

EDITORIAL OFFICE OFFICIAL INFO PAGE**MANUSCRIPT NUMBER:** 19-0199**DOI:** 10.3122/jabfm.2020.04.190199**SECTION:** Original Research**ORIGINAL TITLE:** A Scoping Review on Clinical Decision Support Systems for Opioid Prescribing for Chronic Non-Cancer Pain in Primary Care Settings**NEW TITLE (NOTIFY AUTHOR):** Clinical Decision Support Systems for Opioid Prescribing for Chronic Non-Cancer Pain in Primary Care: A Scoping Review**SHORT TITLE: Cover/Footer:** Clinical Decision Support for Opioid Prescribing**KEYWORDS:** *Biomedical Technology Assessment, Chronic Pain, Clinical Decision-Making, Clinical Decision Support Systems, Electronic Health Records, Information Technology, Opioid-Related Disorders, Outcomes Assessment, Prescription Drug Monitoring Programs, Translational Medical Research***COPY EDITOR NOTES:** NA

Authors

Sheryl Spithoff MD MSc, Staff Physician, Department of Family and Community Medicine Women's College Hospital; Assistant Professor, Department of Family and Community Medicine, University of Toronto; Toronto, ON

Stephanie Mathieson PhD, Research Fellow, Institute for Musculoskeletal Health, Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney; Sydney, Australia

Frank Sullivan FRSE, FRCGP, Professor of Primary Care Medicine, University of St Andrews; St Andrews, Scotland; Professor, Department of Family and Community Medicine, University of Toronto; Toronto, ON

Qi Guan MSc, Doctoral Student, Institute of Health Policy, Management and Evaluation, University of Toronto; Toronto, ON

Abhimanyu Sud, MD CCFP, Assistant Professor, Department of Family and Community Medicine; Research Fellow, Medical Psychiatry Alliance; Doctoral Student, Institute of Health Policy, Management and Evaluation, University of Toronto; Toronto, ON

Susan Hum, MSc, Research Associate, Department of Family and Community Medicine, Women's College Hospital; Toronto, ON

Mary Ann O'Brien PhD, Assistant Professor, Department of Family and Community Medicine, University of Toronto; Project Scientist, Women's College Research Institute; Toronto, ON

Corresponding author

Sheryl Spithoff: sheryl.spithoff@wchospital.ca

Disclosure Statement

None of the authors have any competing interests to declare.

Funding

This project did not receive specific funding. Sheryl Spithoff was supported by a graduate research award from the University of Toronto Department of Family and Community Medicine; Stephanie Mathieson received fellowship support in 2018 from a National Health and Medical Research Council (NHMRC) program grant (#AP1113532) and 2019 NHMRC Early Career Fellowship (#APP1158463); Frank Sullivan was supported by NYGH as the Gordon F Cheesbrough Research Chair in Family and Community Medicine; Abhimanyu Sud was supported by a graduate research award from the University of Toronto, Department of Family and Community Medicine and a research fellowship from the Medical Psychiatry Alliance, University of Toronto; Qi Guan was supported by a graduate research award from the Institute of Health Policy, Management and Evaluation, University of Toronto.

Acknowledgements

Kaitlin Fuller, Education & Liaison Librarian for the MD Program and the Institute of Medical Science; Gerstein Science Information Centre, University of Toronto

Word count: 3,013

Abstract

Background and objectives: Clinical decision support systems (CDSSs) may help clinicians prescribe opioids for chronic non-cancer pain (CNCP) more appropriately. This scoping review determined the extent and range of the current evidence on CDSSs for opioid prescribing for CNCP in primary care, and whether investigators followed best evidence and current guidance in designing, implementing and evaluating these complex interventions.

Methods: We searched nine electronic databases and other data sources for studies from January 1st 2008 to October 11th 2019. Two reviewers independently screened the citations. One reviewer extracted data and a second verified for accuracy. Inclusion criteria: study of a CDSS for opioid prescribing for CNCP in a primary care clinical setting. We reported quantitative results in tables and qualitative results in narrative form.

Results: Our search yielded 5068 records of which 14 studies met our inclusion criteria. All studies were conducted in the United States. Six studies examined local (eg, health centre) CDSSs and eight examined prescription drug monitoring program (PDMP) CDSSs. Three CDSSs incorporated evidence-based components. Study aims were heterogeneous and study designs included both quantitative and qualitative methodologies. No studies assessed patient health outcomes. Few studies appeared to be following guidance for evaluating complex interventions.

Conclusions: Few studies have rigorously assessed the use of CDSSs for opioid prescribing for CNCP in primary care settings. Going forward, investigators should include evidence-based components into the design of CDSSs and follow guidance for the development and evaluation of complex interventions.



**A Scoping Review on Clinical Decision Support Systems for Opioid Prescribing for
Chronic Non-Cancer Pain in Primary Care Settings**

1 **Abstract**

2 **Background and objectives:** Clinical decision support systems (CDSSs) may help clinicians
3 prescribe opioids for chronic non-cancer pain (CNCP) more appropriately. This scoping review
4 determined the extent and range of the current evidence on CDSSs for opioid prescribing for
5 CNCP in primary care, and whether investigators followed best evidence and current guidance in
6 designing, implementing and evaluating these complex interventions.

7 **Methods:** We searched nine electronic databases and other data sources for studies from January
8 1st 2008 to October 11th 2019. Two reviewers independently screened the citations. One
9 reviewer extracted data and a second verified for accuracy. Inclusion criteria: study of a CDSS
10 for opioid prescribing for CNCP in a primary care clinical setting. We reported quantitative
11 results in tables and qualitative results in narrative form.

12 **Results:** Our search yielded 5068 records of which 14 studies met our inclusion criteria. All
13 studies were conducted in the United States. Six studies examined local (eg, health centre)
14 CDSSs and eight examined prescription drug monitoring program (PDMP) CDSSs. Three
15 CDSSs incorporated evidence-based components. Study aims were heterogeneous and study
16 designs included both quantitative and qualitative methodologies. No studies assessed patient
17 health outcomes. Few studies appeared to be following guidance for evaluating complex
18 interventions.

19 **Conclusions:** Few studies have rigourously assessed the use of CDSSs for opioid prescribing for
20 CNCP in primary care settings. Going forward, investigators should include evidence-based
21 components into the design of CDSSs and follow guidance for the development and evaluation
22 of complex interventions.

23

24 **Introduction**

25 Two countries at the epicentre of the opioid crisis, Canada and the US, (1–4) recently released
26 clinical practice guidelines for opioid prescribing for chronic non-cancer pain (CNCP) (5,6).
27 These guidelines recommend against using opioid analgesics for CNCP because the harms
28 frequently outweigh benefits (7–10). When opioids are prescribed for CNCP, the guidelines
29 recommend risk mitigation strategies and opioid dose tapering. Both guidelines target primary
30 care providers (PCPs), since they write about half of all opioid analgesic prescriptions in North
31 America (11–13). However, evidence shows that PCPs may have difficulty adopting
32 recommended clinical practices (14–21). Clinical decision support may provide assistance.

33
34 Clinical decision support systems (CDSSs) are electronic systems that assist health care
35 providers in clinical decision-making, by providing patient-specific data at the point-of-care (14–
36 16). Studies show that CDSSs lead to improvements in clinician performance (a care process
37 measure), such as ordering appropriate tests and safer prescribing (17–25). Some CDSS design
38 components are evidence-based, including; requiring a reason for an over-ride; activating
39 automatically (i.e., the CDSS runs without requiring provider initiation); integrating into the
40 electronic medical record (EMR); and providing advice to patients (e.g. written materials), as
41 well as clinicians (14,20,26–28). These components lead to improvements in care process
42 outcomes. Studies in which the CDSS evaluators are also the developers tend to show positive
43 impact on process outcomes (26,27).

