Reading;
- Glossary;
- Abbreviations and Acronyms.

CLINICAL QUESTIONS

For the development of the guidelines, evidence should be sought, critically appraised and synthesized before recommendations are formulated in response to these questions. Each question and its related sub-questions should lead to a specific recommendation. For gathering evidence, a separate search needs to be carried out for adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain.
The outcomes that should be considered during evidence retrieval, evaluation and synthesis for each of the questions below include: effectiveness of pain reduction, speed at which pain relief may be achieved, maintenance of pain relief, functional capacity, effect on quality of life and adverse effects, and complications of treatments/interventions.

The relative importance of each of these outcomes will depend on the clinical question being addressed. For management of chronic pain - quality of life, functional capacity, potential severe adverse effects are the most important. Also important is the time frame of outcomes. For chronic pain, the time frame of outcomes should be in the medium to long term if possible (i.e. months, not weeks).

A risk/benefit profile would then need to be prepared for each question. Each question and its related sub-questions should lead to a specific recommendation. Separate recommendations may be required for specific aetiologies and age groups if the evidence is found to support these.

The clinical and health systems questions were initially developed by Dr Bee Wee in collaboration with the WHO Secretariat in 2007/2008. They were reviewed by the WHO Steering Group on Pain Guidelines, then by the Expanded Review Panel. They were presented in two separate scoping documents (one on non-malignant and one on malignant pain), which were approved by the Guidelines Review Committee in 2008. Already at the time of submission to the GRC it was mentioned that both scoping documents would serve for the development of one single guideline. After having developed the WHO Guidelines for the pharmacological treatment of persisting pain in children with medical illnesses, there were several reasons for updating the existing scopes:

- Initial clinical questions needed reformulating in order to reflect better the PICO format
- The need of having one single scoping document
- Inclusion of some other aspects in the document

After the two scoping documents were merged and updated, the new document was reviewed again by the WHO Steering Group on Pain Guidelines and then by approximately 15 external reviewers in Autumn 2011. Comments received were implemented and the document was approved by the Steering Group, followed by a submission to the GRC in January 2012. After addressing the concerns of the GRC as expressed in it minutes of 18 April 2012, the document was revised and then approved by the Steering Group for resubmission.

The current revision addresses the re-wording of the clinical questions, with a view on reducing the number of resulting PICO questions. However, in the context of development of a total of three guidelines on the pharmacological treatment of pain that together need to cover all types of pain, a further reduction is considered not to be helpful for improving access for patients to pain management. Therefore, the current

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2 The WHO Guidelines Review Committee approved this scoping document in August 2012.
clinical and health-systems questions, although reduced from 31 to 22, are still large in number, but this is considered to be the bare minimum for these guidelines.

Use of opioids in the treatment of chronic pain

1. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the use of morphine compared to non-opioid analgesic medicines in order to achieve rapid, effective, sustained and safe pain control?

2. In patients with chronic pain related to advancing and end-stage disease, what is the risk of hastening death when strong opioids are properly prescribed for pain control as compared to a similar group of patients who are not taking opioids?

3. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence that the use of opioids can impact a person's quality of life, disability and long term pain when taken for prolonged periods in terms of efficacy, adverse effects and cost-benefit in order to achieve and maintain rapid, effective and safe pain control as compared to a similar group of patients who are taking non-opioid analgesics?

4. In the management of pain in adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for establishing determinants for patients that have an increased risk of developing dependence syndrome on opioid medicines?

5. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, who have a history of dependence (on opioids or other substances), what is the evidence for treating patients with opioids compared to treating with non-opioid medicines for effective and safe pain control?

