Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain

Part A: Executive Summary and Background
Part B: Recommendations for Practice

PART A

— Executive Summary and Background —

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NOTES:

- Throughout this document, *Canadian Guideline* (italicized) refers to "Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain."
- Numbering of Tables and Figures
  Tables and Figures are numbered to correspond with the associated section in Part A, and the associated recommendation in Part B, e.g.,
  - Table A-10.3 is located in Part A, section 10.3.
  - Table B-12.1 is located in Part B, under Recommendation 12.
- Acronyms used in Part A:
  CNCP = chronic non-cancer pain
  CPG = clinical practice guideline
  CPSO = College of Physicians and Surgeons of Ontario
  CPSA = College of Physicians & Surgeons of Alberta
  FMRAC = Federation of Medical Regulatory Authorities of Canada
  MRA = medical regulatory authority
  NAP = National Advisory Panel
  NOUGG = National Opioid Use Guideline Group
  RCT = randomized controlled trial.
- The complete reference list is located in Part B.

Executive Summary

Impetus for the *Canadian Guideline*

Canadian medical regulatory authorities undertook guideline development in response to:

1) physicians and other stakeholders seeking guidance regarding safe and effective use of opioids
2) a growing concern about opioid misuse creating patient and public safety issues, and
3) the lack of systematically developed national guidelines on opioid use for CNCP.

In November 2007, the **National Opioid Use Guideline Group** (NOUGG) formed under the umbrella of the Federation of Medical Regulatory Authorities of Canada (FMRAC) with support and/or representation from all provincial and territorial medical regulatory authorities (MRA). NOUGG's aim was to oversee the development and implementation of a guideline *to assist physicians in managing patients with CNCP by prescribing opioids in a safe and effective manner.* To achieve its aim, NOUGG established objectives:

1) develop a national guideline for safe and effective opioid use for CNCP that relies on the best available evidence and expert opinion consensus
2) develop and implement a knowledge-transfer strategy that ensures transition of the national guideline to practice as a useful decision-making tool for physicians who treat CNCP patients
3) evaluate the transfer of knowledge impact on practice
4) find a permanent home for the national guideline to ensure currency and ongoing transfer of evidence to practice
5) report on the project as a model for MRAs national collaboration.

NOUGG Principles

NOUGG's work in developing the "Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-cancer Pain" (*Canadian Guideline*) was shaped by the following principles and values.

- **Treatment of pain:** Patients deserve to have their chronic pain treated. Opioids can be a useful and appropriate treatment option. Harms associated with opioid use can be reduced when 1) drugs are prescribed and monitored with knowledge of the patient's history and risks, 2) patients understand potential benefits and harms and participate in reducing harms, and 3) clinicians assess outcomes for both effectiveness and harms.
- **Evidence**: Effective national guideline development requires rigorous methods to 1) search, appraise, and synthesize the best available evidence, and 2) create a national consensus of expert opinion to provide guidance where evidence is not available or insufficient.
- **Collaboration**: Collaboration among Canadian physician organizations and other key stakeholders is central to the development and implementation.
- **Autonomy**: The *Canadian Guideline* will be free from commercial bias from the pharmaceutical industry and any other commercial entities.
- **Clinician and Patient Input**: Practicing physicians from multiple disciplines, other healthcare providers, and patients all have defined roles in the formulation and ongoing evaluation.
- **Practice Improvement**: The *Canadian Guideline* is intended to educate/inform clinicians and to assist and guide practice decisions. Although MRAs oversaw the development, it is not intended for use as a standard of practice.
- **Implementation**: An implementation strategy will incorporate evidence-based principles of knowledge transfer and continuing professional development.
- **Practice Resources**: User-friendly resources, freely accessible to all, will enhance implementation to practice.

NOUGG Resources

NOUGG assembled key resources to meet its objectives.

A **Research Group** comprising a physician/epidemiologist, four physician-researchers, and a research librarian was responsible for the literature review, quality appraisal, evidence summary, and the first draft of recommendations. A **National Advisory Panel** (NAP) comprising 49 individuals was structured to reach consensus and advise on recommendations. Recruitment criteria included representation from across Canada, the target audience, other healthcare providers, patients with CNCP, clinical expertise, and academia. NAP used a Modified Delphi technique to reach consensus on recommendations for practice, and also provided open-ended narrative comment used in iterative revision.

The **National Faculty** comprising approximately 35 people (representing 9 provinces, 1 territory, and 8 national associations) held their inaugural meeting in June 2009 with a goal to guide and assist NOUGG with implementing the *Canadian Guideline* to practice.

NOUGG Outputs

In total, 6,580 studies were identified from the literature; from this search, 184 met inclusion criteria and were used to create 49 draft recommendations. The National Advisory Panel critically examined these 49 recommendations. With their direction, consensus was built to finalize 24 practice recommendations that were organized into five clusters:

1. Deciding to Initiate Opioid Therapy
2. Conducting an Opioid Trial
3. Monitoring Long-Term Opioid Therapy (LTOT)
4. Treating Specific Populations with LTOT
5. Managing Opioid Misuse and Addiction in CNCP Patients.

The *Canadian Guideline* includes tools intended to assist busy clinicians in decision making.

Throughout development, NOUGG engaged with various academics to find a permanent home for the *Canadian Guideline.* McMaster University's Michael G. DeGroote National Pain Centre assumed responsibility for keeping the *Canadian Guideline* current, working collaboratively with national partners and alerting clinicians to new evidence.

NOUGG's Message to Users

The number of patients with CNCP is significant and growing. Responsibility for care of these patients should rest with primary-care providers who use consultation/referral for specialized input selectively. With this in mind, the intent of the *Canadian Guideline* is to improve comfort and confidence in using opioids for CNCP among clinicians, particularly primary-care providers, while preserving patient and public safety. To achieve these ends, recommendations and practice tools are both supported by the best available evidence or expert opinion consensus, and also feasible in day-to-day practice.

Funding

All funding to support the development of the *Canadian Guideline* was provided by Canadian medical regulatory authorities and the Federation of Medical Regulatory Authorities of Canada. The Canadian Institute of Health Research (CIHR) provided a one-time grant to support two meetings of the National Faculty who are focused on implementation. The project received no funding from commercial organizations.

Part A: *Canadian Guideline* Background

1. Core Concepts

Many contributors engaged in developing the *Canadian Guideline*:

- Canadian medical regulatory authorities were responsible for the initiation and oversight.
- A Research Group searched, appraised, and synthesized the evidence into recommendations.
- A National Advisory Panel reviewed, critiqued, and reached consensus on the recommendations.
- A National Faculty continues to assist with building a plan for active implementation.
- McMaster University created the Michael G. DeGroote National Pain Centre that will assume responsibility for keeping the *Canadian Guideline* current, working collaboratively with national partners and alerting clinicians about new evidence.

Through the countless hours of research, writing, reviewing, revising, discussing, and debating that culminated in this *Canadian Guideline*, the notion of a common ground at times seemed elusive. Even though the landscape of chronic non-cancer pain management appeared to be characterized more by differences of opinion and divergent views than consensus, a common ground that contributors *do* share emerged from this collaborative process. It seemed a fitting beginning to describe the core concepts that represent contributor's values and beliefs:

1. Patients with chronic pain have a right to be treated.
2. Opioids can be an effective treatment for chronic non-cancer pain (CNCP) and should be considered.
3. Opioids are not indicated in all CNCP conditions, and medication alone is often insufficient to manage CNCP; other effective treatments should also be considered.
4. Opioid use does present risks and potential harms — prescribers and dispensers have an obligation to assess risks and minimize harms.
5. Not enough is known about the long-term benefits, risks, and side effects of opioid therapy; more research is needed in these areas.
6. Many clinicians can play a role in managing CNCP; patient care is improved with good communication and collaboration between clinicians across disciplines within primary care, and between primary care and specialty care.
7. Guidelines are necessary but not sufficient to change practice — guidelines need to be actively implemented to practice and supported with useful, easy-to-use tools.
8. Across Canada, systemic barriers exist that could reduce *Canadian Guideline* compliance. Implementation efforts should include raising awareness with multiple-system stakeholders about the role they can play in improving the effectiveness and safety of opioid prescribing.
9. Guidelines provide information and recommendations but are not to be considered training manuals. Some recommendations in the *Canadian Guideline* may require some clinicians to acquire specific knowledge and skills.
10. Overdose, addiction, and opioid diversion are problems associated with opioid use — striking a balance between effective treatment of chronic pain and preventing harms is a challenge.
11. Patients have an important role to play in ensuring opioids are used safely. Implementation should include education of patients and the general public about the potential benefits and harms of opioids and their role in using opioids safely and effectively.

2. Funding

All funding to support the development of the *Canadian Guideline* was provided by Canadian medical regulatory authorities and the Federation of Medical Regulatory Authorities of Canada. The Canadian Institute of Health Research (CIHR) provided a one-time grant to support two meetings of the National Faculty who are focused on implementation. The project received no funding from commercial organizations.

3. Scope

The *Canadian Guideline* is intended to assist physicians with decisions to initiate appropriate trials of opioid therapy for patients with chronic non-cancer pain, to monitor long-term opioid therapy, and to detect and respond appropriately to situations of opioid misuse including addiction. It was not designed to serve as a standard of care nor as a training manual.

The document addresses safe and effective prescribing of opioids for CNCP (defined as pain that persists for more than six months) in male and female adolescents and adults. The target audience is primary-care physicians and medical and surgical specialists who manage patients with CNCP. Pharmacists, nurses, and dentists may also find it useful. The scope does not include using opioids for acute pain and end-of-life pain, or CNCP treatment modalities and approaches other than opioids.