44
45 However, the impact of CDSS on important patient health outcomes or population health
46 outcomes is unclear (17–20), and widespread adoption is often limited by implementation issues
47 (29–34). Additionally, CDSSs can be difficult to develop and evaluate because they are complex
48 interventions that seek to change the functioning of a complex adaptive system such as a primary
49 care clinic (35). Therefore, the Medical Research Council in the United Kingdom (UK)
50 recommends that researchers design and evaluate these interventions through a carefully staged
51 series of studies targeting key uncertainties as well as a definitive evaluation (35,36). All steps
52 should include process evaluations and assess for unintended consequences (37).

53 CDSSs can have a variety of roles in improving adherence to opioid prescribing guidelines for
54 CNCP. They can be used to reduce the number of new opioid prescriptions for acute pain (38)

55 and to reduce the initiation of opioid prescribing for CNCP. They can also be used to improve
56 prescribing and other measures like risk mitigation strategies for patients already receiving
57 opioids for CNCP. This is the most challenging role for a CDSS these patients are at high risk of
58 harms and changing prescribing is very difficult (39,40).

59 Several studies have evaluated CDSSs for opioid prescribing for CNCP in primary care settings
60 (41–44). These studies report that the use of a CDSS led to a reduction in opioid prescribing or
61 improved adherence to clinical practice guidelines (41–44). Several studies have also evaluated
62 prescription drug monitoring program (PDMP) CDSSs for opioid prescribing for CNCP in
63 primary care settings. PDMP CDSSs are large, centralized, government-run databases that
64 prescribers can provide point-of-care for information on a patient’s opioid prescriptions (45,46).
65 While one PDMP CDSS study found that physicians wrote fewer opioid prescription in 61% of
66 cases, (47); another study reported no association between PDMP implementation status and
67 requirement levels (from no requirements to a mandatory requirement to check the PDMP before
68 prescribing) and physicians’ opioid prescribing for CNCP (48). Four other PDMP CDSS studies
69 examined PCPs’ use of, and views on PDMPs (49–52). To date, however, the literature in this
70 emerging field has not been systematically summarized and analyzed so the benefits and risks of
71 implementing a CDSS are unclear.

72
73 This scoping review determined the extent and range of the current evidence on CDSSs for
74 opioid prescribing for CNCP in primary care. Our secondary aim was to determine whether
75 researchers followed best evidence for the design of the CDSSs and current guidance for the
76 evaluation of complex interventions.

78 **Methods**

79 We conducted a scoping review using the frameworks (53,54) described by Colquhoun et al (55),
80 and the methods outlined by The Joanna Briggs Institute (56). We followed the reporting
81 guidelines from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-
82 Analyses) Extension for Scoping reviews (PRISMA-ScR) (57). We created an a priori protocol
83 and used an iterative approach. Modifications included a secondary research aim and a change to
84 the data extraction plan.

85

86 **Study eligibility:** We included peer- and non-peer reviewed studies that used quantitative,
87 qualitative and mixed-methods methodologies. We excluded non-systematic reviews, letters,
88 opinion articles, analysis articles, clinical practice guidelines and policy documents. We included
89 all studies where the population was PCPs (ie, family physicians, emergency medicine
90 physicians, nurse practitioners (NPs) and primary care internists) working in a primary care
91 setting. Studies that reported less than 50% PCPs or did not report the percentage of PCPs were
92 excluded unless results were reported by subgroup. We included all studies that assessed a CDSS
93 that sought to improve to improve opioid prescribing for CNCP patients in a primary care
94 clinical setting. We excluded studies where primary care providers were working in a secondary
95 and tertiary settings such as a pain clinic or addiction clinic. We excluded primary care pediatric
96 clinics. We defined a CDSS as an electronic system that assisted health care providers in clinical
97 decision-making, by providing patient-specific data at the point-of-care (14–16). We included
98 studies where the CDSS was integrated into the EMR, or functioned independently (eg, web-
99 accessed), or was embedded within a larger intervention. We excluded studies where CDSS use
100 was not specified, where it was used for another reason, or where it was not implemented in
101 clinical settings.

102

103 ***Data sources and searches***

104 We searched electronic databases (MEDLINE (via OVID), EMBASE, CINAHL, CENTRAL,
105 PsycINFO and International Pharmaceutical Abstracts (via OVIDSP)) from January 1st 2008 –
106 October 11 2019. CDSSs developed prior to this period likely evolved or became obsolete (59).
107 We built a comprehensive search strategy, including the terms “opioid,” and “clinical decision
108 support systems.” Since studies used a large number of different keywords and medical subject
109 headings (MeSH) for a CDSS, we had to conduct a broad search using a large variety of terms,
110 including; computer systems, health informatics, clinical decision making (Appendix 1 Medline
111 search strategy). The Medline strategy (Appendix 1) was adapted for the other databases. We
112 used the Canadian Agency for Drugs and Technologies (CADTH) approach to our grey literature
113 search (Appendix 2 Grey literature search) (60). We also searched trial registries
114 (ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform

115 (WHO ICTRP)), checked reference lists of additional eligible studies and contacted experts (ie,
116 lead authors on included studies, registered protocols and systematic reviews of CDSSs).

117

118 *Screening and selection*

119 Two researchers independently screened abstracts to determine if they met inclusion criteria.

120 Two researchers then independently screened the full-text of all relevant articles. For both steps,
121 after we screened 10 to 15 titles and articles, we checked inter-reviewer agreement to ensure it
122 was least 80% before continuing further. When there were disagreements, a third researcher
123 (MAO) assisted in making the final decision. We contacted authors for more information when
124 full text was not available online (58).

125

126 *Data extraction*

127 We created and pilot-tested a data extraction form to record the following items: study
128 population and setting, description of the intervention and implementation process, type of
129 CDSS, inclusion of evidence-based CDSS components (components that the literature has
130 consistently found to have an impact on outcomes: requiring a reason for an over-ride; activating
131 automatically; integrating into the electronic medical record (EMR); and providing advice to
132 patients and clinicians (14,20,26–28), study aims, methodology and design, study outcomes,
133 funding information, conflicts of interest, and adherence to guidance for complex interventions
134 (eg, study was part of a stepped approach to development and evaluation; assessment for
135 unintended consequences; planned process evaluation; process and outcome measures;
136 theoretical approach to guide implementation and/or evaluation). One reviewer extracted data
137 and another researcher reviewed their work (SMS, MAO, QG, SM, SH). This was a modification
138 from our protocol that specified that two researchers would independently extract the data.

139

140 *Data synthesis*

141 We used a flow diagram to report on study selection. We reported quantitative data in tabular
142 format. We wrote narrative summaries using contextual and process-oriented data. We did not
143 conduct a detailed assessment of study quality, assess for reporting bias, or risk of bias consistent
144 with current guidance on conducting scoping reviews (55–57).

145

146

147 **Results**

148 Our literature search identified 5068 citations from which 14 were included in the scoping
149 review (Figure 1). Six studies examined local CDSSs (e.g., specific health system, centre or
150 clinic) (41,43,44,61–63) while eight examined state-run, web-based, central PDMP CDSSs
151 (47,49–52,64–66) Results using these two typologies are summarized in Table 1. Study
152 descriptions are detailed in Appendix 3.

153

154

155 *CDSS description*

156 Types of CDSSs included protocols (i.e., forms that guide clinical management) in the EMR,
157 intranet dashboards, EMR alerts, data repositories and web-based clinical tools. Four local
158 CDSSs were integrated into the EMR (43,44,62) and two automatically activated (44,62). The
159 other two required the PCP to activate the CDSS. Studies assessing PDMP CDSSs did not report
160 any evidence-based design components.

