

Supplementary Information

Appendix A – PRISMA Flow Diagram

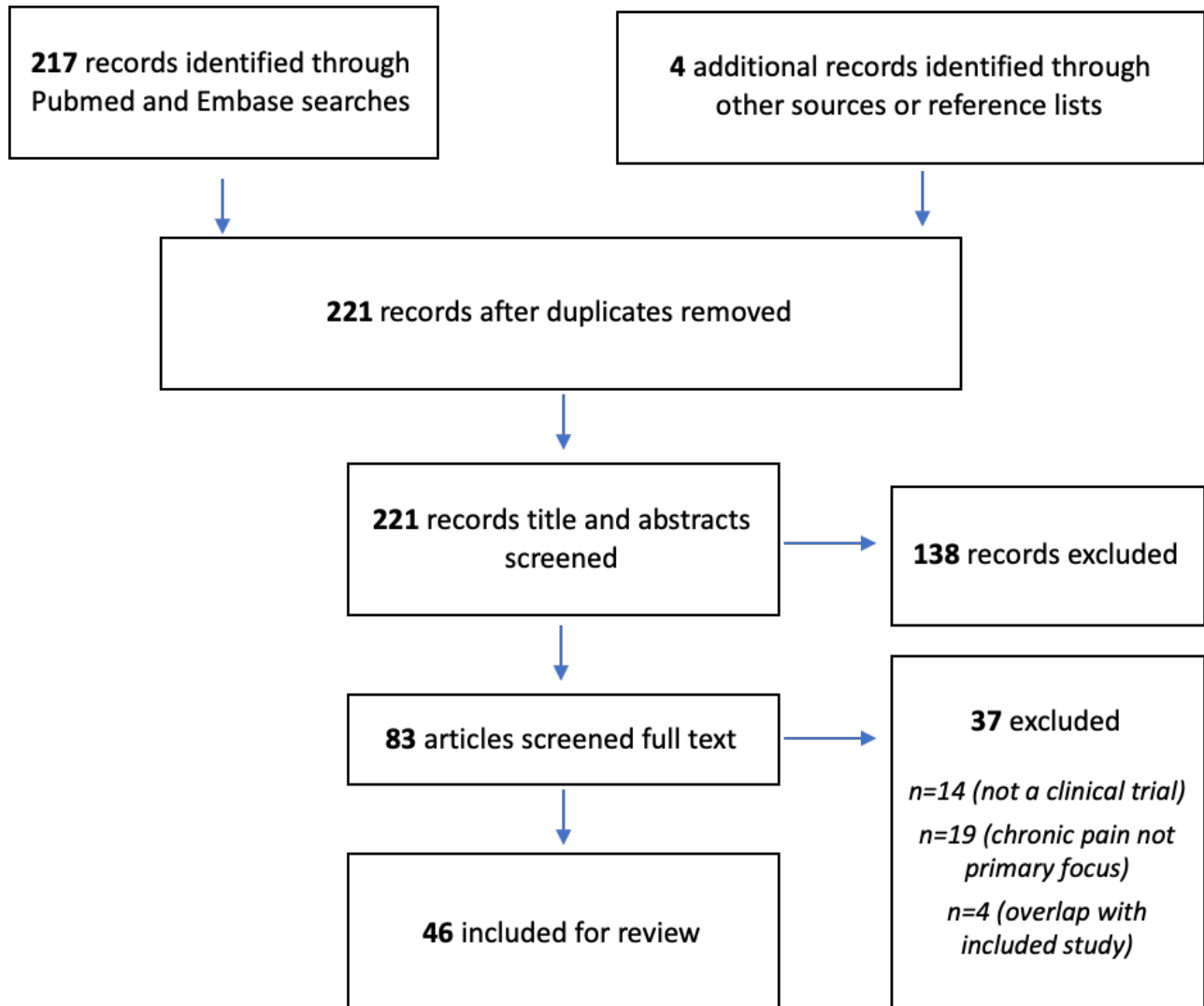
Appendix B – Overview of Published Clinical Trials of Chronic Pain Treatments and Benefit-Risk Assessment

Appendix C – United States Food and Drug Administration and Benefit-Risk Assessment

Appendix D – European Medicines Agency and Benefit-Risk Assessment

Appendix E – National Academies of Science, Engineering, and Medicine (including Institute of Medicine) and Benefit-Risk Assessment

Appendix A. PRISMA Flow Diagram



Appendix B. Overview of Published Clinical Trials of Chronic Pain Treatments and Benefit-Risk Assessment