4. Limitations

The *Canadian Guideline* is constrained by the paucity of evidence to support most of the topics where recommendations for practice were considered necessary and relevant. This required a heavy reliance on the opinion and expertise of the National Advisory Panel to develop recommendations. The literature searches for observational studies used broad terms and might have missed relevant studies. Of the 184 studies used to support the recommendations, only 62 were randomized trials; the remaining were observational studies. Given that the quality of the observational studies was not formally assessed, the grading system of the Canadian Task Force on Preventive Health Care (CTFPHC) was adapted (Woolf 1990).

Another limitation of the published evidence was that functional outcomes studied were predominantly “activity of daily living” and “quality of life” — other important outcomes such as return to work, productivity, and cognitive impairment were rarely reported. Potential long-term complications of opioid use (hypogonadism, opioid-induced hyperalgesia, addiction) cannot be ruled out even if the recommendations are strictly followed.

It addresses only one modality for managing CNCP — opioid therapy, and it does not discuss or provide guidance about selecting other options.

An attempt was made to maintain national perspective but NAP pointed out numerous instances where recommendations were dependent on access to resources not available in all parts of Canada (e.g., access to pain or addiction specialists, multi-disciplinary pain management teams, prescription-monitoring databases).

In spite of its narrow focus, it is a lengthy and detailed document, and will need to be translated into feasible and practical tools for day-to-day use by busy practitioners. Screening tools, e.g., the Opioid Risk Tool, are only valid when the patient’s reporting is accurate.

Finally, the group overseeing guideline development (NOUGG) represents medical regulatory authorities, and this could create concern that the *Canadian Guideline* will be used as a standard of practice rather than for its intended purpose as advice to assist physicians.

5. *Canadian Guideline* Inception

In 2000, the College of Physicians and Surgeons of Ontario (CPSO) released "Evidence-based Recommendations for Medical Management of Chronic Non-Malignant Pain," which was accepted by the Ontario Guidelines Advisory Committee as its recommended guideline for chronic pain management. This document was completed by a CPSO-appointed task force of physicians with expertise in pain management. The topics included chronic headache, migraines, neuropathic pain, opioid management for chronic non-malignant pain, and chronic musculoskeletal pain. In 2007, the task force co-chairs recommended updating the 2000 guideline. It was agreed that completing a methodologically rigorous update of all the sub-topics in the 2000 guideline was beyond the resources and the scope of the College's mandate. However, CPSO agreed that one section, the use of opioids for chronic non-malignant pain, presented a pressing problem in practice and should be revised and further developed.

At the same time, other Canadian medical regulatory authorities (MRAs) were meeting to discuss issues of common interest and it became evident that Colleges across Canada shared the need to provide physicians with guidance on prescribing opioids for CNCP. In response, Canadian MRAs created the **National Opioid Use Guideline Group** (NOUGG) to oversee the development and implementation of a guideline for safe and effective opioid use for CNCP. NOUGG is a unique collaboration of MRAs with the active support and/or representation from **all provincial Colleges, Yukon Medical Council, Government of Nunavut,** and the **Federation of Medical Regulatory Authorities of Canada** (FMRAC). See Appendix A-1 for NOUGG members.

NOUGG's primary aim was *to assist physicians in managing patients with CNCP by prescribing opioids in a safe and effective manner.* Three key goals were to:

- facilitate development of a national evidence-based guideline
- implement the guideline to clinical practice, and
- find a permanent home for the guideline to ensure the evidence remains current and useful.

From the outset, NOUGG grappled with the notion that creating clinical practice guidelines (CPG) is a task traditionally, and probably best, left to researchers, academics, and clinicians. MRAs do, however, have a central mandate to regulate the practice of medicine in the pubic interest that includes a responsibility to provide guidance and contribute to ensuring the quality of practice.

At its annual June 2008 meeting, FMRAC discussed the regulators' role in creating CPGs, citing NOUGG's work as a case in point. It was reasoned that, ideally, CPGs are created by clinical/research groups, but the topic of opioid prescribing met the requisites of a "special case," in that:

- No academic body can be clearly identified to take responsibility.
- The topic extends beyond clinical care into other areas, e.g., criminality, professional conduct.
- Societal impacts are significant.
- MRAs have a unique role to play in implementation.
- Membership or other stakeholders are requesting MRAs participation.

With the FMRAC meeting confirmation, NOUGG's work began. Two NOUGG co-chairs convened monthly meetings to facilitate and oversee the development and implementation.

6. Players Involved in Development

Three groups were involved in developing the *Canadian Guideline*: National Opioid Use Guideline Group (NOUGG), Research Group, and National Advisory Panel (NAP).

6.1 National Opioid Use Guideline Group

NOUGG is a task-specific group convened with the assistance and support of FMRAC. It was formed in November 2007 with support and/or representation from all provincial medical regulatory authorities and subsequently the Medical Council of Yukon and the Government of Nunavut. NOUGG's role was to oversee the development and implementation of a guideline. The regulatory bodies and FMRAC appointed the Group members, and two co-chairs were selected. FMRAC provided funding over a 12-month period to support work of the two co-chairs. For NOUGG members, see Appendix A-1.

6.2 Research Group

The Research group comprised six members: a physician/epidemiologist, four physician-researchers, and a research librarian. It was responsible for the literature review, quality appraisal, evidence summary, and the first draft of recommendations for practice. Two physician-researchers were previous members of the CPSO task force responsible for the predecessor guideline, "Evidence-based Recommendations for Medical Management of Chronic Non-Malignant Pain." The physician/epidemiologist, research librarian, and one physician-researcher were secured from the Institute for Work & Health, which has a systematic review program of research that includes the Cochrane Back Review Group. NOUGG approached IWH, and they agreed to contribute their expertise to oversee the systematic review process from literature search to data extraction. See Appendix A-2 for Research Group members and for information on the Institute for Work & Health.

6.3 National Advisory Panel

NAP is a group of 49 individuals from across Canada who were invited in September 2008 to participate in the *Canadian Guideline* development. They were identified by NOUGG members, using common selection criteria to ensure the group included a wide cross-section of medical expertise, patient perspectives, other healthcare providers, and geographic representation. NAP's role was to review draft materials prepared by the Research Group and, using a Modified Delphi technique, reach consensus on recommendations for practice. In addition, NAP members provided extensive narrative comment that was organized by theme and used in iterative revision. See Section A-11 for a more detailed explanation of NAP and Appendix A-3 for members.

7. Epidemiology of Chronic Non-cancer Pain (CNCP)

CNCP is a major problem in modern society. The negative effects on quality of life and productivity have an immense social and economic impact.

Chronic pain in persons older than 65 years of age is a significant problem for Canada. A recently published study (Ramage-Morin 2009) used data from 1) the Health Institutions and Household components of the "National Population Health Survey" (NPHS; Statistics Canada 1994/1995 through 2002/2003) and 2) the 2005 "Canadian Community Health Survey" (CCHS). Thirty-eight percent of institutionalized seniors experienced pain on a regular basis, compared with 27% of seniors living in households. In both populations, rates were higher for women than men. Given the fact that Canada's population is aging, chronic pain promises to become an even larger problem in the near future.

Osteoarthritis affects 3 million (1 in 10) Canadians. It affects men and women in equal numbers. Most people develop osteoarthritis after the age of 45, but it can occur at any age (www.arthritis.ca).

The Canadian Pain Society (CPS) has suggested that up to 1 million Canadians live with neuropathic pain (Moulin 2007). This is based on an estimate of the prevalence of 8.2% chronic neuropathic pain in the general population (Torrance 2006).

The "Canadian Chronic Pain Study II" (CCPS-II) was set to study the prevalence of chronic pain by conducting a general population computer-assisted telephone interview. The response rate was only 20%, and they found the prevalence of chronic pain to be 25% of the respondents (Boulanger 2007). In comparison with the CCPS-I, the prevalence of chronic pain was 29% in 2001.

Low-back pain is among the most common causes of CNCP, and there are no studies conducted in Canada to examine its prevalence. A recent national survey conducted in the United States showed that 15% reported "back pain on most days for at least one month in the past year" (Ricci 2006).

In a United Kingdom study, 46.5% of the general population reported chronic pain; low-back problems and arthritis were the leading causes (Elliott 1999).

A recent epidemiological study in Denmark found that CNCP had a prevalence of 19%, and 12% of those who had CNCP (corresponding to 130,000 adults or 3% of Denmark's population) used opioid medications regularly (Eriksen 2004).

It is reasonable to conclude that CNCP affects substantial and growing numbers of the Canadian population. Not all treatment approaches have been well studied, but opioids are a modality that has been shown to be effective in reducing intensity of pain in many of these chronic pain conditions.

8. Need for a Guideline on Opioid Use and for CNCP

Canadian medical regulatory authorities undertook guideline development in response to:

1) physicians and other stakeholders seeking guidance regarding safe and effective use of opioids
2) a growing concern about opioid misuse creating patient and public safety issues, and
3) the lack of systematically developed national guidelines on opioid use for CNCP.