161

162 *Study characteristics*

163 All studies occurred in the US and practice settings were mostly primary care clinics. Three were
164 set in the emergency department (44,47,49). All of the local CDSSs, and three of the PDMP
165 CDSS studies (47,64,66) were designed to assess whether a CDSS alone or incorporated into a
166 multi-faceted intervention improved prescribing or adherence to guidelines. The remaining
167 PDMP CDSS studies determined providers' behaviour, knowledge of, attitudes toward and use
168 of CDSSs. Local CDSS study designs included four pre-post interventions, a cluster RCT and a
169 mixed-methods evaluation. The eight PDMP CDSS studies included a wide variety of study
170 designs including: three pre-post interventions, a cross-sectional survey, two qualitative, one
171 mixed methods and one retrospective cohort. Study aims and designs are summarized in Table 2
172 and described in detail in Appendix 3. One study was part of a stepped approach in evaluating a
173 complex intervention (63). About half of the studies that assessed the impact of an intervention
174 included a process evaluation (measures assessing if program components had been implemented

175 as intended) (41,43,47,49,62–64). Two studies reported using a theoretical approach in
176 implementation and evaluation processes (61,63).

177

178 ***Implementation processes***

179 All of the studies on local CDSSs described their implementation process, but provided little
180 detail. None of the PDMP CDSS studies described implementation processes.

181

182 ***Study Findings***

183 *Local CDSSs*

184 Anderson et al. found that the CDSS and summary reports improved compliance with guidelines
185 (41); Canada et al. reported that a CDSS plus monetary incentives improved adherence to
186 guidelines (43); Downes et al. found that a CDSS and electronic reports reduced opioid
187 prescribing and increased urine drug testing and use of pain contracts (62); Gugelmann et al.
188 found that the CDSS reduced opioid prescribing (44); Liebschutz et al. reported that a multi-
189 faceted intervention that included a CDSS in both study arms also reduced opioid prescribing
190 (61); and Seal et al. found in a multi-component intervention (with CDSS in both arms) that
191 providers “abandoned use” of the CDSS (63).

192

193 *PDMP CDSSs*

194 Baehren et al. found that physicians who used PDMP data wrote fewer opioid prescriptions in
195 61% of cases and more opioid prescriptions in 39% of cases (47); Binswanger et al. found that a
196 multi-component intervention improved adherence to guidelines (64); Chaudhary et al. found
197 that most PCPs reported always checking the PDMP before prescribing opioids to new patients
198 (52). Click et al. found that providers have positive views about PDMPs, but reported barriers in
199 using them (50). Coleman et al. found that in five of seven records of patient prescribed opioids,
200 providers accessed the PDMP (51). Freeman et al. reported that PDMPs are key tools for PCPs
201 and that barriers include a lack of integration (65); Kohlbeck et al. reported that an educational
202 intervention increased providers’ knowledge of, behaviour and attitudes toward PDMP CDSSs
203 (49); Patchett et al. reported that a multi-component intervention increased use of a PDMP and
204 led to a reduction in opioid prescribing (66).

205

206

207 ***Funding and conflict of interest***

208 All but two local CDSS studies reported on funding for CDSS evaluation (44,62); and three
209 others were missing information on funding for CDSS development (44,63). All PDMP studies
210 except one (66) provided information on funding for evaluation, but none provided information
211 on funding for developmentFor all six local CDSS studies, the developers were also the
212 evaluators or the relationship was unclear or not stated. No evaluators of PDMPs provided
213 information on their relationship to the PDMP developer (Table 3).

214

215

216 **Discussion**

217 We identified 14 studies published between 2009 and 2019 that examined CDSSs for opioid
218 prescribing for CNCP in primary care clinical settings. Six of the studies examined local CDSSs
219 (that were used locally within a specific health centre, health system or clinic) and eight
220 examined PDMP CDSSs. Studies evaluating CDSS impact found that the CDSS (alone or more
221 commonly, part of a dual or multi-component intervention) led to more appropriate prescribing
222 practices and/or adherence to guidelines. Several PDMP CDSS studies assessed providers' views
223 on, and/or their use of PDMP CDSSs. These studies reported frequent use of the PDMP CDSS
224 and positive views towards the CDSS with some acknowledgement of the barriers and
225 limitations. These findings are similar to a recent qualitative rapid review that asked providers
226 about the use of PDMPs (67). No study, however, contained an assessment of patient health
227 outcomes or assessed for unintended consequences. Additionally, in four studies the evaluators
228 were also the CDSS developers, a potentially useful situation but one that presents a potential
229 conflict of interest (26,27), that was not addressed by the investigators. We also found that few
230 CDSSs included evidence-based components and that in only one study investigators reported
231 following current guidance for development and evaluation of complex interventions (35,36).

232

233 Our finding that there were only 14 studies, and only one RCT, which met our inclusion criteria
234 is surprising. In contrast, a 2015 systematic review found seven RCT studies of CDSSs for
235 antibiotic prescribing by primary care providers (28). There may be several contributing factors.
236 The prescription opioid crisis only gained widespread attention in the last decade (68), and it

237 takes time to develop a complex intervention like a CDSS (36). It is also possible that some
238 CDSSs failed to show promise early on and development was subsequently stalled or halted.
239 Accordingly, there are a number of reports on the development of a CDSSs for opioid
240 prescribing for CNCP where clinical outcomes have not been reported yet (69–72). And finally,
241 it is possible that CDSSs are being used without an evaluation plan, as has occurred with many
242 PDMP CDSSs (73). This may be because of a demand for immediate solutions to the opioid
243 crisis and an evaluation of a CDSS takes significant time and money. However, since CDSSs
244 frequently do not improve patient outcomes (17–20), and may lead to unintended consequences,
245 a comprehensive evaluation is essential (74).

246

247 Most studies in our review that assessed the impact of the CDSS reported an improvement in
248 prescribing or better adherence to clinical practice guidelines. This aligns with previous research
249 in other fields: CDSSs have a modest impact on clinician performance (a care process outcome)
250 (17–25). However, these results need careful interpretation. Most studies were pre-post, non-
251 randomized control or observational designs. Although—consistent with guidance for scoping
252 reviews (55,56)—we did not conduct a quality assessment; these types of study designs have
253 greater threats to validity (75). Additionally, in most of the studies, the CDSS was part of a larger
254 intervention, so its specific impact was unclear. Another reason for caution is that no studies
255 assessed patient health outcomes, such as quality of life, morbidity and mortality (76–78).
256 Reductions in opioid prescribing and better adherence to guidelines may have unintended
257 consequences (36). For example, studies report that patients often turn to illicit sources of
258 opioids when they have reduced access to prescribed opioids, increasing their risk of overdose
259 (79–84). Several studies in a systematic review found that heroin overdoses increased after a
260 PDMP CDSS was implemented (74). A more recent systematic review, however, found no
261 consistent association between population-level opioid-related harms (including heroin use and
262 overdoses) and PDMP CDSSs (85). We also noted a conflict of interest in some studies where
263 the developers were also the evaluators. Systematic reviews in other fields have demonstrated
264 that when the CDSS evaluator is also the developer, outcomes are better (26,27). It is possible
265 that developers achieve better outcomes because they design effective implementation plans
266 (26), but it is possible that the conflict of interest leads to conscious or unconscious bias (26,86–
267 92). Interestingly, none of the studies reported funding from or involvement of for-profit entities.

268 It is possible that CDSSs developed by for-profit entities are not undergoing a publicly-reported
269 evaluation. This is problematic, and as a recent criminal case demonstrated, can lead to potential
270 harm to patients (93).