Analgesic ladder

6. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for using the 2-step analgesic ladder compared to the 3-step analgesic ladder? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

7. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence to support the use of paracetamol as compared to aspirin or other non-steroidal anti-inflammatory medicines (NSAIDs) at each step of the analgesic ladder in terms of benefit against adverse effects in order to achieve and maintain rapid, effective and safe pain control?
8. If the evidence supports the continuing use of a 3-step analgesic ladder, what is the evidence to support the use of codeine as compared to tramadol at step 2 of the analgesic ladder, in terms of benefit balanced against adverse effects such as constipation, nausea and vomiting, sedation, confusion and adverse effects and interactions? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

9. In patients with pain related to low back pain, other orthopedic pain and fibromyalgia, what is the evidence to support the use of flupirtine, in comparison to the use of other non-opioid analgesics (in NSAIDS) in terms of efficacy, adverse effects and cost-benefit? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

**Choice of strong opioids**

10. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence to support the use of morphine as a gold standard for strong opioids, in comparison to the use of other strong opioids (in particular fentanyl, hydromorphone, oxycodone and methadone) in terms of efficacy, adverse effects and cost-benefit? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

11. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant moderate and severe pain, what is the evidence for a pharmacotherapy regimen that includes opioid rotation as compared to continuing use of one opioid? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

**Administration of opioids**

12. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the benefit of administering modified-release morphine regularly as compared to immediate-release morphine on a 4-hourly or as required basis? Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

13. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the benefit of using immediate-release morphine as the top-up as-required analgesic of choice (in addition to regular background analgesia), as compared to other strong opioids (in particular
fentanyl, hydromorphone, oxycodone and methadone) in order to maintain effective and safe control of episodic or breakthrough pain?

14. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the benefit of using the oral route versus transdermal administration of opioids?
Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

15. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the benefit of using
a. subcutaneous versus intramuscular;
b. subcutaneous versus intravenous;
c. transdermal versus intramuscular;
d. transdermal versus intravenous administration of opioids, when the oral route for opioids is unavailable (e.g. patients with diminished consciousness, ineffective swallowing or vomiting)?
Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

16. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the recommendation that a double dose of immediate-release morphine be given at bedtime for those taking 4-hourly immediate-release morphine during the day compared to single dose before bedtime and waking up during the night for the next single dose as their regular analgesic in order to maintain effective and safe pain control through the night?

Co-analgesic and adjuvant medicines

17. In adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what is the evidence for the use of:
   a. steroids
   b. cannabinoids
   c. muscle relaxants such as diazepam and baclofen
   d. amitryptiline, other tricyclic antidepressants and SSRIs
   e. first generation anti-epileptics such as carbamezapine or sodium valproate
   f. second generation anti-epileptics, such as gabapentin
   g. N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. ketamine)
   h. systemic local anesthetic agents
   i. antiarrhythmic agents
   as compared to placebo, to each other and with and without combining with strong opioids in order to achieve and maintain effective and safe pain control?

18. In adult (including elderly) and adolescent patients with bone pain related to chronic malignant and non-malignant pain what is the evidence for the use of:
   a. non-selective NSAIDs

b. bisphosphonates
c. radioactive isotopes

as compared to placebo and to each other, and in which specific subsets of patients, in order to achieve rapid, effective and safe control of bone pain?

HEALTH SYSTEMS QUESTIONS

19. In the management of pain in adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what evidence is there to support the practice of shifting the task of prescribing, titrating and monitoring analgesics from medically-qualified professionals to other health care professionals at different levels of care. Consider how to achieve rapid, effective and safe pain control in the short term, and how to maintain effective and safe pain control in the long term.

20. In the management of pain in adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what are the safeguards that need to be in place for the successful introduction of the practice of task-shifting, in particular training and continuing supervision, and what resources are required to provide and maintain these safeguards?

21. In the management of pain in adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what evidence is there about the level of pain management that can be provided at the primary care or generalist level, as compared to specialist level, in order to ensure that rapid, effective and safe pain control can be achieved for all those who need it?

22. In the management of pain in adult (including elderly) and adolescent patients with chronic malignant and non-malignant pain, what are determinants for an increased risk that a patient will divert controlled medicines and what safeguards exist for the prevention of diversion (including monitoring and control of prescribing and dispensing)?