8.1 Need for Guidance regarding Safe and Effective Opioid Use

Medical regulators, through various interactions with physician members and other stakeholders, recognized a growing need for guidance on opioid use for CNCP. The College of Physicians and Surgeons of Ontario, in 2007, completed an environmental scan to better understand needs in the area of chronic pain treatment — and their findings resonated with regulators across Canada. The environmental scan gathered information through multiple methods — surveys, key informant interviews, and focus groups:

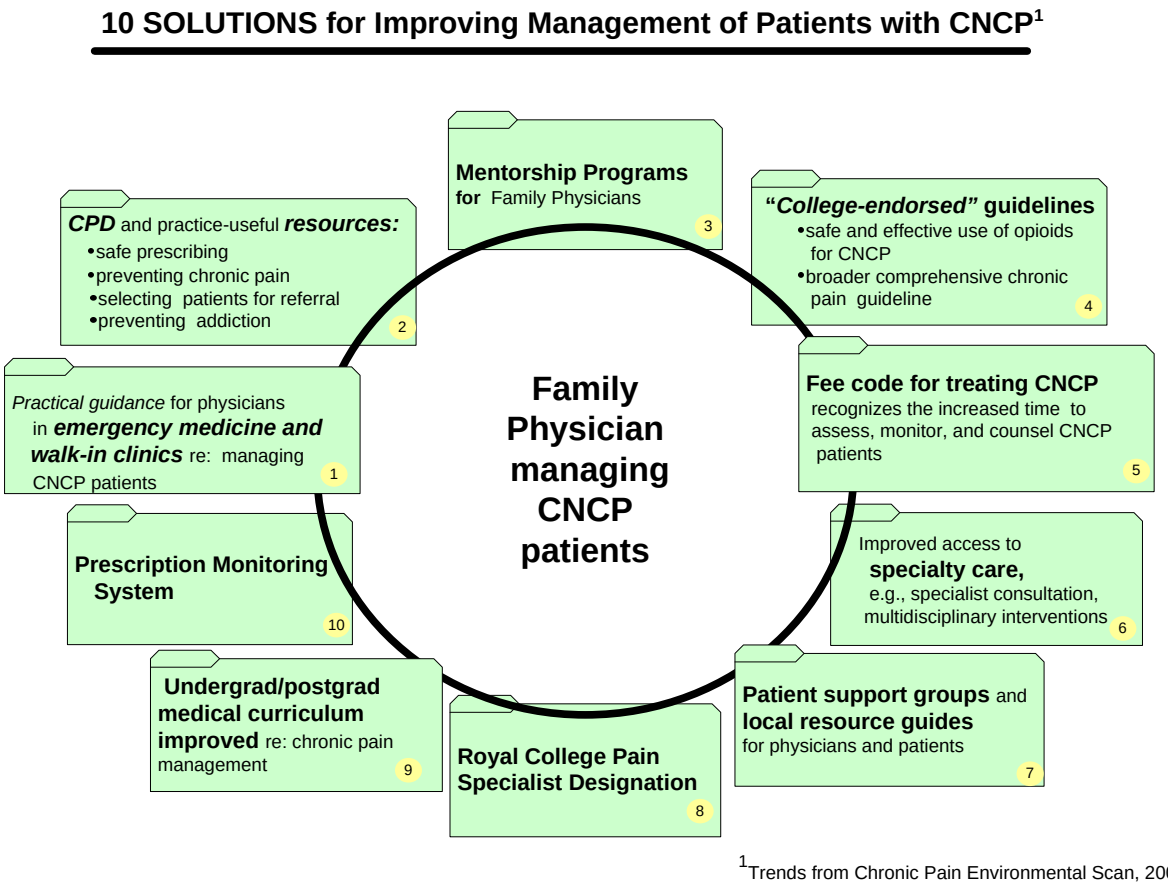
1) key informant interviews with three teams of chronic-pain researchers (Ontario, Alberta, and international)
2) key informant interviews with medical professional practice leaders in pain and addiction
3) focus groups with two multidisciplinary chronic pain treatment teams
4) focus groups with nurses and pharmacists
5) consumer consultation using two focus groups and one-on-one interviews:
   - focus group 1: self-identified chronic-pain sufferers recruited at a public information session
   - focus group 2: consumer-support group for chronic-pain sufferers
   - one-on-one interviews: chronic-pain sufferers recruited from an inner-city pain clinic
6) survey of a network of approximately 175 family physicians identified by peers as "educationally influential"
7) survey of approximately 50 physicians who work with CPSO in the quality management division, completing peer-assessments with family practitioners.

Results for each data-gathering method were qualitatively analyzed for trends. These trends were organized into a model that depicts the potential solutions that should result in an ideal system for CNCP management (see Figure A-8.1). The most common input from physicians centered on the need for guidance about prescribing opioids safely. Physicians expressed their fears and uncertainty in light of "mixed messages from educators, pain specialists, and the College" and highlighted the need for clear, evidence-based practice guidance to assist with managing chronic-pain patients without fear of exposing themselves or their patients to unnecessary risk.

More recently, Wenghofer et al. completed a random survey of 658 primary-care physicians in Ontario. This study found:

- only 44% of physicians reported opioid prescribing to be satisfying
- 57% agreed that "many patients become addicted to opioids"
- 58% had at least one patient with an opioid-related adverse event in the past year, and
- another 58% had concerns about the opioid use of one or more patients (Wenghofer 2009 in press).

Figure A-8.1 10 Solutions to Improving Management of CNCP



[1]Trends from Chronic Pain Environmental Scan, 2007

CPD = continuing professional development.

8.2. Concerns regarding Patient and Public Safety Risks from Opioid Misuse

Medical regulators and others are concerned about 1) patient and public safety regarding opioid misuse and 2) disturbing prescribing trends emerging in the past decade in Canada.

Canada's recorded prescription-opioid consumption increased by about 50% between 2000 and 2004 (International Narcotics Control Board 2006); the rate of increase for this period is greater than that of the United States. Canada is currently the world's third-largest opioid analgesic consumer per capita (overall consumption includes use of opioids for acute and palliative pain) (International Narcotics Control Board 2009). In Ontario, oxycodone prescriptions rose by 850% from 1991 to 2007, from 23 prescriptions/1000 individuals per year to 197/1000 per year, and the average amount per prescription of long-acting oxycodone increased from 1830 mg to 2280 mg (Dhalla 2009). In other words, more patients are receiving opioids in larger quantities.

The increase in opioid prescribing has been accompanied by simultaneous increases in abuse, serious injuries, and overdose deaths among individuals taking these drugs (Kuehn 2007). From 1991 to 2004 in Ontario, the mortality rate due to unintentional opioid overdose increased from 13.7/million to 27.2/million/year, more than double the mortality rate from HIV (12/million) (Dhalla 2009). Studies have documented a major increase in prescription-opioid misuse and addiction throughout North America. For example, a prospective Canadian study found that illicit opioid users are more likely to use prescription opioids than heroin (Fischer 2006).

It has been argued that legitimate prescribers bear little direct responsibility for this, because overdose deaths and addiction arise primarily from drug diversion. However, a recent study (Dhalla 2009) showed that of 1095 overdose deaths in Ontario, 56% of patients had been given an opioid prescription within four weeks before death. In a study of opioid-dependent patients admitted to the Centre for Addiction and Mental Health in Toronto, 37% received their opioid from physician prescriptions, 26% from both a prescription and "the street," and only 21% entirely from the street (Sproule 2009). A United States national study found that, of 1408 patients entering treatment of opioid abuse, 79% of male and 85% of female patients were first exposed to opioids through a prescription to treat pain (Cicero 2008). Furthermore, the total amount of diverted opioids is directly related to the total amount of prescribed opioids (Dasgupta 2006).

8.3 Lack of a Systematically Developed National Guideline on Opioids and CNCP

Although consensus statements existed and other jurisdictions had published guidelines on chronic pain management and opioid use, no single Canadian guideline existed that used a combination of 1) systematic methods for searching and appraising the literature and 2) a consensus process that included clinicians from multiple disciplines and specialties along with patients.

9. Implementation to Practice

From its inception, NOUGG viewed developing the guideline as only the first step, and articulated an additional goal: *Develop and implement a knowledge transfer strategy that ensures the guideline moves into practice as a useful decision-making tool for physicians treating patients with chronic non-cancer pain.*

An effective implementation plan would ensure that clinicians can easily apply the recommendations in demanding day-to-day practice environments. NOUGG created the National Faculty to guide and assist with moving the recommendations to practice. Individuals were selected from across the country, based on matching one or more of the following criteria:

- involvement in physician, inter-professional or patient education
- focus/interest in the topic of chronic pain and opioid use for CNCP
- contribution of relevant materials, teaching resources, or expertise (e.g., continuing professional development, knowledge transfer, guideline implementation)
- connection to some knowledge-to-practice infrastructure, and
- *Canadian Guideline* "ambassador" potential.

At the June 2009 inaugural meeting[1], participants (representing 9 provinces, 1 territory, and 8 national associations) agreed on a set of goals:

1) define **targeted outcomes for implementation** to promote safe and effective use of opioids for CNCP
2) develop an **implementation strategy** considering multiple audiences
3) contribute to creating a **funding plan** for implementing to practice, and
4) define **strategies to evaluate impact** of the *Canadian Guideline*.

The Michael G. DeGroote National Pain Centre (along with ongoing responsibility for the *Canadian Guideline*) will coordinate continuing activities initiated by the National Faculty to ensure the *Canadian Guideline* improves practice and patient outcomes.

10. Literature Search Methods

Development of this *Canadian Guideline* relied on the 2006 meta-analysis by Furlan et al. "Opioids for chronic non-cancer pain: a meta-analysis of effectiveness and side effects" (Furlan 2006). In addition, three new literature searches were completed:

- **Search One:** Search for randomized controlled trials (RCT) published since May 2006 to update the Furlan meta-analysis.
- **Search Two:** Search for additional literature (multiple designs) that answered questions about the treatment of CNCP with opioids and managing the patient with problematic opioid use.
- **Search Three:** Search for additional literature (multiple designs) that answered questions about long-term outcomes of opioid use.

[1] Sponsored by Canadian Institute of Health Research (CIHR).

10.1 Description of Literature Search One

For details of the original Furlan meta-analysis search (Furlan 2006), see http://www.cmaj.ca/cgi/data/174/11/1589/DC1/1 and http://www.cmaj.ca/cgi/data/174/11/1589/DC1/10

The following bibliographic data sources were used to update the review to July 2009:

- *Cochrane Central Register of Controlled Trials* (CENTRAL) 2009
- MEDLINE (OVID) from 2005 to July 2009 (same strategy as the 2006 review)
- EMBASE from 2005 to July 2009 (same strategy as the 2006 review)
- reference lists of retrieved articles
- articles forwarded by the National Advisory Panel.