271

272 We found that few of the CDSSs incorporated evidence-based design components. In only one
273 study did researchers follow guidance for designing and evaluating complex interventions.
274 Developers may not have incorporated evidence-based components because of the lag time
275 between development and evaluation: when the CDSS was created the developers may not have
276 had access to systematic reviews on the various components. The developer may also feel that
277 the evidence does not apply to this particular subspecialty or setting (94). Another reason may be
278 a general excitement and overconfidence in e-health technologies (95). Funders and developers
279 may be too eager to solve the problem of unsafe opioid prescribing using e-health technologies
280 and are not ensuring that developers are building on information from the medical literature (95).
281 Changes are occurring. Between 2012 and 2016, the Substance Abuse and Mental Health
282 Services Administration (SAMHSA) funded nine projects to integrate PDMP data into EMRs
283 (96). Investigators might not follow guidance for complex evaluations because it is a lengthy and
284 expensive iterative process prior to a definitive evaluation (35–37,97). This is a widespread
285 issue—few complex interventions appear to undergo modelling, pilot and feasibility testing (98),
286 and many lack process evaluations (99,100). This is problematic. If researchers conduct a trial
287 without testing components, possible causal pathways, uncertainties, contextual factors, and
288 implementation approaches, they risk wasting resources on an expensive trial and perhaps
289 causing harm (35,37,101). Conversely, if the evaluation takes too long, the technology could
290 become obsolete before it gains widespread uptake (59). Adopting rapid, concurrent and iterative
291 pilot and feasibility studies may be the best approach (102–104).

292

293 *Limitations*

294 There are two main limitations in our review. In the grey literature search we may have missed
295 non-English language studies, as we conducted the searches only in English. Second, several of
296 the studies included both PCPs and other provider types (we excluded those with less than 50%
297 PCPs), and, as these studies only reported aggregate outcomes, they may not accurately reflect
298 the PCP population.

299
300
301
302
303
304
305
306
307
308
309
310

Conclusion and next steps

Our review reveals that few studies have rigorously assessed the use of CDSSs in the context of opioid prescribing for CNPP in the primary care setting. More high quality studies are needed. Going forward, investigators should include evidence-based components into the design of CDSSs and follow guidance for the development and evaluation of complex interventions, including pilot studies, process evaluations and an assessment for unintended consequences.

311 **References**

- 312 1. Fischer B, Keates A, Bühringer G, Reimer J, Rehm J. Non-medical use of prescription
313 opioids and prescription opioid-related harms: why so markedly higher in North America
314 compared to the rest of the world? *Addict Abingdon Engl*. 2014 Feb;109(2):177–81.
- 315 2. Report of the International Narcotics Control Board for 2017 [Internet]. International
316 Narcotics Control Board; 2017. Available from:
317 <https://www.incb.org/incb/en/publications/annual-reports/annual-report-2017.html>
- 318 3. Seth P. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants — United
319 States, 2015–2016. *MMWR Morb Mortal Wkly Rep* [Internet]. 2018 [cited 2018 Apr 23];67.
320 Available from: <https://www.cdc.gov/mmwr/volumes/67/wr/mm6712a1.htm>
- 321 4. Government of Canada. National Report: Apparent opioid-related deaths in Canada
322 [Internet]. 2018 [cited 2018 Apr 23]. Available from: [www.canada.ca/en/public-
323 health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-
324 released-march-2018.html](http://www.canada.ca/en/public-health/services/publications/healthy-living/national-report-apparent-opioid-related-deaths-released-march-2018.html)
- 325 5. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic
326 Pain--United States, 2016. *JAMA*. 2016 Apr 19;315(15):1624–45.
- 327 6. Busse J. The 2017 Canadian Guideline for Opioids for Chronic Non-Cancer Pain [Internet].
328 National pain center; 2017. Available from:
329 [http://www.cmaj.ca/content/suppl/2017/05/03/189.18.E659.DC1/170363-guide-1-at-
330 updated.pdf](http://www.cmaj.ca/content/suppl/2017/05/03/189.18.E659.DC1/170363-guide-1-at-
330 updated.pdf)
- 331 7. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al.
332 Overdose and prescribed opioids: Associations among chronic non-cancer pain patients. *Ann
333 Intern Med*. 2010 Jan 19;152(2):85–92.
- 334 8. Bohnert AB, Valenstein M, Bair MJ, et al. Association between opioid prescribing patterns
335 and opioid overdose-related deaths. *JAMA*. 2011 Apr 6;305(13):1315–21.
- 336 9. Gomes T, Mamdani MM, Dhalla IA, Paterson JM, Juurlink DN. Opioid dose and drug-
337 related mortality in patients with nonmalignant pain. *Arch Intern Med*. 2011 Apr
338 11;171(7):686–91.
- 339 10. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness
340 and risks of long-term opioid therapy for chronic pain: a systematic review for a National
341 Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med*. 2015 Feb
342 17;162(4):276–86.
- 343 11. Volkow ND, McLellan TA, Cotto JH, Karithanom M, Weiss SRB. Characteristics of Opioid
344 Prescriptions in 2009. *JAMA*. 2011 Apr 6;305(13):1299–301.
- 345 12. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic-Prescribing Rates by
346 Specialty, U.S., 2007-2012. *Am J Prev Med*. 2015 Sep;49(3):409–13.

- 347 13. Health Quality Ontario. Starting on Opioids in Ontario [Internet]. 2017 [cited 2018 Jul 12].
348 Available from: <http://startingonopioids.hqontario.ca/>
- 349 14. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using
350 clinical decision support systems: a systematic review of trials to identify features critical to
351 success. *BMJ*. 2005 Apr 2;330(7494):765.
- 352 15. Sim I, Gorman P, Greenes RA, Haynes RB, Kaplan B, Lehmann H, et al. Clinical Decision
353 Support Systems for the Practice of Evidence-based Medicine. *J Am Med Inform Assoc*
354 *JAMIA*. 2001;8(6):527–34.
- 355 16. Haynes RB, Wilczynski NL. Effects of computerized clinical decision support systems on
356 practitioner performance and patient outcomes: Methods of a decision-maker-researcher
357 partnership systematic review. *Implement Sci IS*. 2010 Feb 5;5:12.
- 358 17. Jia P, Zhang L, Chen J, Zhao P, Zhang M. The Effects of Clinical Decision Support Systems
359 on Medication Safety: An Overview. *PLOS ONE*. 2016 Dec 15;11(12):e0167683.
- 360 18. Sahota N, Lloyd R, Ramakrishna A, Mackay JA, Prorok JC, Weise-Kelly L, et al.
361 Computerized clinical decision support systems for acute care management: A decision-
362 maker-researcher partnership systematic review of effects on process of care and patient
363 outcomes. *Implement Sci IS*. 2011 Aug 3;6:91.
- 364 19. Roshanov PS, Misra S, Gerstein HC, Garg AX, Sebaldt RJ, Mackay JA, et al. Computerized
365 clinical decision support systems for chronic disease management: A decision-maker-
366 researcher partnership systematic review. *Implement Sci IS*. 2011 Aug 3;6:92.
- 367 20. Moja L, Kwag KH, Lytras T, Bertizzolo L, Brandt L, Pecoraro V, et al. Effectiveness of
368 Computerized Decision Support Systems Linked to Electronic Health Records: A Systematic
369 Review and Meta-Analysis. *Am J Public Health*. 2014 Dec;104(12):e12–22.
- 370 21. Jaspers MWM, Smeulders M, Vermeulen H, Peute LW. Effects of clinical decision-support
371 systems on practitioner performance and patient outcomes: a synthesis of high-quality
372 systematic review findings. *J Am Med Inform Assoc JAMIA*. 2011;18(3):327–34.
- 373 22. Nieuwlaat R, Connolly SJ, Mackay JA, Weise-Kelly L, Navarro T, Wilczynski NL, et al.
374 Computerized clinical decision support systems for therapeutic drug monitoring and dosing:
375 A decision-maker-researcher partnership systematic review. *Implement Sci IS*. 2011 Aug
376 3;6:90.
- 377 23. Souza NM, Sebaldt RJ, Mackay JA, Prorok JC, Weise-Kelly L, Navarro T, et al.
378 Computerized clinical decision support systems for primary preventive care: A decision-
379 maker-researcher partnership systematic review of effects on process of care and patient
380 outcomes. *Implement Sci IS*. 2011 Aug 3;6:87.
- 381 24. Hemens BJ, Holbrook A, Tonkin M, Mackay JA, Weise-Kelly L, Navarro T, et al.
382 Computerized clinical decision support systems for drug prescribing and management: a
383 decision-maker-researcher partnership systematic review. *Implement Sci IS*. 2011;6:89.

