**Supplemental Online Material. Appendix A.**
**Protocol for Knowledge Synthesis: Opioid Adjuncts in Drug Tapering**

**1) Stating the objectives of the research.** As described above, the objectives will guide the methods and processes of the knowledge synthesis,[S1] which will be applied toward development of opioid tapering guidance. Lack of consensus regarding appropriate and effective use of opioid adjunct drugs presents a challenge to clinicians and researchers.

**2) Defining eligibility criteria for studies to be included.** The eligibility criteria directly inform the development of the search strategies and provides the basis for assessing search results for potentially relevant studies. The inclusion criteria for obtaining full text of an article are: 1) the article described the results of empirical quantitative or qualitative research, and 2) the article referred to the use of opioids with adjunct drugs to treat primarily chronic non-cancer pain (CNCP). Articles published in all languages are considered for inclusion. In addition to randomized trials the inclusion of non-randomized designs such as observational studies of treatment harms may be considered. The exclusion criteria for obtaining full text of an article are: 1) Studies published prior to 2010, 2) editorials, letters to the editor, or protocols, 3) in vitro studies, and 4) studies with too few participants (e.g., fewer than 10).

**3) Identifying potentially eligible studies.** Key issues considered when identifying potentially eligible studies include the specific bibliographic databases to search, the development of appropriate search strategies and other strategies to identify relevant studies.[S2] The bibliographic databases for ongoing searches include MEDLINE (1950 to present); EMBASE (1980 to present); SCOPUS (2004 to present); CINAHL (1982 to present); and CENTRAL (Cochrane Central Register of Controlled Trials); PsychINFO (1967–present); Web of Science SSCI (1956–present); Google Scholar, and/or regional bibliographic databases and/or specialized databases as determined by the consultant medical librarian. Development of appropriate search strategies include both content and methodological terms based upon the controlled vocabulary of bibliographic databases being searched (e.g., MeSH in MEDLINE) and free text terms related to pain management and opioids and adjunctive drug therapy. In addition to searches of major bibliographic databases, project participants (i.e., synthesis team) may employ other strategies to identify potentially eligible studies including:

Searching 'grey' literature: Grey literature includes studies that are not formally published in books or journals and can include conference proceedings and abstracts, dissertations and theses, project reports, government documents etc. Several grey literature databases are available.[S3]

Searching databases of ongoing research: Searches may be conducted for ongoing studies given initiatives to register clinical trials[S4-S6] and the availability of research databases of ongoing studies. This search may identify studies that are nearing completion that might influence the results of the review. It may also identify completed studies that have not been published.

Tracking citations: Studies may be identified that have cited key studies in citation indexes such as the Science Citation Index. In addition, if possible, citations may be checked in potentially relevant studies.

Hand searching journals: Hand searching involves a 'manual page-by-page examination of the entire contents of a journal issue' to identify eligible studies.[S3] This method may be employed if relevant studies are not indexed in electronic bibliographic databases. Or if indexed, they may be done so in a way that alludes being identified by search strategies.

Contacting experts in the field: Content experts may be aware of research studies that may not be easily identified through any of the above channels, and may be contacted after the searches have been screened to identify any missing studies.

**4) Applying eligibility criteria.** Titles and abstracts may be examined to exclude irrelevant reports. Results from multiple searches may be merged using reference management software and duplicate records of the same study may be removed. Full-text copies of potentially relevant reports will be retrieved and examined against eligibility criteria. Authors may be contacted, when appropriate, to seek further information needed to judge the eligibility of potentially relevant studies. Screening may be conducted by two independent reviewers to minimize the risk that relevant studies will be discarded. Flow diagrams may be employed to represent how studies were identified and selected.[S7]