Search strategies for MEDLINE and EMBASE are available (see Appendix A-4 Literature Search Strategies). A research librarian ran the electronic searches and coordinated the data entry into Reference Manager® 11, removing all duplicates.

10.1.1 Relevance Screening for Search One

Three CPSO research associates independently reviewed the titles and abstracts using the following criteria: 1) not a letter, editorial or short commentary (usually less than three pages in length); 2) focus of the article is not dealing with surgical pain, 3) article is not dealing with cancer pain, 4) population studied had chronic non-cancer pain, and 5) focus is on opioids. Studies that passed the relevance screen were forwarded to the Research Group for inclusion/exclusion criteria screening.

10.1.2 Inclusion/Exclusion Screening for Search One

Text of full articles was obtained for studies that passed the relevance screening. Two Research Group members independently reviewed these studies and applied inclusion/exclusion criteria as follows:

1. *Study characteristics:* Included RCTs published in English, French, Portuguese, or Spanish (languages that could be read by Research Group members). Excluded studies published only as abstracts.
2. *Study population:* Included adults (>18 years) with CNCP (defined as pain that persists for more than six months) including neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back and musculoskeletal pain. Excluded migraines, dental pain, ischemic pain due to vascular disease and abdominal pains (e.g., chronic pancreatitis, kidney stones) because these conditions are not usually classified as CNCP.
3. *Types of intervention:* Included any opioid administered by oral, transdermal, transmucosal or rectal route for seven days or more. Opioids were classified as weak (propoxyphene, codeine, tramadol, hydrocodone) or strong (oxycodone, morphine, fentanyl, hydromorphone or buprenorphine). Excluded methadone.
4. *Types of comparison group:* Included placebo or other analgesics. Excluded comparisons of different opioids.
5. *Outcomes*: Quantifying pain (intensity or relief), function, and side effects.

For Search One, two reviewers reviewed selected titles, abstracts, and full texts and determined the articles for inclusion. If consensus could not be achieved, a third reviewer was consulted. On some occasions, authors of the randomized trials were contacted to obtain more details that were not reported in the publication.

10.1.3 Methodological Quality Screen for Search One

The same two Research Group members completed an independent appraisal of methodological quality on studies admitted after inclusion/exclusion screening. Where needed, they reached consensus through discussion. Reviewers were not blinded with respect to authors, institution and journal because they were familiar with the literature. In cases of disagreement, a third reviewer was consulted. Each study was scored from 0 to 5 with the instrument developed by Jadad and colleagues (Jadad 1996). The instrument includes three questions about randomization methods, double-blinding, and number of withdrawals. Studies scoring 3, 4, or 5 were considered to be of high quality; scoring 0, 1, or 2, of low quality. Study scores were recorded in a Microsoft Excel® spreadsheet (see Appendix B-13, Part B).

10.1.4 Data extraction and synthesis for Search One

Research Group members extracted the data from the high quality studies using Microsoft Excel®. Meta-analyses and meta-regression were conducted using Comprehensive Meta-Analysis© software, with calculations of effect sizes for pain relief and functional outcomes.

Effect Size: Cohen's three levels (Cohen 1988) were used and adapted to a scale developed by the Cochrane Back Review Group (Furlan 2009):

- Small = ES <0.5 = Mean difference less than 10% of the scale (e.g., <10mm on a 100mm visual analog scale).
- Medium = ES from 0.5 to <0.8 = Mean difference 10 to 20% of the scale.
- Large = ES ≥0.8 = Mean difference >20% of the scale.

For side effects, all meta-analyses were done using RevMan 5[2] using risk differences. Statistical heterogeneity was tested by Q test (chi-square) reported as I^2 (higher values indicate higher heterogeneity).

All meta-analyses were conducted using a random effects model. Sub-groups were decided *a priori* to assess the variations in effect sizes. Clinical significance of side effects was considered when the incidence was 10% or higher in the opioid or reference group.

10.2 Description of Literature Search Two and Search Three

Search Two was conducted to find articles that could be useful in drafting the recommendations on the treatment of CNCP with opioids and managing the patient with problematic opioid use. Search Three was conducted to understand the effects of prolonged opioid use. These searches were not limited to RCTs. (See Appendix A-5 Flowchart of Literature Review Process and Appendix A-4: Literature Search Strategies.)

The following bibliographic data sources were used:

- *Cochrane Central Register of Controlled Trials* (CENTRAL) 2009
- MEDLINE (OVID) from 1950 to July 2009
- EMBASE from 1982 to July 2009
- reference lists of retrieved articles
- articles forwarded by the National Advisory Panel.

[2] Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

10.2.1 Relevance Screen for Search Two and Search Three

A CPSO research associate independently reviewed the titles and abstracts using the following criteria: 1) not a letter, editorial or short commentary (usually less than three pages in length), 2) population studied has chronic non-cancer pain, 3) focus on opioids, and 4) focus on addiction.

10.2.2 Inclusion/Exclusion Screen for Search Two and Search Three

From the titles and abstracts that passed the relevance screen, text of full articles was obtained, and two out of four Research Group members applied inclusion criteria:

1. *Study characteristics:* Included any study design with primary data collection, conducted in humans, with no language restriction. Studies could be experimental (e.g., clinical trials), observational (e.g., cohort, case-control, cross-sectional) or descriptive (e.g., before-and-after, case series, case reports). Studies published in a language other than English were judged for inclusion/exclusion, based on the English abstract.
2. *Study population:* Included adults (>18 years) with CNCP (defined as pain that persists for more than six months) including neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back and musculoskeletal pain. Excluded acute pain, post-surgical pain, or experimental pain in healthy volunteers. In some circumstances, a study in a population with cancer pain could be included if information could be extrapolated to non-cancer pain.
3. *Types of intervention:* Included any opioid administered by oral, transdermal, transmucosal or rectal route for pain for seven days or more. Studies of methadone were included.
4. *Useful Topics:* Included topics deemed to be of value in drafting the recommendations on the treatment of CNCP with opioids and managing the patient with problematic opioid use:
   - dose of opioids to achieve maximum benefits with minimum adverse events
   - urine drug screening
   - initiation, titration and tapering of opioids
   - assessments and monitoring during treatment with opioids
   - frequency of follow-up
   - identification of patients at risk for medical complications, overdose, misuse or addiction
   - recommendations for practice regarding screening, management, follow-up
   - approaches to dealing with conflicts with patients
   - treating chronic pain patients in acute care settings
   - mechanisms to prevent prescription fraud
   - use of opioids and driving
   - identifying patients at risk of opioid addiction
   - managing an opioid addicted patient with chronic pain
   - tapering and stopping opioids or other drugs, e.g., benzodiazepines
   - dealing with challenging or threatening patients
   - long-term outcomes of opioid use.

For Searches Two and Three, four reviewers worked in pairs to select articles for inclusion. When in doubt, a third reviewer from the other pair was consulted.

10.2.3 Additional Strategies for Search Two and Search Three

All included and excluded studies from Search One were also evaluated by two reviewers against the list of useful topics developed for inclusion of studies in the Searches Two and Three.

10.2.4. Methodological Quality Screen for Searches Two and Three

Observational studies were not assessed for methodological quality due to lack of resources to fund experts in epidemiological methods necessary to complete the more complex and subjective review required.

10.3 Using Extracted Evidence to Develop Recommendations for Practice

10.3.1. Recommendation Development Process

The Research Group provided methodological and clinical expertise in the area of chronic pain and addiction medicine. They summarized evidence from the studies and drafted 49 initial recommendations that each included a discussion and related evidence. An iterative course of action ensued, using a Modified Delphi technique with the National Advisory Panel (NAP), to produce final recommendations. NAP member identities were blind to the Research Group and each other until the last round of review.

NAP received material via email and responded using an on-line survey tool to rate their opinion on relevance, feasibility, clarity, and their degree of agreement with each recommendation. They also provided open-ended narrative comments.

Consensus was defined as 80% of NAP members supporting a recommendation. Recommendations that did not receive this level of consensus were revised using feedback provided by NAP and re-rated in the next round. With each round of review, each NAP member received a complete transcript of all written comments made by NAP in the previous round.

While participation rates declined as the Modified Delphi progressed, the portion of NAP members involved remained high throughout, as summarized in Table A-10.3.1. A drop in the last two rounds could have been due to Panel fatigue, or related to the H1N1 pandemic occurring in Canada at the time. Consensus on recommendations resulted after four rounds of electronic review and rating, culminating with a final telephone and web-assisted meeting.

Table A-10.3.1 National Advisory Panel Participation in Modified Delphi Process

Round	Number of Recommendations Under Review	Panelists Participating
1	49	84%
2	20	80%
3	4	65%
4	2	60%

10.3.2 Recommendation Grading

The evidence-grading system was adapted from the Canadian Task Force on Preventive Health Care (CTFPHC) (Woolf 1990); see Table A-10.3.2. A single recommendation statement can be supported by one, two, or three different grades of evidence.

Each recommendation includes a key word, recommendation statement, discussion, and evidence summary. References may be provided in both the discussion and evidence summary. There are two types of references used: those that 1) provide direct or indirect support for the recommendation statement and 2) provide contextual information.

If a reference supported ***directly***, the recommendation statement was graded consistent with the study design of that reference, i.e., "A" or "B." (See Table A-10.3.2)
If a reference supported ***indirectly***, the recommendation statement was graded to reflect the primary source driving the recommendation.