- 384 25. Bright TJ, Wong A, Dhurjati R, Bristow E, Bastian L, Coeytaux RR, et al. Effect of clinical
385 decision-support systems: a systematic review. *Ann Intern Med.* 2012 Jul 3;157(1):29–43.
- 386 26. Roshanov PS, Fernandes N, Wilczynski JM, Hemens BJ, You JJ, Handler SM, et al. Features
387 of effective computerised clinical decision support systems: meta-regression of 162
388 randomised trials. *BMJ.* 2013 Feb 14;346:f657.
- 389 27. Garg AX, Adhikari NKJ, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al.
390 Effects of computerized clinical decision support systems on practitioner performance and
391 patient outcomes: a systematic review. *JAMA.* 2005 Mar 9;293(10):1223–38.
- 392 28. Holstiege J, Mathes T, Pieper D. Effects of computer-aided clinical decision support systems
393 in improving antibiotic prescribing by primary care providers: a systematic review. *J Am
394 Med Inform Assoc JAMIA.* 2015 Jan;22(1):236–42.
- 395 29. Stultz JS, Nahata MC. Computerized clinical decision support for medication prescribing
396 and utilization in pediatrics. *J Am Med Inform Assoc JAMIA.* 2012;19(6):942–53.
- 397 30. Moxey A, Robertson J, Newby D, Hains I, Williamson M, Pearson S-A. Computerized
398 clinical decision support for prescribing: provision does not guarantee uptake. *J Am Med
399 Inform Assoc JAMIA.* 2010;17(1):25–33.
- 400 31. Patterson ES, Doebbeling BN, Fung CH, Militello L, Anders S, Asch SM. Identifying
401 barriers to the effective use of clinical reminders: bootstrapping multiple methods. *J Biomed
402 Inform.* 2005 Jun;38(3):189–99.
- 403 32. Arts DL, Medlock SK, van Weert HCPM, Wyatt JC, Abu-Hanna A. Acceptance and barriers
404 pertaining to a general practice decision support system for multiple clinical conditions: A
405 mixed methods evaluation. *PLoS ONE [Internet].* 2018 Apr 19 [cited 2018 Jul 19];13(4).
406 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5908177/>
- 407 33. Dalleur O, Seger DL, Slight SP, Amato M, Egualé T, Nanji KC, et al. Inappropriate
408 overrides of age-related alerts in prescriber order entry. *J Gen Intern Med.* 2015
409 Apr;2):S189–90.
- 410 34. Slight SP, Beeler PE, Seger DL, Dalleur O, Amato M, Egualé T, et al. An evaluation of
411 drug-allergy interaction alert overrides in inpatients. *J Gen Intern Med.* 2015 Apr;2):S81.
- 412 35. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and
413 evaluating complex interventions: the new Medical Research Council guidance. *The BMJ*
414 [Internet]. 2008 Sep 29 [cited 2018 Jul 26];337. Available from:
415 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2769032/>
- 416 36. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M. Developing and
417 evaluating complex interventions: The new Medical Research Council guidance. *Int J Nurs
418 Stud.* 2013 May 1;50(5):587–92.

- 419 37. Catwell L, Sheikh A. Evaluating eHealth Interventions: The Need for Continuous Systemic
420 Evaluation. *PLoS Med* [Internet]. 2009 Aug 18 [cited 2018 Sep 24];6(8). Available from:
421 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2719100/>
- 422 38. Shah A. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid
423 Use — United States, 2006–2015. *MMWR Morb Mortal Wkly Rep* [Internet]. 2017 [cited
424 2020 Feb 14];66. Available from: <https://www.facebook.com/CDCMMWR>
- 425 39. Dasgupta N, Beletsky L, Ciccarone D. Opioid Crisis: No Easy Fix to Its Social and
426 Economic Determinants. *Am J Public Health*. 2018 Feb;108(2):182–6.
- 427 40. Brooks EA, Unruh A, Lynch ME. Exploring the lived experience of adults using prescription
428 opioids to manage chronic noncancer pain. *Pain Res Manag J Can Pain Soc*. 2015;20(1):15–
429 22.
- 430 41. Anderson D, Zlateva I, Khatri K, Ciaburri N. Using health information technology to
431 improve adherence to opioid prescribing guidelines in primary care. *Clin J Pain*.
432 2015;31(6):573–9.
- 433 42. Patel S, Carmichael JM, Taylor JM, Bounthavong M, Higgins DT. Evaluating the Impact of
434 a Clinical Decision Support Tool to Reduce Chronic Opioid Dose and Decrease Risk
435 Classification in a Veteran Population. *Ann Pharmacother*. 2017 Oct 1;1060028017739388.
- 436 43. Canada RE, DiRocco D, Day S. A better approach to opioid prescribing in primary care. *J*
437 *Fam Pract*. 2014;63(6):E1-8.
- 438 44. Gugelmann H, Shofer FS, Meisel ZF, Perrone J. Multidisciplinary intervention decreases the
439 use of opioid medication discharge packs from 2 urban EDs. *Am J Emerg Med*. 2013 Sep
440 1;31(9):1343–8.
- 441 45. Sproule BA. Prescription Monitoring Programs in Canada: Best Practice and Program
442 Review [Internet]. Canadian Centre on Substance Abuse, Ottawa, ON; 2015 [cited 2018 Jun
443 14]. Available from: [http://www.ccsa.ca/Resource%20Library/CCSA-Prescription-](http://www.ccsa.ca/Resource%20Library/CCSA-Prescription-Monitoring-Programs-in-Canada-Report-2015-en.pdf)
444 [Monitoring-Programs-in-Canada-Report-2015-en.pdf](http://www.ccsa.ca/Resource%20Library/CCSA-Prescription-Monitoring-Programs-in-Canada-Report-2015-en.pdf)
- 445 46. Rutkow L, Smith KC, Lai AY, Vernick JS, Davis CS, Alexander GC. Prescription drug
446 monitoring program design and function: A qualitative analysis. *Drug Alcohol Depend*.
447 2017;180:395–400.
- 448 47. Baehren DF, Marco CA, Droz DE, Sinha S, Callan EM, Akpunonu P. A statewide
449 prescription monitoring program affects emergency department prescribing behaviors. *Ann*
450 *Emerg Med*. 2010 Jul;56(1):19-23.e1-3.
- 451 48. Lin HC, Wang Z, Boyd C, Simoni-Wastila L, Buu A. Associations between statewide
452 prescription drug monitoring program (PDMP) requirement and physician patterns of
453 prescribing opioid analgesics for patients with non-cancer chronic pain. *Addict Behav*.
454 2018;76:348–54.