WORKING METHODS AND PLANNING

A. Collaborators

The guidelines will be developed in collaboration with the following individuals or groups:

- WHO Steering Group
  
  Marco Antonio de Avila Vitoria  
  John Roland Beard  
  
  HTM/HIV/TACHIV/AIDS  
  FWC/ALC

Florence Bitalabeho  
Meena Nathan Cherian  
Tarun Dua  
Lulu Mussa Muhe  
Vladimir B. Poznyak  
Willem Karel Scholten (Chair)  
Maria Cecilia Sepulveda Bermedo

- Guideline Development Group
  A provisional membership list with analysis of its composition is included in Annex 1

- External Review Group
  A provisional membership list with analysis of its composition is included in Annex 2

- External Partners
  WHO is working with support of interns and volunteers from various universities on the development of the guidelines, e.g. a health-technology assessment student from Radboud University, Nijmegen, the Netherlands, will work for five months on evidence retrieval and so will a qualified Yale Medical School student for one year. He will be coached by his professor, who was a member of the WHO Guidelines Development Group on treatment of substance dependence.

  Dr Philip Wiffen, a methodologist experienced on GRADE and on opioid analgesics, will be contracted to perform the evidence-retrieval subject to the availability of funding. He is also listed as a member of the Expanded Review Panel and the Guidelines Development Group.

  Various donor organizations who contributed financially to the development of the WHO Guidelines on the pharmacological treatment of persisting pain in children with medical illnesses will be invited to contribute again and so will other organizations be invited. The guidelines will be developed with the expertise of many specialists on an individual basis. However, these specialists will be identified with the help of NGOs in official relations with WHO, like the International Association for the Study of Pain (IASP), the International Association for Hospice and Palliative Care (IAHPC), the Federation internationale pharmaceutique (FIP) and the Union for International Cancer Control (UICC). Other NGOs may be involved as needed.

B. Sources of Funding

For the development of guidelines on persisting pain in adults, various potential donors have been approached. [Two international organizations] consider to provide all the necessary funding for this guideline and the guideline on acute pain. Furthermore the cluster is actively seeking the support of governments either through a secondment or through financial contributions.

For the continuation of the project, the ACMP and the departmental officer responsible for fundraising are actively raising funds for the further development of pain treatment guidelines.
Like it was the case with the pediatric persisting pain guidelines, it is expected that over the years additional grants will be received. The recent on-line publication of the pediatric persisting pain guidelines triggered the donation of the funds for printing and for a Spanish translation. Similarly, it is expected that this publication will show other donors what they may expect from the effects of a donation to WHO for the development of adult pain guidelines. Such a donation will also allow the employment of a dedicated staff member for the development of these pain guidelines.

C. Budget

**Budget: (present-summer 2014)**

<table>
<thead>
<tr>
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D. Management of Guidelines Development group

- Declaration of interests
Declaration of interests documentation will be performed during March- July 2012. The task will be undertaken by an Access to Controlled Medicine intern supervised by the Team Leader, Access to Controlled Medicines.

- Potential conflicts of interest
All consultants, experts and contributors involved in the development of the guidelines will be requested to declare any conflicts of interest. The management of conflicts of interest will be a key task throughout the process, with particular attention for the appraisal of evidence, the formulation of recommendations and the external peer review process of the drafted guidelines. Owners, co-owners and members of advisory boards of pharmaceutical companies will be excluded from Expanded Review Panel and Guidelines Development membership and from pertinent participation to other parts of the development process. Furthermore, individuals found to have another conflict of
interest, financial or non-financial, will be excluded from participation on any topics where interests are conflicting. There will be an agenda item "Conflicts of Interests" at the beginning of the Guidelines Development Group meeting. Relevant declared conflicts of interest of Guidelines Development Group members will be mentioned in the guidelines publication as well as their handling.

- Decision making

WHO policies on conflicts of Interests will be fully applied. Initially the evidence on each clinical and systems question will be retrieved under the Secretariat's responsibility. The documentation will be reviewed according to the GRADE methodology. The Expanded Review Panel will be requested to verify if any relevant publications are missing. This panel, consisting of around 80 members, will not convene as a group, but be requested to give its input by e-mail. The updated evidence will be presented to the Guidelines Advisory Group, together with a draft for the guidelines book and the draft recommendations as prepared by the Secretariat based on the available evidence. The GDG will convene for several days (up to a full week) and will first decide on the content of the final recommendations and for each recommendation discuss its wording. This will be a consensus process. Then, the draft will be finalized and edited. After editing, the chair of the GDG will be requested to declare if he agrees with the manuscript and thereafter it will be submitted to the GRC for clearance. Any decisions on changes on the content to be made after the meeting of the GDG will be taken in consultation with the GDG Chair, who will also be requested to endorse the edited document before typesetting. The GDG is considered to be the decisive authority for the content of the guidelines.