- Example 1: a RCT informed the recommendation but the recommendation is graded "B" or "C" (rather than "A") — this is because the recommendation statement is not directly extracted from the main hypothesis of the RCT.
- Example 2: references are graded "B" in the evidence summary, but the recommendation statement is graded "C" — this is because expert opinion from NAP was the predominant driver of the recommendation statement, even though some of the recommendation's concepts were backed by the studies mentioned in the evidence summary.
- Example 3: a reference conflicts with the recommendation, and the recommendation statement is graded "C" — this reflects NAP expert opinion assessing the evidence as weak or not generalizable.

Table A-10.3.2 Recommendation Grading

CTFPHC Evidence Grading System*	*Canadian Guideline* Recommendation Grading
I. –Evidence from RCTs	**Grade A**: Recommendations are supported by evidence from RCT(s).
II – 1 Evidence from controlled trial(s) without randomization. II – 2 Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group. II – 3 Evidence from comparisons between times or places with or without the intervention; dramatic results from uncontrolled studies could be included here.	**Grade B**: Recommendations are supported by: • Evidence from controlled trial(s) without randomization, or, • Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group, or • Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here.
III – Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees.	**Grade C**: Recommendations are supported by consensus opinion of the National Advisory Panel.

*(Woolf 1990).

11. National Advisory Panel (NAP) Consultation

11.1 Need for the National Advisory Panel

The available evidence on safe and effective use of opioids for managing CNCP was necessary but not sufficient to create practical clinical guidance. Clinical expertise was also required. In response to this need, NOUGG created a process to capture expert opinion through consultation with a variety of experts and stakeholders. NOUGG's intent was to create a well-balanced advisory panel so that multiple perspectives and experience were included in feedback for the developing guideline. Participation and selection requirements included:

- Representation from:
  - —across Canada
  - —the target audience (family physicians and other physicians who manage CNCP)
  - —other healthcare providers who work with physicians in using opioids to manage CNCP (e.g., pharmacists, nurses, psychologists)
  - —patients with CNCP.
- Specific relevant expertise: clinical focus in pain and/or addictions, research, or teaching in pain and/or addictions.

11.2 Establishing NAP

MRAs participating in NOUGG invited potential participants from their jurisdiction (see Appendix A-6 for selection criteria).The College of Physicians & Surgeons of Alberta (CPSA), on behalf of NOUGG, coordinated NAP activities. A total of 49 individuals agreed to participate on the Panel. All NAP members returned a signed conflict of interest disclosure to CPSA. (See Appendix A-7 for a copy of the form, and Appendix A-3 for NAP members and their declared competing interests.)

11.3 NAP Consultation Process

Throughout the initiative, NOUGG's process for NAP consultation was transparent. Before the consultation started, all NAP members received background information describing the NOUGG initiative, the rationale for MRA's involvement, the approach for guideline development, the role of the panel, and NOUGG's intent to pursue implementation strategies that included knowledge transfer and evaluation.

For the consultation process details, see Table A-11.3.

Table A-11.3 NAP Consultation Tasks and Outcomes

	Material Provided to NAP	NAP Task	Outcomes
First Consultation Oct 2008	Background, methods, evidence summary from RCTs and references.	Task: Respond to the following questions: 1) What questions do you have after reviewing the enclosed document with background and context for the draft guideline? 2) What clarifications would be helpful in the document? 3) Are there any references missing that should have been considered for Section A of *Guideline*?	75% of Panel members (37 individuals) responded. •Constructive comments on how to improve description of methods. •Suggestions of other relevant literature. •CPSA summarized all NAP feedback for submission to the Research Group (Note: NAP responders not identified).
Modified Delphi Round 1 Mar '09	49 draft practice recommendations with discussion notes and evidence summaries.	Modified Delphi Process used; see Appendix A-8. Task: using an electronic survey tool: 1) rate opinion on clarity, feasibility and agreement for each of 49 recommendations (See Appendix A-9 for detail) 2) provide narrative feedback.	84% of Panel members (41 individuals) responded. •**29/49** recommendations supported by consensus. •**20/49** recommendations unsupported. •Qualitative analysis of narrative feedback organized into specific themes and used to revise unsupported recommendations.
Modified Delphi R2 R3 June 2009	•Individual responses and NAP aggregate response from Round 1. •For each of the 21[3] revised recommendations: -original recommendation -revised recommendation -NAP feedback from Round 1, organized into themes.	Task: using an electronic survey tool: 1) rate opinion on clarity, feasibility and agreement for 21 revised recommendations 2) provide narrative feedback.	80% of Panel members (40[4] individuals) responded. •**9/21** recommendations supported by consensus. •**12/21** recommendations unsupported. •Three grade C-only recommendations eliminated. •Narrative feedback organized in themes and used to revise (some merged) unsupported recommendations for NAP Modified Delphi Round 3.
Modified Delphi R3 Nov 2009	•Substantively revised *Guideline* including: -20 supported recommendations -4 recommendations that required voting •NAP feedback from Round 2, organized into themes.	Task: using an electronic survey tool: 1) rate opinion on clarity, feasibility and agreement for 4 revised recommendations 2) provide narrative feedback.	65% of Panel members (32 individuals) responded. •**2/4** recommendations supported by consensus. •**2/4** recommendations unsupported. •Narrative feedback organized in themes and used to revise 2 unsupported recommendations for NAP Modified Delphi Round 4.
Modified Delphi R4 Dec 2009	•2 recommendations that required voting •NAP feedback from Round 2, organized into themes.	Task: •Participate in a real time virtual meeting to address topics/issues identified by NAP members. •Agree on core concepts for Guideline. •Final 2 recommendations approved.	60% of Panel members (29 individuals) responded. •2/**2** recommendations supported by consensus.

[3] One of the 20 unsupported recommendations from previous round had been split into 2 recommendations.
[4] Includes one partially completed response.

11.4 Overview: Revising with NAP Input

NAP input included quantitative and qualitative data.

- Quantitative data, i.e., the scoring of degree of support for a given recommendation, was used to identify recommendations targeted for revision.
- Qualitative data, i.e., narrative comment from NAP members, guided the evolution of the recommendations at both macro and micro levels. At the macro level, dominant themes in NAP feedback influenced revisions. See Table A-11.4 for a summary of themes and resulting modifications.

11.4.1 NAP Feedback at the Macro Level

Table A-11.4 NAP-Response Dominant Themes and Modifications

No.	Dominant Theme	*Canadian Guideline* Modification
1	Background/Methods section too long; methods section confusing, grading system not clear.	•Part A streamlined; Methods section revised with more detailed information moved to Appendix. •Grading system and insertion of grades in recommendation statements clarified.
2	*Guideline* lacks a clear opening, stating purpose and fundamental position on opioids and pain.	• Executive summary written.
3	*Guideline* too long; too many recommendations: redundancy and overlap.	•49 recommendations reduced to 24. • 8 clusters reduced to 5.
4	*Guideline* too "universal," i.e., too often directed physicians toward actions that "should" or "must" always be followed: • this creates an unnecessary burden, especially on family physicians, making them even **less likely** to use opioids for CNCP – this runs contrary to *Guideline* goal of increasing prescriber comfort and confidence in using opioids for this population •in some cases the "universal" approach assumed access to resources inaccessible across the country.	•Recommendations modified to provide latitude for prescriber judgment. •More "how to" guidance provided without the indication of "must" or "should", e.g., urine drug screening, use of screening tools, use if treatment agreements, seeking consultation, selecting opioids.
5	*Guideline* too "addiction-focused;" concern that it included recommendations more appropriate in an addiction guideline than a CNCP guideline.	•More focus on preventing misuse and screening for risk. •Addiction management recommendations merged into a single recommendation that provides information about treatment options (see Recommendation 21, Part B).
6	•Confusing and inappropriate use of terminology, e.g., dependence and addiction. •Glossary and appendices need greater clarity.	•Terms clarified and used consistently. •Glossary clarified with the majority of definitions referenced. •Appendices culled. •Professional editor engaged.

11.4.2 NAP Feedback at the Micro Level

Panelist's comments were organized into themes, preserving the comments in their entirety. Strong themes were incorporated into recommendation revisions, and individual suggestions were used where possible to add useful detail and clarity.

In a few cases, the Panel's comments were polarized. This was observed most often where there was a lack of evidence and the recommendation was advocating a specific approach. Modifications were made in these cases to reflect the range of clinical opinion. This is illustrated in the urine drug screening recommendation (Recommendation 3) that carries forward the opposing views and provides the prescriber with decision-making options.

12. Updating

The Michael G. DeGroote National Pain Centre at McMaster University accepted responsibility for stewardship of the *Canadian Guideline*. This will include updating as new evidence becomes available and continuing knowledge transfer to practice. The mission of the Centre also includes further updating and development of guidelines for the treatment of CNCP, including a wide range of treatment modalities. McMaster will foster collaboration and partnerships for knowledge transfer and exchange, building on the partnerships and networks established by NOUGG.

13. Comparison with Other Guidelines

There are numerous other clinical practice guidelines that address the management of CNCP with opioids. In preparation for developing the *Canadian Guideline*, searches in MEDLINE and www.guideline.gov up to February 2009 were conducted with 15 relevant guidelines selected for a detailed evaluation. This evaluation determined that most guidelines were either focused on a specific health problem (fibromyalgia, neuropathic pain, osteoarthritis, low-back pain) or were out-of-date.

Three current guidelines are similar to the *Canadian Guideline* in terms of scope, population, development, sponsorship, recommendations, and presentation.

When work began on the *Canadian Guideline*, only one of these was published — the American Society of the Interventional Pain Physicians guideline, originally published in 2006 (Trescot 2006) and updated in 2008 (Trescot 2008): however, the target audience was interventional pain specialists.

In 2009, when the *Canadian Guideline* development was well underway, two other similar guidelines were published. The guideline of the American Pain Society/American Academy of Pain Medicine (Chou 2009) has additional recommendations not included in the *Canadian Guideline*: treatment of breakthrough pain, management of side effects, selection of short-acting versus long-acting preparations, special issues with methadone, and awareness of state laws. The Utah Department of Health guideline (Utah Department of Health 2009) is in fact a compilation of recommendations from six other guidelines on the management of CNCP with opioids. There are no major discrepancies between the Utah and the *Canadian Guideline*.