- 455 49. Kohlbeck S, Akert B, Pace C, Zosel A. A multistep approach to address clinician knowledge,
456 attitudes, and behavior around opioid prescribing. *Wis Med J.* 2018;117:38–41.
- 457 50. Click IA, Basden JA, Bohannon JM, Anderson H, Tudiver F. Opioid Prescribing in Rural
458 Family Practices: A Qualitative Study. *Subst Use Misuse.* 2018 Mar 21;53(4):533–40.
- 459 51. Coleman CD. Evidence-Based Strategies To Minimize Risk For Opioid Pain Medication
460 Misuse Among Patients With Chronic Pain In A Primary Care Setting. *Diss Abstr Int Sect B*
461 *Sci Eng.* 2016;64.
- 462 52. Chaudhary S, Compton P. Use of risk mitigation practices by family nurse practitioners
463 prescribing opioids for the management of chronic nonmalignant pain. *Subst Abuse.* 2017
464 Mar;38(1):95–104.
- 465 53. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. *Int J Soc Res*
466 *Methodol.* 2005 Feb 1;8(1):19–32.
- 467 54. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology.
468 *Implement Sci.* 2010 Sep 20;5:69.
- 469 55. Colquhoun HL, Levac D, O'Brien KK, Straus S, Tricco AC, Perrier L, et al. Scoping
470 reviews: time for clarity in definition, methods, and reporting. *J Clin Epidemiol.* 2014
471 Dec;67(12):1291–4.
- 472 56. Peters M, Godfrey C, McInerney P, Soares C, Khalil H, Parker D. The Joanna Briggs
473 Institute Reviewers' Manual 2015: Methodology for JBI Scoping Reviews. 2015 Jan 1 [cited
474 2018 Feb 7]; Available from: <https://espace.library.uq.edu.au/view/UQ:371443>
- 475 57. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA
476 Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*
477 [Internet]. 2018 Sep 4 [cited 2018 Sep 21]; Available from:
478 <http://annals.org/article.aspx?doi=10.7326/M18-0850>
- 479 58. Li G, Abbade LPF, Nwosu I, Jin Y, Leenus A, Maaz M, et al. A scoping review of
480 comparisons between abstracts and full reports in primary biomedical research. *BMC Med*
481 *Res Methodol.* 2017 Dec 29;17(1):181.
- 482 59. Main C, Moxham T, Wyatt JC, Kay J, Anderson R, Stein K. Computerised decision support
483 systems in order communication for diagnostic, screening or monitoring test ordering:
484 systematic reviews of the effects and cost-effectiveness of systems [Internet]. *NIHR Journals*
485 *Library;* 2010 [cited 2018 Jan 7]. Available from:
486 <https://www.ncbi.nlm.nih.gov/books/NBK56829/>
- 487 60. Grey Matters: a practical tool for searching health-related grey literature | CADTH.ca
488 [Internet]. [cited 2018 Sep 24]. Available from: [https://www.cadth.ca/resources/finding-](https://www.cadth.ca/resources/finding-evidence/grey-matters)
489 [evidence/grey-matters](https://www.cadth.ca/resources/finding-evidence/grey-matters)

- 490 61. Liebschutz JM, Xuan Z, Shanahan CW, LaRochelle M, Keosaian J, Beers D, et al.
491 Improving Adherence to Long-term Opioid Therapy Guidelines to Reduce Opioid Misuse in
492 Primary Care: A Cluster-Randomized Clinical Trial. *JAMA Intern Med.* 2017;177:1265–72.
- 493 62. Downes JM, Klepser DG, Foster J, Nelson M. Development of a standardized approach for
494 managing opioids in adults with chronic noncancer pain. *Am J Health-Syst Pharm AJHP Off*
495 *J Am Soc Health-Syst Pharm.* 2018;75(5):321–6.
- 496 63. Seal K.H., Borsari B., Tighe J., Cohen B.E., Delucchi K., Morasco B.J., et al. Optimizing
497 pain treatment interventions (OPTI): A pilot randomized controlled trial of collaborative care
498 to improve chronic pain management and opioid safety-Rationale, methods, and lessons
499 learned. *Contemp Clin Trials.* 2019;77((Trafton) Program Evaluation and Resource Center
500 (PERC), VA Office of Mental Health Operations, United States):76–85.
- 501 64. Binswanger IA, Joseph N, Hanratty R, Gardner EM, Durfee J, Narwaney KJ, et al. Novel
502 Opioid Safety Clinic Initiative to Deliver Guideline-Concordant Chronic Opioid Therapy in
503 Primary Care. *Mayo Clin Proc Innov Qual Outcomes.* 2018;2(4):309–16.
- 504 65. Freeman PR, Curran GM, Drummond KL, Martin BC, Teeter BS, Bradley K, et al.
505 Utilization of prescription drug monitoring programs for prescribing and dispensing
506 decisions: Results from a multi-site qualitative study. *Res Soc Adm Pharm RSAP.*
507 2019;15(6):754–60.
- 508 66. Patchett D., Grover M., Kresin M., Bryan M., Nordrum J., Buras M., et al. The benefits of a
509 standardized approach to opioid prescribing. *J Fam Pract.* 2019;68(6):E1–7.
- 510 67. Prescribing and Dispensing Policies to Address Harms Associated With Prescription Drug
511 Abuse | CADTH.ca [Internet]. [cited 2018 Aug 20]. Available from:
512 [https://www.cadth.ca/prescribing-and-dispensing-policies-address-harms-associated-](https://www.cadth.ca/prescribing-and-dispensing-policies-address-harms-associated-prescription-drug-abuse)
513 [prescription-drug-abuse](https://www.cadth.ca/prescribing-and-dispensing-policies-address-harms-associated-prescription-drug-abuse)
- 514 68. McCarthy M. Containing the opioid overdose epidemic. *BMJ.* 2012 Dec 14;345(dec14
515 2):e8340–e8340.
- 516 69. Trafton J, Martins S, Michel M, Lewis E, Wang D, Combs A, et al. Evaluation of the
517 acceptability and usability of a decision support system to encourage safe and effective use
518 of opioid therapy for chronic, noncancer pain by primary care providers. *Pain Med.*
519 2010;11:575–85.
- 520 70. Furlan AD, Reardon R, Salach L. The opioid manager: a point-of-care tool to facilitate the
521 use of the Canadian Opioid Guideline. *J Opioid Manag.* 2012;8(1):57–61.
- 522 71. Midboe AM, Lewis ET, Cronkite RC, Chambers D, Goldstein MK, Kerns RD, et al.
523 Behavioral medicine perspectives on the design of health information technology to improve
524 decision-making, guideline adherence, and care coordination in chronic pain management.
525 *Transl Behav Med.* 2011;1:35–44.

- 526 72. Harle CA, Bauer SE, Hoang HQ, Cook RL, Hurley RW, Fillingim RB. Decision support for
527 chronic pain care: how do primary care physicians decide when to prescribe opioids? a
528 qualitative study. *BMC Fam Pract.* 2015;16:48.
- 529 73. Finley EP, Garcia A, Rosen K, McGeary D, Pugh MJ, Potter JS. Evaluating the impact of
530 prescription drug monitoring program implementation: a scoping review. *BMC Health Serv*
531 *Res.* 2017;17(1):420.
- 532 74. Fink DS, Schleimer JP, Sarvet A, Grover KK, Delcher C, Castillo-Carniglia A, et al.
533 Association Between Prescription Drug Monitoring Programs and Nonfatal and Fatal Drug
534 Overdoses: A Systematic Review. *Ann Intern Med.* 2018 Jun 5;168(11):783.
- 535 75. Grading quality of evidence and strength of recommendations. *BMJ.* 2004 Jun
536 19;328(7454):1490.
- 537 76. Health Quality Ontario. Recommendations for Adoption: Opioid Prescribing for Chronic
538 Pain [Internet]. 2018 [cited 2018 Jul 20]. Available from:
539 [http://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-opioid-chronic-](http://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-opioid-chronic-pain-recommendations-for-adoption-en.pdf)
540 [pain-recommendations-for-adoption-en.pdf](http://www.hqontario.ca/Portals/0/documents/evidence/quality-standards/qs-opioid-chronic-pain-recommendations-for-adoption-en.pdf)
- 541 77. Ciani O, Buyse M, Drummond M, Rasi G, Saad ED, Taylor RS. Time to Review the Role of
542 Surrogate End Points in Health Policy: State of the Art and the Way Forward. *Value Health.*
543 2017 Mar 1;20(3):487–95.
- 544 78. Wittes J, Lakatos E, Probstfield J. Surrogate endpoints in clinical trials: Cardiovascular
545 diseases. *Stat Med.* 1989 Apr 1;8(4):415–25.
- 546 79. Gomes T, Khuu W, Martins D, Tadrour M, Mamdani MM, Paterson JM, et al. Contributions
547 of prescribed and non-prescribed opioids to opioid related deaths: population based cohort
548 study in Ontario, Canada. *BMJ.* 2018 Aug 29;362:k3207.
- 549 80. Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. “Every ‘never’ I ever said
550 came true”: transitions from opioid pills to heroin injecting. *Int J Drug Policy.* 2014
551 Mar;25(2):257–66.
- 552 81. Compton WM, Jones CM, Baldwin GT. Relationship between Nonmedical Prescription-
553 Opioid Use and Heroin Use. *N Engl J Med.* 2016 Jan 14;374(2):154–63.
- 554 82. Baldwin N, Gray R, Goel A, Wood E, Buxton JA, Rieb LM. Fentanyl and heroin contained
555 in seized illicit drugs and overdose-related deaths in British Columbia, Canada: An
556 observational analysis. *Drug Alcohol Depend.* 2018 Apr 1;185:322–7.
- 557 83. Rubin R. Illicit Fentanyl Driving Opioid Overdose Deaths. *JAMA.* 2017 Dec
558 12;318(22):2174–2174.
- 559 84. O’Donnell J, Gladden RM, Seth P. Trends in Deaths Involving Heroin and Synthetic Opioids
560 Excluding Methadone, and Law Enforcement Drug Product Reports, by Census Region —
561 United States, 2006–2015 [Internet]. 2017 [cited 2018 Oct 1]. Available from: <https://www->