E. Assessment of the available evidence

A comprehensive search will be performed through the following databases: PubMed (including MEDLINE), EMBASE (accessed via OvidSP), and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategies will combine both text words and MeSH/EMTREE terms. In addition to this search strategy, the reference lists of the included reviews and papers will be checked, as well as articles listed in the 'Related Article' option in PubMed and the 'Find Similar' option in Ovid. Papers identified by the search strategy will be screened for inclusion based on title and then on abstract. Full text will be reviewed in the absence of an abstract, and for trials with eligible abstracts. The systematic review will be based on the GRADE methodology. This system is a widely used approach to separate the quality of evidence from the strength of recommendations. It is adopted by the Cochrane Collaboration and WHO as a standardized approach for developing systematic reviews and recommendations. GRADE tables will summarize specific details about the studies included, such as study outcomes, limitations, possible inconsistency, indirectness, imprecision and other factors that might change the quality of evidence. Based on that, the overall quality of evidence will be defined as very low, low, moderate, or high. (see table below).
Definition of quality of evidence according to the GRADE methodology:

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<th>Description</th>
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</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on confidence in the estimate of the effect and may change the estimate.</td>
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<tr>
<td>Low</td>
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<tr>
<td>Very low</td>
<td>Any estimate of effect is very uncertain.</td>
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F. Timeline

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<tr>
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<td>Review of evidence used by individual ERP Members</td>
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G. Presentation and Dissemination of the Guidelines

Guidelines will be available online at the WHO Library database with a webpage at the Access to Controlled Medicines pages referring to this (these) links. The publication will also be announced in the WHO Access and Control Newsletter (> 2000 subscribers) and organizations with whom we are working will be requested to copy the announcement in their newsletters.

The guidelines package will be distributed in print to WHO sales agents, subscribers to WHO publications, to the WHO mailing list for mandatory free distribution (national chief health executives, ministers of health or directors-general of health, depository libraries for WHO publications, WHO representatives/liaison officers, WHO/HQ library, WHO Regional Offices and off-site offices libraries), additional non-mandatory free recipients (competent national authorities for drug control treaties, national centres for the WHO International Drug Monitoring Programme, medicines regulatory authorities), WHO Staff in HQ and elsewhere, relevant NGOs in official relations with WHO (including: Médecins sans Frontières, International Federation of Pharmaceutical Manufactures & Associations, International Pharmaceutical Association FIP, World Organization of Family Doctors, International Council of Nurses (ICN), the European Society for Medical Oncology, the International Association for Hospice and Palliative Medicine).
Care), scientific journals (including general medical journals and journals specialized on pain, palliative care, oncology and nursing), international organizations (including the International Narcotics Control Board, the United Nations Office on Drugs and Crime and the UN Special Rapporteur for the Right to Health); NGOs not in official relations with WHO (e.g. Human Rights Watch, Help the Hospices (HtH), the African Palliative Care Association, Douleurs sans Frontières, and the Worldwide Palliative Care Alliance) as well as donors, potential donors, potential publishers of translated versions, and all those who contributed to the documents.

Conference invitations to discuss and present the guidelines will be accepted.

Initially, the guidelines will be available in English only and translations will be developed subject to the availability of funding. Translation into non-UN languages and publication in these languages by third parties will be encouraged.

H. Quality Assessment of Guidelines

It is predictable that there will be insufficient evidence for a number of the clinical questions. For that reason a research agenda is foreseen. Based on that research agenda, a call will be published to work on these topics. In that way, chances are increased for having more evidence available when updating the guidelines around five years after the publication of the current planned guidelines.