14. Topics for Future Research

Questions remain that cannot be confidently answered by the currently published randomized trials and that require appropriately designed studies of long-term opioid use for CNCP. Topics include:

1. Alternative routes of administration: There is a need for more information on efficacy and risk/benefits of intramuscular, subcutaneous, transdermal, rectal, and infusion routes of administration of opioids for CNCP.
2. Opioids compared with non-opioid drugs: There is a need for well-designed equivalence and non-inferiority trials to assess the relative effectiveness and risk-to-benefit ratios of opioids compared with non-opioid drugs.
3. Various clinical diagnoses: Most of the RCTs on opioids for CNCP have concerned musculoskeletal pain and neuropathic pain. There is limited literature on treating fibromyalgia pain and chronic headache with opioids other than tramadol, and no useful literature on opioids for chronic visceral pain.
4. Long-term follow-up: CNCP is a long-term disorder, but the RCTs included in the current systematic review had fairly short follow-up periods, e.g., six weeks. Well-designed long-term studies are needed to clarify: a) the proportion of CNCP patients for whom opioids remain effective over months or years, and b) the potential over extended timeframes for developing opioid tolerance; hyperalgesia; loss of efficacy; complications such as hypogonadism, sexual dysfunction, or central sleep apnea; or probability of developing opioid misuse.
5. Assessment of opioid misuse: There is a need for more well-designed trials of sufficient duration, with appropriate measures to identify prevalence and risks of opioid-related problems such as addiction.
6. Populations with co-morbidities: There is a need for more trials dealing with safe and appropriate management of chronic pain where there is significant co-morbidity, e.g., pain in the elderly or psychiatric co-morbidity.
7. Impact of research sponsorship: The majority of the randomized trials included in the systematic review were funded by the pharmaceutical industry. However, there was not sufficient information in these studies to determine if pharmaceutical industry funding might introduce publication bias. It is not known if there were small or unfavourable studies that were not submitted for publication.
8. Genetic Factors: There is a need for trials regarding the influence of genetic factors in opioid metabolism, analgesic response, incidence of side effects and predisposition to misuse and addiction.

Appendix A-1: National Opioid Use Guideline Group (NOUGG)

Medical Regulatory Authority	Representative(s)
Federation of Medical Regulatory Authorities of Canada	• Dr. Fleur-Ange Lefebvre, PhD, Executive Director and CEO • Ms Connie Côté, Director, Professional Affairs
College of Physicians & Surgeons of British Columbia	Dr. Robbert Vroom, Deputy Registrar
College of Physicians & Surgeons of Alberta	• Mr. Clarence Weppler, Manager-Physician Prescribing Practices • Dr. Janet Wright, Assistant Registrar
College of Physicians and Surgeons of Saskatchewan	• Mr. Doug Spitzig, Consultant Pharmacist, Prescription Review Program • Dr. Karen Shaw, Deputy Registrar
College of Physicians & Surgeons of Manitoba	• Dr. Lindy Lee, Family Physician • Dr. Bill Pope, Registrar • Dr. Anna Ziomek, Assistant Registrar
College of Physicians and Surgeons of Ontario	• Ms Rhoda Reardon, Manager (A), Research and Evaluation • Dr. Angela Carol, Family Physician; Medical Officer, Quality Management Division
Collège des médecins du Québec	Dre. Carole Santerre, Inspector, Practice Improvement Division
College of Physicians and Surgeons of PEI	Dr. Don Ling, Family Physician; President of Council
College of Physicians and Surgeons of Nova Scotia	Dr. Cameron Little, Registrar
College of Physicians and Surgeons of New Brunswick	Dr. Ed Schollenberg, Registrar
College of Physicians and Surgeons of Newfoundland and Labrador	Dr. Robert Young, Registrar
Yukon Medical Council	Dr. Said Secerbegovic, Family Physician; member of Council
Government of Nunavut	Dr. Patricia DeMaio, Family Physician

Appendix A-2: Research Group

Name and Research Group Role	Title	Disclosure of Competing Interests
Andrea Furlan Physician-Epidemiologist, Systematic Review Lead	Assistant Professor, Department of Medicine, University of Toronto Associate Scientist, Institute for Work & Health Editorial Board, Cochrane Back Review Group Medical Staff, Toronto Rehabilitation Institute	None.
Meldon Kahan Physician-Researcher	Associate Professor, Department of Family and Community Medicine, University of Toronto	Schering-Plough: Unrestricted research and educational grant and stipends.
Angela Mailis-Gagnon Physician-Researcher	Director, Comprehensive Pain Program, Toronto Western Hospital Professor, Department of Medicine, University of Toronto	Pfizer: Advisory Board Member and unrestricted grant to fund a research fellow; Boehringer Ingelheim: Advisory Board Member.
Anita Srivastava Physician-Researcher	Assistant Professor & Staff Physician, St. Joseph's Health Centre, Department of Family and Community Medicine, University of Toronto	Schering-Plough: Honorarium re: buprenorphine educational course development.
Luis Chaparro Physician-Researcher	Clinical Fellow, Comprehensive Pain Program, Toronto Western Hospital, University Health Network	None.
Emma Irvin Research Librarian	Director, Research Operations Institute for Work & Health, Toronto	None.

Institute for Work & Health
The Institute for Work & Health (IWH) is an independent, not-for-profit research organization based in Toronto, Ontario. Its mission is to conduct and share research that protects and improves the health of working people and is valued by policy-makers, workers and workplaces, clinicians, and health and safety professionals.

The Institute operates with support from the Ontario Workplace Safety and Insurance Board (WSIB). In addition to this core funding, IWH scientists are also awarded competitive grants from funding agencies across North America.

Appendix A-3: National Advisory Panel (NAP)

Name	Title	Disclosure of Competing Interests
Ms. Lori Adler	Outreach Program Coordinator College of Nurses of Ontario Toronto ON	
Dr. John F. Anderson	Senior Research Fellow Centre for Addictions Research of B.C. Victoria BC	
Ms. Catherine Biggs	Clinical Pharmacist Orofacial Pain and Medicine Clinic Edmonton AB	
Dr. Aline Boulanger	Director, Pain Clinic, CHUM (HD) and Sacre-Coeur Hospital Montreal QC	Conferences for Pfizer, Purdue, Janssen-Ortho, Bayer, Merck, Valeant, Paladin, Biovail, and Wyeth (> $5000 annually)
Dr. Robert James Boyd	Professor and Head, Family Medicine, University of Manitoba Winnipeg MB	
Dr. Norman Buckley	Professor and Chair, Department of Anesthesia, McMaster University Hamilton ON	PI or Co-investigator – Purdue, Pfizer, Janssen-Ortho, Abbott
Dr. Peter Butt	Associate Professor, Department of Family Medicine University of Saskatchewan Saskatoon SK	
Dr. Michel Cauchon	Professeur Médecine Familiale Université Laval Laval QC	
Dr. Alexander J. Clark	Medical Director, Chronic Pain Centre Calgary Pain Program Alberta Health Services Calgary, AB	PI or Co-investigator – Pfizer, Purdue, AstraZeneca and Bayer Consultant or Honoraria (>$5000 annually) – Pfizer, Biovail and College of Physicians & Surgeons of Alberta
Dr. John Collingwood	Family Physician St. John's NL	
Ms. Lynn Cooper	President, Canadian Pain Coalition Kitchener ON	
Dr. Ann Crabtree	Consulting Physician, Calgary Health Region Chronic Pain Centre Calgary AB	
Dr. Etienne de Medicis	Professeur d'enseignement cliniquie agrege, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke QC	PI or Co-investigator – Pfizer and Purdue
Dr. Ted Findlay	Consultant physician, Regional Pain Program, Alberta Health Services Calgary AB	
Dr. Ian Forster	Medical Director, Lifemark Health Edmonton AB	Consultant or Honoraria (>$5000 annually) -Valiant, Purdue Pharma and Janssen-Ortho stock shareholder (>$5000) -Pfizer, Biovail and Paladin

…continued

…Appendix A-3: NAP Members, continued

Name	Title	Disclosure of Competing Interests
Dr. John Fraser	Family Physician North End Community Health Centre Halifax NS	
Dr. Brian Goldman	Staff Emergency Physician Mount Sinai Hospital Toronto ON	Consultant or Honoraria (>$5000 annually) – Purdue and Paladin
Dr. Allan Gordon	Neurologist and Director Wasser Pain Management Centre Toronto ON	PI or Co-investigator – Canadian Institutes of Health Research, Purdue Pharma, Pfizer, Merck and Paladin. Consultant or Honoraria (>$5000 annually – Pfizer, Purdue Pharma and Janssen-Ortho
Dr. Neil Hagen	Professor and Head Division of Palliative Medicine, University of Calgary Calgary AB	Research support in trials of a non-opioid analgesic, approximately $100,000 over two years for WEX Pharmaceuticals
Dr. Lydia Hatcher	Family Physician Family Wellness Place Mount Pearl NL	PI or Co-investigator – Purdue Consultant or Honoraria (>$5000 annually) – Purdue and Janssen-Ortho
Dr. Phillipa Hawley	Palliative Medicine Specialist B.C. Cancer Agency Vancouver BC	
Dr. Howard Intrater	Medical Director Pain Clinic, Health Sciences Centre Winnipeg MB	Consultant or Honoraria (<$5000 annually) – Janssen-Ortho, Purdue, Valeant and Medtronic
Dr. Margaret Jin	Clinical Pharmacist Hamilton Family Health Team Hamilton ON	
Dr. Roman Jovey	Program Medical Director, CPM Centres for Pain Management Physician Director, Addictions & Concurrent Disorders Centre Credit Valley Hospital Mississauga ON	Consultant or Honoraria (>$5000 annually) for Biovail, Janssen-Ortho, Glaxo-Smith-Kline, Merck-Frost, Nycomed, Pfizer, Paladin, Purdue, Sanofi-Aventis and Valeant
Dr. Milan Khara	Clinical Director, Tobacco Dependence Clinic, Vancouver Coastal Health, Addiction Services Clinical Assistant Professor, Faculty of Medicine, University of British Columbia Vancouver BC	PI or Co-investigator – Pfizer, Johnson & Johnson (smoking cessation products only) Consultant or Honoraria (>$5000 annually) – Pfizer, Johnson & Johnson (smoking cessation products only)
Dr. Brian Knight	Anesthesiologist, Misericordia Hospital Edmonton AB	Consultant or Honoraria (>$5000 annually) – Purdue
Dr. Jill Konkin	Associate Dean, Rural and Regional Health Faculty of Medicine and Dentistry University of Alberta Edmonton AB	
Mr. James Krempien	Complaints Director Alberta College of Pharmacists Edmonton AB	