- 562 cdc-
563 gov.myaccess.library.utoronto.ca/mmwr/volumes/66/wr/mm6634a2.htm?s_cid=mm6634a2_
564 e
- 565 85. Rhodes E, Wilson M, Robinson A, Hayden JA, Asbridge M. The effectiveness of
566 prescription drug monitoring programs at reducing opioid-related harms and consequences: a
567 systematic review. *BMC Health Serv Res.* 2019 Nov 1;19(1):784.
- 568 86. Heres S, Davis J, Maino K, Jetzinger E, Kissling W, Leucht S. Why Olanzapine Beats
569 Risperidone, Risperidone Beats Quetiapine, and Quetiapine Beats Olanzapine: An
570 Exploratory Analysis of Head-to-Head Comparison Studies of Second-Generation
571 Antipsychotics. *Am J Psychiatry.* 2006 Feb 1;163(2):185–94.
- 572 87. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and
573 research outcome and quality: systematic review. *BMJ.* 2003 May 31;326(7400):1167.
- 574 88. Lesser LI, Ebbeling CB, Gozner M, Wypij D, Ludwig DS. Relationship between funding
575 source and conclusion among nutrition-related scientific articles. *PLoS Med.* 2007
576 Jan;4(1):e5.
- 577 89. Procyshyn RM, Chau A, Fortin P, Jenkins W. Prevalence and outcomes of pharmaceutical
578 industry-sponsored clinical trials involving clozapine, risperidone, or olanzapine. *Can J*
579 *Psychiatry Rev Can Psychiatr.* 2004 Sep;49(9):601–6.
- 580 90. Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective Publication of
581 Antidepressant Trials and Its Influence on Apparent Efficacy. *N Engl J Med.* 2008 Jan
582 17;358(3):252–60.
- 583 91. Doshi P, Dickersin K, Healy D, Vedula SS, Jefferson T. Restoring invisible and abandoned
584 trials: a call for people to publish the findings. *BMJ.* 2013 Jun 13;346(jun13 2):f2865–f2865.
- 585 92. Chan A-W, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. Empirical Evidence for
586 Selective Reporting of Outcomes in Randomized Trials: Comparison of Protocols to
587 Published Articles. *JAMA.* 2004 May 26;291(20):2457–65.
- 588 93. Electronic Health Records Vendor to Pay \$145 Million to Resolve Criminal and Civil
589 Investigations [Internet]. 2020 [cited 2020 Feb 14]. Available from:
590 [https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-](https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0)
591 [criminal-and-civil-investigations-0](https://www.justice.gov/opa/pr/electronic-health-records-vendor-pay-145-million-resolve-criminal-and-civil-investigations-0)
- 592 94. Mair FS, May C, O'Donnell C, Finch T, Sullivan F, Murray E. Factors that promote or
593 inhibit the implementation of e-health systems: an explanatory systematic review. *Bull*
594 *World Health Organ.* 2012 May 1;90(5):357–64.
- 595 95. Black AD, Car J, Pagliari C, Anandan C, Cresswell K, Bokun T, et al. The Impact of eHealth
596 on the Quality and Safety of Health Care: A Systematic Overview. *PLoS Med* [Internet].
597 2011 Jan 18 [cited 2018 Jul 18];8(1). Available from:
598 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3022523/>

- 599 96. National Center for Injury Prevention and Control. Integrating & Expanding Prescription
600 Drug Monitoring Program Data: Lessons from Nine States. Centre for Disease Control and
601 Prevention; 2017.
- 602 97. Moore GF, Audrey S, Barker M, Bond L, Bonell C, Hardeman W, et al. Process evaluations
603 of complex interventions: UK Medical Research Council (MRC) guidance [Internet]. MRC
604 Population Health Science Research Network; 2014 [cited 2018 Jul 23]. Available from:
605 <https://mrc.ukri.org/documents/pdf/mrc-phsrn-process-evaluation-guidance-final/>
- 606 98. Chan CL, Leyrat C, Eldridge SM. Quality of reporting of pilot and feasibility cluster
607 randomised trials: a systematic review. *BMJ Open*. 2017 Nov 8;7(11):e016970.
- 608 99. Liu H, Muhunthan J, Hayek A, Hackett M, Laba T-L, Peiris D, et al. Examining the use of
609 process evaluations of randomised controlled trials of complex interventions addressing
610 chronic disease in primary health care—a systematic review protocol. *Syst Rev* [Internet].
611 2016 Aug 15 [cited 2018 Sep 24];5. Available from:
612 <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4986376/>
- 613 100. Oakley A, Strange V, Bonell C, Allen E, Stephenson J. Process evaluation in randomised
614 controlled trials of complex interventions. *BMJ*. 2006 Feb 16;332(7538):413–6.
- 615 101. Greenhalgh T, Russell J. Why Do Evaluations of eHealth Programs Fail? An Alternative
616 Set of Guiding Principles. *PLoS Med* [Internet]. 2010 Nov 2 [cited 2018 Sep 24];7(11).
617 Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2970573/>
- 618 102. Basit MA, Baldwin KL, Kannan V, Flahaven EL, Parks CJ, Ott JM, et al. Agile
619 Acceptance Test–Driven Development of Clinical Decision Support Advisories: Feasibility
620 of Using Open Source Software. *JMIR Med Inform* [Internet]. 2018 Apr 13 [cited 2019 May
621 3];6(2). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5924365/>
- 622 103. Kannry J, McCullagh L, Kushniruk A, Mann D, Edonyabo D, McGinn T. A Framework
623 for Usable and Effective Clinical Decision Support: Experience from the iCPR Randomized
624 Clinical Trial. *EGEMS Wash DC*. 2015;3(2):1150.
- 625 104. Kannan V, Fish J, Mutz J, Carrington A, Lai K, Davis L, et al. Rapid Development of
626 Specialty Population Registries and Quality Measures from Electronic Health Record Data:
627 An Agile Framework. *Methods Inf Med*. 2017 Jun 14;56(99):e74–83.