Furthermore, the number of downloads from the WHO website and the sales of printed copies can be measured. The number of translations by third parties is also an indication of the impact that others expect that the guidelines will have.
GLOSSARY

Adolescent: a person from 10 to 18 years of age.

Adjuvant analgesic: medicine which has a primary indication other than pain, but is analgesic in some painful conditions. This excludes medicines administered primarily to manage adverse effects associated with analgesics, such as laxatives and anti-emetics.

Analgesic (medicine): medicine that relieves or reduces pain.

Breakthrough pain: temporary increase in the severity of pain over and above the pre-existing baseline pain level.

Controlled medicines: medicines that contain controlled substances.

Dependence syndrome: a cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use, and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, and a higher priority given to drug use than to other activities and obligations. (ICD-10 definition.)

Neuropathic pain: pain caused by structural damage and/or nerve cell dysfunction in either the peripheral or central nervous system (CNS). Pain is persistent even without ongoing stimuli.

Pain assessment tools: tools used to assess pain intensity or, in addition, other features of pain such as location, characteristics, frequency. Pain intensity measurement tools are often referred to as pain scales. Alternative terms are pain assessment instrument, method or measure.

Pain intensity: term is used interchangeably with pain severity and referring to the level of pain experienced and reported by the patient.

Pain severity: term is used interchangeably with pain intensity and referring to the level of pain experienced and reported by the patient.

Persisting pain: term as used in this scoping document intended to cover long-term pain related to medical illness, for example pain associated with major infections (e.g. HIV), cancer, chronic neuropathic pain (e.g. following amputation).

Somatoform pain disorders: the occurrence of one or more physical complaints for which appropriate medical evaluation reveals no explanatory physical pathology or pathophysiological mechanism, or, when pathology is present, the physical complaints or resulting impairment are grossly in excess of what would be expected from the physical findings. Pain disorder is one of the somatoform disorders.
Switching of opioids: for the purposes of this scoping document, switching of opioids is defined as the clinical practice of changing to an alternative opioid because of dose limiting side effects and/or lack of analgesic effect.

Rotation of opioids: for the purposes of this scoping document, rotation of opioids is defined as the clinical practice of changing between different opioids in a set schedule, not in response to a clinical problem, such as a side effect, but as a preventive measure to limit future potential side effects and dose escalation in patients that are anticipated to require long-term opioid therapy.

Tolerance: a reduction in the sensitivity to a pharmacological agent following repeated administration. As a consequence, increased doses are required to produce the same magnitude of effect.

ABBREVIATIONS AND ACRONYMS

- **DALY**: Disability-adjusted Life Years
- **EAPC**: European Association of Palliative Care
- **ERP**: Expanded Review Panel
- **HIV/AIDS**: Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
- **IASP**: International Association for the Study of Pain
- **NMDA**: N-Methyl-D-Aspartate
- **NSAID**: Nonsteroidal anti-inflammatory medicines

REFERENCES

1. WHO normative guidelines on pain management. Report of a Delphi Study to determine the need for guidelines and to identify the number and topics of guidelines that should be developed by WHO. Report prepared by Prof Neeta Kumar, WHO Geneva, 2007.


ADDITIONAL READING


ANNEX 1: Provisional composition of the Guidelines Development Group

<table>
<thead>
<tr>
<th>Family name</th>
<th>Nationality</th>
<th>WHO Region</th>
<th>M/F</th>
<th>Profession</th>
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For privacy reasons not listed in the published scoping document. The guidelines will acknowledge those who actually contributed to the guidelines.

Final invitations subject to active contributions during the earlier stages of the development process. Experts not active on the work of the Expanded Review Panel will be replaced with active members with similar specialties, taking into consideration gender and regional balance.

Analysis:

**Gender Balance**

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<td>F</td>
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**By Expertise**

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Total > total membership because of doubles

**Regional Balance**

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ANNEX 2: Provisional Composition of the Expanded Review Panel

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For privacy reasons not listed in the published scoping document. The guidelines will acknowledge those who actually contributed to the guidelines.

* invited (all others accepted)
** Declaration of Interest needs further investigation

Analysis:

### Gender Balance

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Total > total membership because of doubles

**Regional Balance**

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