…continued

…Appendix A-3: NAP Members, continued

Name	Title	Disclosure of Competing Interests
Dr. Roger Ladouceur	Médecin responsable du Plan d'autogestion du Développement professionnel continu Collège des médecins du Québec Montreal QC	
Dr. Andre Lalonde	Expert Clinicien Hôpital de Sacre-Coeur Laval QC	Consultant or Honoraria (>$5000 annually) – Pfizer, Purdue, Biovail, Paladin, Valeant, Boehringer, Lilly and Merck
Dr. Vernon Lappi	Director, Medical Services, Workers' Compensation Board of Alberta Edmonton AB	
Dr. Lindy Lee	Medical Director, Health Sciences Centre Addiction Unit Winnipeg MB	
Dr. Joël Loiselle	Anesthesiologist, St. Boniface Hospital, and Chronic Pain and Palliative Care Consultant Winnipeg Regional Health Authority Winnipeg MB	$10,000 for research support from the University of Manitoba Consultant or Honoraria (<$5000 annually) – Purdue Pharma
Dr. Mary Lynch	Director Pain Management Unit Capital District Health Authority Halifax NS	Co-investigator on a tramadol study in PHN with Purdue
Dr. David MacPherson	Assistant Professor, Family Medicine Queens University Kingston ON	
Dr. David Marsh	Medical Director, Addiction, HIV/AIDS, Aboriginal Health Services Vancouver Coastal Health Vancouver BC	Advisory Board Member for Schering Canada
Dr. Gary Mazowita	Chair, Family and Community Medicine Providence Health Centre Vancouver BC	
Dr. Gordon McFadden	Physician, Dr. Gordon R. McFadden Inc., Burnaby BC	
Dr. Patricia K. Morley-Forster	Medical Director, Pain Management Program, St. Joseph's Health Care London ON	Co-investigator ($820,000) for Neuropathic Pain Registry, Multi-centre Honoraria ($6,000 for 4 talks) – Pfizer Financial/Material Support ($200,000) – grant from Purdue for operating costs of Pain Clinic
Dr. Murray Opdahl	Medical Director Saskatoon Chronic Pain Centre Saskatoon SK	Pain management consults for Worker's Compensation Board and Saskatchewan Government Insurance Speak regarding pain management and receive honoraria from Purdue, Janssen-Ortho and Pfizer

…continued

…Appendix A-3: NAP Members, continued

Name	Title	Disclosure of Competing Interests
Dr. R. Keith Phillips	Assistant Clinical Professor Department of Family Practice, University of British Columbia Nanaimo BC	PI for hepatitis C treatment with Hoffman - La Roche.
Dr. Saifee Rashiq	Director, Division of Pain Medicine, University of Alberta Edmonton AB	PI or Co-investigator – Purdue, Janssen-Ortho, AstraZeneca, WCB Alberta
Mr. Loren Regier	Pharmacist, Saskatoon Health Region Saskatoon SK	
Dr. Toomas Sauks	Family Physician Owen Sound ON	Consultant or honoraria (>$5000 annually) – College of Physicians and Surgeons of Ontario
Dr. Roger Shick	Physician Leader, St. Paul's Pain Centre, St. Paul's Hospital Vancouver BC	
Dr. Chris Spanswick	Medical Leader, Regional Pain Program Calgary AB	
Dr. Paul Taenzer	Specialist/Clinical Psychologist, Regional Pain Program Calgary, AB	
Dr. Eldon Tunks	Emeritus Professor Psychiatry McMaster University Regional Rehabilitation Center Hamilton Health Sciences Hamilton ON	
Dr. Preston Zuliani	President, College of Physicians and Surgeons of Ontario, and Family Physician St. Catherines ON	

Appendix A-4: Literature Search Strategies

(1a) Search strategy in MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. Randomized Controlled Trials/
4. Random Allocation/
5. Double-Blind Method/
6. Single-Blind Method/
7. or/1-6
8. Animal/ not Human/
9. 7 not 8
10. clinical trial.pt.
11. explode Clinical Trials/
12. (clinic$ adj25 trial$).tw.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj(mask$ or blind$)).tw.
14. Placebos/
15. placebo$.tw.
16. random$.tw.
17. Research Design/
18. (latin adj square).tw.
19. or/10-18
20. 19 not 8
21. 20 not 9
22. Comparative Study/
23. explode Evaluation Studies/
24. Follow-Up Studies/
25. Prospective Studies/
26. (control$ or prospectiv$ or volunteer$).tw.
27. Cross-Over Studies/
28. or/22-27
29. 28 not 8
30. 29 not (9 or 21)
31. 9 or 21 or 30
32. PAIN/pc, dt, rh, th [Prevention & Control, Drug Therapy, Rehabilitation, Therapy]
33. Chronic Disease/dt, pc, rh, th [Drug Therapy, Prevention & Control, Rehabilitation, Therapy]
34. (chronic adj3 pain).mp
35. Low Back Pain/
36. (low adj back adj pain).mp
37. or/ 32-36
38. exp Analgesics, opioid/
39. Codeine.mp.
40. Fentanyl.mp.
41. Hydrocodone.mp.
42. Hydromorphone.mp.
43. Levorphanol.mp.
44. Meperidine.mp.
45. Morphine.mp.
46. Oxycodone.mp.
47. Oxymorphone.mp.
48. Pentazocine.mp.
49. Propoxyphene.mp.
50. Sufentanil.mp.
51. Tramadol.mp
52. or/ 38-51
53. Or/ 39-51
54. 31 and 37 and 53

(1b) Search in EMBASE

1. Randomized Controlled Trial/
2. (random: adj2 control: trial:).mp.
3. 1 or 2
4. control: clinical trial:.mp.
5. (control: adj2 trial:).mp.
6. 4 or 5
7. randomization/
8. random: allocation:.mp.
9. (random: adj2 allocation:).mp.
10. 8 or 9
11. Double Blind Procedure/
12. double-blind method:.mp.
13. Single Blind Procedure/
14. single-blind method:.mp.
15. or/1-14
16. limit 15 to (amphibia or ape or bird or cat or cattle or chicken or dog or "ducks and geese" or fish or "frogs and toads" or goat or guinea pig or "hamsters and gerbils" or horse or monkey or mouse or "pigeons and doves" or "rabbits and hares" or rat or reptile or sheep or swine)
17. exp animal/
18. 15 and 17
19. 16 or 18
20. limit 15 to human
21. 20 not 19
22. Clinical Trial/
23. exp clinical trial/
24. (clinic: adj25 trial:).tw.
25. ((singl: or doubl: or trebl: or tripl:) adj (mask: or blind:)).tw.
26. PLACEBO/
27. placebo:.mp.
28. random:.tw.
29. methodology/
30. latin square design/
31. (latin adj square).tw.
32. or/22-31
33. 32 not 19
34. Comparative Study/
35. evaluation/
36. follow up/
37. prospective study/
38. (control: or prospectiv: or volunteer:).tw.
39. Crossover Procedure/
40. or/34-39
41. 40 not 19
42. 21 or 33 or 41
43. Pain/pc, rh, dt, th [Prevention, Rehabilitation, Drug Therapy, Therapy]Chronic Disease/pc, rh, dt, th [Prevention, Rehabilitation, Drug Therapy, Therapy]
44. (chronic adj3 pain).mp.
45. Low Back Pain/
46. (low adj back adj pain).mp.
47. or/43-47
48. exp Narcotic Analgesic Agent/
49. Codeine.mp.
50. Fentanyl.mp.
51. Hydromorphone.mp.
52. Levorphanol.mp.
53. Meperidine.mp.
54. Morphine.mp.
55. Oxycodone.mp.
56. Oxymorphone.mp.
57. Pentazocine.mp.
58. Propoxyphene.mp.
59. Tramadol.mp.sufentanil.mp
60. Tramadol.mp
61. or/49-63
62. or/50-63
63. 64 not 65
64. 65 not 49
65. 42 and 48 and 65