628
629
630
631
632

Table 1. Study setting, participants, clinical decision support system (CDSS) type and inclusion of evidence-based components

Characteristic		Local	PDMP
		CDSS*	CDSS**
		N (%)	N (%)
Country	United States	6/6 (100%)	8/8 (100%)
Practice settings	Primary care clinic	5/6 (83%)	6/8 (75%)
	Emergency department	1/6 (17%)	2/8 (25%)
Types of PCPs	Physicians	6/6 (100%)	7/8 (88%)
	NPs	6/6 (100%)	4/8 (50%)
CDSS type	Dashboard	2/6 (33%)	0/8 (0%)
	Protocol	2/6 (33%)	0/8 (0%)
	Alert	1/6 (17%)	0/8 (0%)
	Clinical tool	1/6 (17%)	0/8 (0%)
	Data repository	0/6 (0%)	8/8 (100%)
Evidence-based CDSS components^o	Integrated into EMR	3/6 (50%)	0/5 (0%) ***
	Automatically activates	2/6 (33%)	0/5 (0%) ***
	Requires a reason for over-ride	0/6 (0%)	0/5 (0%) ***
	Provides advice to patients and providers	0/6 (0%)	0/5 (0%) ***

Abbreviations: CDSS = Clinical Decision Support System; EMR = electronic medical record;

N/A = Not Applicable; NP = nurse practitioners; PDMP = Prescription Drug Monitoring

Program; PCPs = primary care providers;

*Local CDSSs are used locally within a specific health centre, health system or clinic

**PDMP CDSSs are large, centralized, government-run databases

***We excluded 3 studies because they included multiple PDMP CDSSs, and did not provide information on a specific CDSS (45,47,49)

^o Unless a study stated a component was included (e.g. automatic activation), we assumed it was not

Table 2. Aims and designs of included studies

Aims	Design	Local	PDMP
		CDSS*	CDSS**
		N (%)	N (%)
To determine if a multi-faceted intervention improved prescribing/guideline adherence	• Cluster RCT***	1/6 (17%)	0/8 (0%)
	• Pre-post	4/6 (33%)	0/8 (0%)
To determine if a CDSS improved prescribing/guideline adherence	• Pre-post	0/6 (0%)	1/8 (13%)
To determine if PCPs used a CDSS	• Retrospective cohort	0/6 (0%)	1/8 (13%)
	• Cross-sectional survey	0/6 (0%)	1/8 (13%)
To determine if an intervention affected provider knowledge, behaviour, attitudes and/or use related to CDSS	• Mixed-methods	0/6 (0%)	1/8 (13%)
	• Pre-post	0/6 (0%)	2/8 (25%)
To learn about factors affecting opioid prescribing for CNCP, including use of CDSS	• Qualitative	0/6 (0%)	2/8 (25%)
To pilot a multi-component intervention, including a CDSS	• Mixed-methods	1/6 (17%)	0/8 (0%)

Abbreviations: CDSS = Clinical Decision Support System; CNCP = chronic non-cancer pain;
N/A = Not Applicable; PDMP = Prescription Drug Monitoring Program; RCT = Randomized
controlled trial

*Local CDSSs are used locally within a specific health centre, health system or clinic

**PDMP CDSSs are large, centralized, government-run databases

***CDSS included in both study arms

Table 3. Funding and relationship between developers and evaluators

		Local	PDMP
		CDSS*	CDSS**
		N (%)	N (%)
Funding for CDSS development	Public/Non-profit	3/6 (50%)	0/8 (0%)
	Industry	0/6 (0%)	0/8 (0%)
	Not sponsored	0/6 (0%)	0/8 (0%)
	Unclear or not reported	3/6 (50%)	8/8 (100%)
Funding for evaluation	Public/non-profit	4/6 (67%)	5/8 (63%)
	Industry	0/6 (0%)	0/8 (0%)
	Not sponsored	0/6 (0%)	2/8 (25%)
	Unclear or not reported	2/6 (33%)	1/8 (13%)
Relationship between developers and evaluators	Same person, group or organization	4/6 (67%)	0/8 (0%)
	Different person, group or organization	0/6 (0%)	0/8 (0%)
	Unclear or not reported	2/6 (33%)	8/8 (100%)

Abbreviations: CDSS = Clinical Decision Support System; PDMP = Prescription Drug

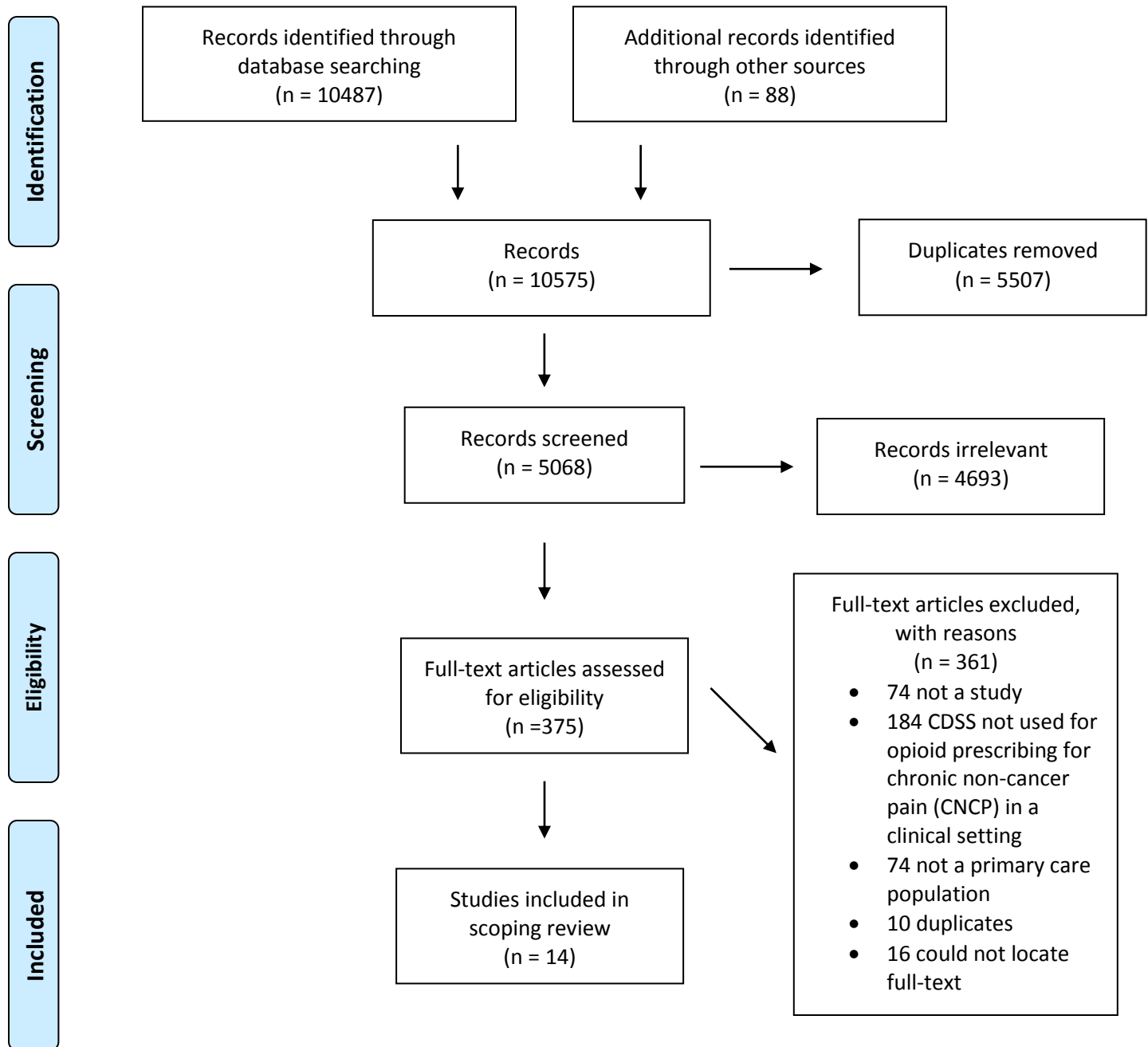
Monitoring Program

*Local CDSSs are used locally within a specific health centre, health system or clinic

**PDMP CDSSs are large, centralized, government-run databases



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.