**5) Assembling the most complete data set feasible; data extraction.** Data extraction involves identification of key data items that need to be collected, development of a data extraction form and coding book, extraction of data from the primary reports, and checking the reliability of data extraction. For this project, the key data items involve bibliographic details, methodology, context and setting, participants, interventions, outcomes, results and other data.[S8] Patient data that is collected, if available, includes age, gender, ethnicity, diagnosis, type of pain, either chronic or acute. Drug and dosing information collected may include the opioid intervention, adjunct drug intervention, doses, frequency and duration of treatment. Methods used to determine if improvement in pain relief occurred, such as subjective or objective pain scales may be collected. In addition, if available, adverse drug event data and risk factors for Opioid Use Disorder (OUD) may be reported. A data extraction form based on recommendations by Petticrew and Roberts[S9] may be used to record the key data items, their source, and their location within the study report records. The data extraction form also acts as a historical record of the decisions that are made during the review process.

Ethical issues related to the data include 1) ensuring informed consent from participants, 2) maintaining confidentiality and privacy, 3) implementing robust data handling and security measures, 4) procurement of ethical approval from relevant boards, 5) assessment and mitigation of potential harm to participants, and 6) adherence to strict data governance protocols to ensure responsible data use and compliance with legal standards.[S10]

**6) Appraising studies.** A key element of undertaking a knowledge synthesis involves an appraisal of the likely validity of the included studies. This element recognizes that individual studies may have problems with their design, conduct, and analysis that raises questions about their potential validity.[S11] The project participants (i.e., synthesis team) may appraise studies to consider any threats to validity during the analysis or interpretation of the eligible studies.

Tools exist for appraising both randomized and non-randomized studies of effects including checklists,[S12,S13] which have been used by Veronin et al, [S14] and may be applied in the project. The Jadad scale is a procedure used to independently assess the methodological quality of a clinical trial and is the most widely used such assessment in the world.[S15,S16] It has been used for critical analysis of an individual paper and to evaluate the general quality of medical research in a particular field. In anticipation of obtaining quantitative and qualitative studies the Modified Jadad Scale may be employed to assess the quality of the quantitative studies.[S17] The Consolidated Criteria for Reporting Qualitative Research (COREQ), developed by Tong, Sainsbury, and Craig and includes 32 appraisal indices, may be used to assess the quality of the qualitative studies.[S18]

**7) Data Analysis and Interpretation; use of statistical synthesis and sensitivity analysis.** Sensitivity analyses determine how the different values of an independent variable, in this case drug treatment, impact a particular dependent variable, in this case outcome assessments such as pain scales, under a given set of clinical conditions.[S19] Analyses of collected data from this project may be conducted with Excel Tools® for conducting sensitivity analyses. Narrative synthesis and meta-analytic approaches may be applied where appropriate to ongoing studies to identify a general framework for synthesis of effectiveness for opioid adjunctive drug therapy.[S20] For the aggregate of research reports, the focus of analysis and

interpretation will be on direction, size, consistency, and strength of the outcomes of the opioid-sparing effects.

**7a. Strength of Evidence.** The Strength-of-Recommendation Taxonomy (SORT) may be used to label key recommendation in clinical reports.[S21] Grades are assigned on the basis of quality and consistency of available evidence. Strength of recommendation grades are designated as A (Consistent, good-quality patient-oriented evidence), B (Inconsistent or limited-quality patient-oriented evidence), or C (Consensus, disease-oriented evidence, usual practice, expert opinion, or case series for studies of diagnosis, treatment, prevention, or screening). Study quality is designated as Level 1 (good-quality such as systematic review, meta-analysis or randomized controlled trials with consistent findings), Level 2 (limited quality such as systematic review, meta-analysis or randomized controlled trials with inconsistent findings, lower quality clinical trial, cohort and case-control studies), or Level 3 (consensus guidelines, usual practice, opinion).

**8) Data Reporting.** The final step involves disseminating the research findings and products to potential users in the health care system. Beyond this, plans may include the reporting of results in the form of an interactive information resource for clinicians.

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