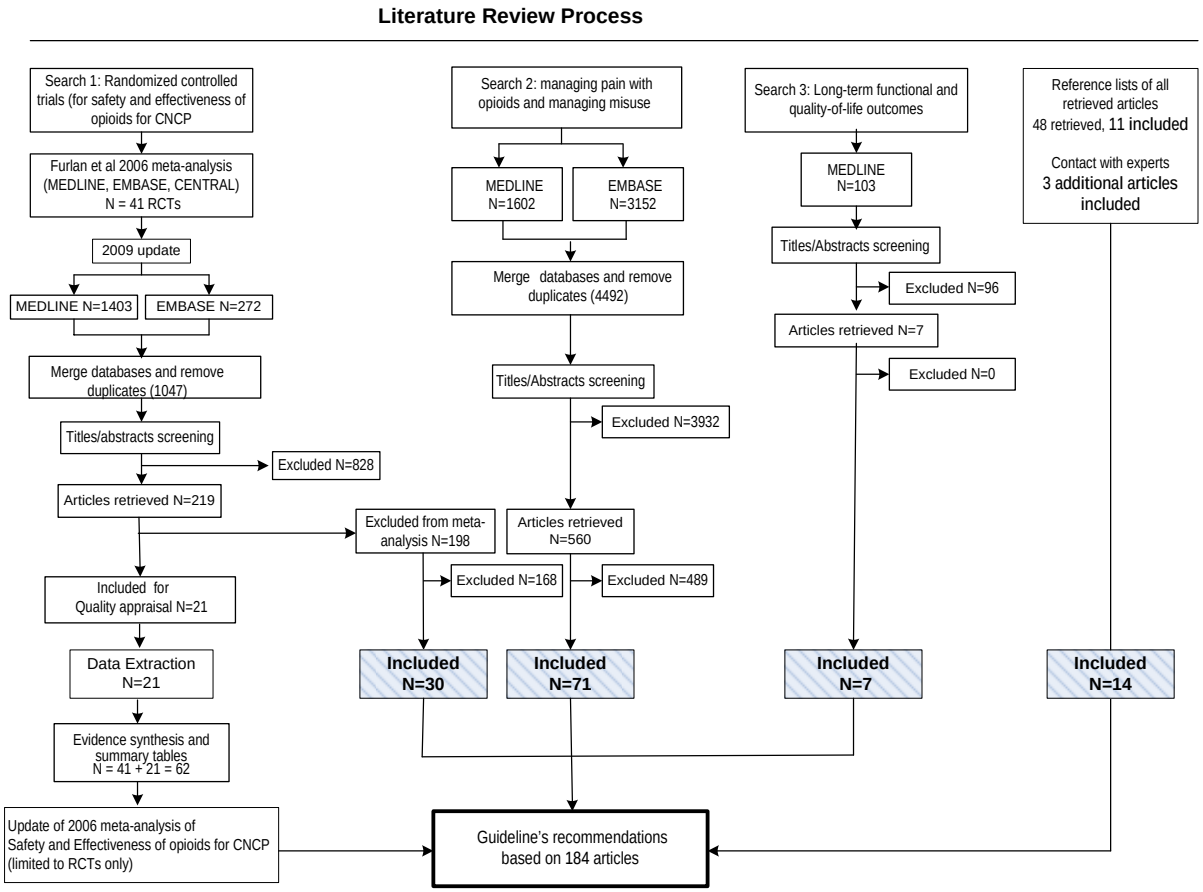
(2) Searches for EMBASE and MEDLINE

1. narcotics/
2. exp Analgesics, Opioid/
3. morphine/
4. codeine/
5. fentanyl/
6. hydromorphone.mp.
7. (levorphanol or meperidine or oxymorphone or pentazocine or propoxyphene or sufentanil or tramadol).mp.
8. hydrocodone.mp.
9. tramacet/
10. 57-27-2.rn.
11. oxycodone/
12. 76-42-6.rn.
13. Buprenorphine/
14. prescription opioid$.mp.
15. or/1-14
16. pain/
17. pain clinics/
18. 16 or 17
19. exp Risk Assessment/
20. substance-related disorders/
21. screening.mp.
22. psychoactive effect$.mp.
23. misuse.mp.
24. dependence.mp.
25. abuse liability.mp.
26. risk factor$.mp.
27. urine drug screening.mp.
28. clinical feature$.mp.
29. substance abuse detection/
30. opioid-related disorders/
31. substance abuse detection/
32. crime/
33. drug.mp. and narcotic control/
34. street drugs/
35. substance withdrawal syndrome/
36. methadone/
37. or/19-36
38. 15 and 18 and 37

(3) Search strategy in MEDLINE

1. randomized controlled trial/
2. Random Allocation/
3. Double-Blind Method/
4. Single-Blind Method/
5. Research Design/
6. Comparative Study/
7. exp Evaluation Studies/
8. Follow-Up Studies/
9. Prospective Studies/
10. Cross-Over Studies/
11. or/1-10
12. exp Chronic Disease/pc, dt, th, rh [Prevention & Control, Drug Therapy, Therapy, Rehabilitation]
13. exp Pain/th, rh, dt, pc [Therapy, Rehabilitation, Drug Therapy, Prevention & Control]
14. (chronic adj5 pain).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
15. exp Analgesics, Opioid/
16. Opioid-Related Disorders/
17. "Quality of Life"/
20. or/12-14
21. or/16-17
22. 11 and 20 and 15 and 21

Appendix A-5: Flowchart of Literature Review Process



Appendix A-6: NOUGG Criteria for Recruiting NAP Members

Organizations participating in NOUGG applied criteria to select advisory panel members included the following:

1. Include those who are physician "influencers" within the province/territory.
2. Include those whose endorsement and assistance with implementation could help identify barriers and contribute to the *Canadian Guideline's* successful implementation to practice.
3. Invite individuals who bring their own perspectives but who are fundamentally committed to blending research evidence and expert consensus in creating practice guidance.
4. Include a range of expertise and perspective (a single panel member might contribute more than one perspective):
   - *Family physicians* – predominant group targeted as the end-user for the *Canadian Guideline*
   - *Focused practice physicians* – pain and/or addictions.
   - *Other health disciplines* who work with physicians when opioids for CNCP are prescribed, e.g., pharmacists and nurses.
   - *Opinion Leaders* – broadly defined as those within the province/territory who others look to for guidance or as models.
   - *Academia* – researchers and teachers who bring a focus on the evidence.
   - *Other relevant stakeholders* who have a distinct role in this area and who are seen as critical to successful implementation of the *Canadian Guideline*.

Appendix A-7: Disclosure of Conflict of Interest Form

National Opioid Use Guideline Group (NOUGG)
Disclosure of Conflict of Interest

COMPLETION OF THIS DISCLOSURE IS MANDATORY FOR ALL EXPERTS PARTICIPATING IN THE NOUGG GUIDELINE DEVELOPMENT PROCESS

The National Opioid Use Guidelines Group wants to ensure balance, independence, impartiality and scientific rigor in the review of the guideline by experts from across the country. All experts are asked to disclose any real or apparent conflict(s) of interest in the past two years that may have a direct bearing on the subject matter of the guidelines. This pertains to relationships with pharmaceutical companies who may manufacture or distribute pharmaceutical products containing opioids or used in the treatment and management of pain, and to work done on behalf of third parties such as insurance companies or workers compensation agencies.

The intent of this disclosure is not to prevent any reviewer from participating in the process but rather to be transparent about any conflicts so that users of the guidelines can form their own judgment to determine the possible existence of bias in review of the guidelines.

The final guideline will include the names of the expert panel members and their disclosures of conflicts of interest.

Name: _____

Address: _____

Email: _____

A. ☐ I have no actual or potential conflict of interest

OR

B. ☐ I have/had financial interest/arrangement or affiliation with the following organizations that could be perceived as a possible or apparent conflict of interest. *(Please list the name of the organization(s) and the nature of your relationship. Please include: Grant or Research support, consultant or Honoraria, shareholding or any other financial or material support.)*

Affiliation/Financial Interest	Name of Organization(s)
Grant or Research Support (PI or Co investigator; any amount)	
Consultant or Honoraria (>$5000 annually)	
Stock Shareholder (>$5000)	
Other Financial/Material Support (>$5000 annually)	
Other	

Signature: _____ Date: _____

Appendix A-8: Modified Delphi Process used in NAP Consultation Rounds 2 to 4

Before Round 1 of the modified Delphi process, all NAP members received the following description of methodology:

1. Through structured responses, NAP members are requested to indicate their degree of support for draft recommendations. A "N/A" response offers an option for NAP members not able to give an opinion about a specific statement.
2. The evidence grade for recommendations lacking Grade A or Grade B evidence will be considered Grade C if NAP reaches consensus.
3. The definition of consensus for this Modified Delphi process is:
   80% of National Advisory Panel respondents indicate that they Agree or Strongly Agree with the statement "I support this recommendation."
4. Results from the Modified Delphi process will identify:
   1) recommendations the NAP supports by consensus, and
   2) recommendations that require further consultation with NAP.
5. Following NOUGG analysis of all NAP replies, each respondent will receive a comparison of their own individual feedback and the aggregate NAP responses.
6. The Modified Delphi process will be used in subsequent guideline rounds as required.
7. After Round 2 of the Modified Delphi process, recommendations based on Grade C evidence only and failing to reach consensus will be eliminated. However, recommendations based on Grade A and/or B evidence that fail to achieve consensus will undergo further revision for consideration by NAP in a third round.

Appendix A-9: NAP Electronic Response Survey Tool

To capture NAP feedback, CPSA used a web-based electronic-response tool developed using SurveyMonkey®.

Electronic responses (using a Likert scale) were required to three statements for each recommendation:

1) This recommendation is clear.
2) It would be feasible for me to follow this recommendation in my usual practice setting.
3) I support this recommendation.

Likert scale:

- Strongly Disagree
- Disagree
- Neither Agree nor Disagree
- Agree
- Strongly Agree
- N/A (offered an option for NAP members not able to give an opinion).

In addition, NAP members had the option of providing open-ended comments or information they would like to add. Members were requested to comment if they felt a recommendation lacked clarity or was not feasible. If they did not support a recommendation, respondents were requested to provide their rationale and identify what changes would be necessary for them to support

Scoring Consensus:
Consensus for a recommendation was predefined as at least 80% of responders indicating they agreed or strongly agreed with the statement "I support this recommendation".
Note: NAP members responding to a statement using "N/A," were removed from the denominator calculating consensus.