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Abdely-Meguid, 2018 [1]	Chronic prostatitis/ pelvic pain syndrome	onabotulinum-toxin-A	<i>Analyzed Separately</i> Benefits: *Proportion of responders represented by 6 points or greater reduction in total score on NIH-Chronic Prostatitis Symptom Index Risks: AEs
Al-Ajlouni, 2015 [2]	Knee osteoarthritis	autologous platelet lysate percutaneous injection.	<i>Analyzed Separately</i> Benefits: *Knee Osteoarthritis and Disability Outcome Score Risks: Complications including infection and hospitalization
Alev, 2017 [3]	Low back	duloxetine	<i>Analyzed Separately</i> Benefits: *Proportion of patients with $\geq 30\%$ reduction in pain Risks: AEs
Asbury, 2012 [4]	Refractory angina	cardiac rehabilitation	<i>Analyzed Separately</i> Benefits: *Anxiety and depression. Risks: None
Blumenfeld, 2018[5]	Chronic migraine	onabotulinum-toxin-A	<i>Analyzed Separately</i> Benefits: *Reduction in headache days Risks: AEs
Brage et al. [6]	Neck	pain education/ training (neck-shoulder exercises, balance and aerobics)	<i>Analyzed Separately</i> Benefits: Reduction in neck pain, function and global perceived effect; no primary outcomes declared Risks: None
Burmester et al. [7]	Rheumatoid arthritis	tofacitinib	<i>Analyzed Separately</i> Benefits: *American College of Rheumatology response rate, *disability, *rates of disease activity score Risk: AEs

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Buvanendran et al. [8]	Knee	pregabalin	<i>Analyzed Separately</i> Benefits: *Reduction in neuropathic pain Risks: AEs
Chen et al. [9]	Knee	acupuncture and exercise-based physical therapy	<i>Analyzed Separately</i> Benefits: *Proportion with at least 36% improvement in Western Ontario and McMaster Universities Osteoarthritis Index score Risks: AEs
Choi and Huang [10]	Functional abdominal pain	dietary supplement	<i>Analyzed Separately</i> Benefits: *Presence of recurrent abdominal pain and reductions in pain; *quality of life Risks: Drug toxicity and psychiatric outcomes
Dear et al. [11]	Variety	internet-delivered pain management program	<i>Analyzed Separately</i> Benefits: *Disability; *health outcomes including anxiety Risks: None
Garland et al. [13]	Non-cancer pain	Mindfulness-Oriented Recovery	<i>Analyzed Separately</i> Benefits: *Reduction in pain severity and interference Risks: *Opioid craving and misuse
Garland et al. [12]	Bone cancer pain	Mindfulness-Oriented Recovery Enhancement	<i>Analyzed Separately</i> Benefits: Reduction in pain severity Risks: Opioid misuse
Hale et al. [14]	Variety	hydrocodone extended release	<i>Analyzed Separately</i> Benefits: None Risks: *AEs
Hardy et al. [15]	Cancer pain	ketamine	<i>Analyzed Separately</i> Benefits: *Pain improvement Risks: AEs

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Hearn and Finlay [16]	Spinal cord injury	internet-delivered mindfulness	<i>Analyzed Separately</i> Benefits: Reduction in depression symptom severity Risks: none
Hofmann et al. [17]	Osteoarthritis and low back	tapentadol prolonged release	<i>Analyzed Separately</i> Benefits: *Reduction in pain intensity Risks: AEs
Izquierdo Perez et al. [18]	Neck	manual therapy	<i>Analyzed Separately</i> Benefits: *Reduction in pain intensity Risks: AEs
Jay et al. [19]	Variety	physical, cognitive, and mindfulness group-based training	<i>Analyzed Separately</i> Benefits: *Pain intensity Risks: None
Kendall et al. [20]	Neck	instrument-assisted cervical and thoracic spine manipulation plus massage/mobilization/exercises/heat	<i>Analyzed Separately</i> Benefits: *Reductions in dizziness handicap inventory and neck disability Risks: AEs
Kimball et al. [21]	Hidradenitis suppurativa	Adalimumab	<i>Analyzed Separately</i> Benefits: *Improvement in hidradenitis suppurativa severity score Risks: AEs
Kivitz et al. [22]	Low back	intravenous tanezumab	<i>Analyzed Separately</i> Benefits: *Pain intensity Risks: AEs
Lee et al. [23]	Prostatitis/pelvic pain syndrome	acupuncture	<i>Analyzed Separately</i> Benefits: *Integrity of blinding Risks: None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Licciardone et al. [24]	Low back	osteopathic manual treatment and ultrasound therapy	<i>Analyzed Separately</i> Benefits: Pain ratings Risks: None
Lluch et al. [25]	Neck	assisted plus active cranio-cervical flexion exercise	<i>Analyzed Separately</i> Benefits: Cranio-cervical flexion test, cervical range of motion, and pain were assessed Risks: None
Masala et al. [26]	Pudendal neuralgia	computed tomography-guided percutaneous pulse-Dose radiofrequency	<i>Analyzed Separately</i> Benefits: Reduction in pain intensity Risks: None
Mecklenburg et al. [27]	Knee	Hinge Health digital care remotely delivered	<i>Analyzed Separately</i> Benefits: *Reduction in pain; *improved physical functioning Risks: AEs
Molegraaf et al. [28]	Abdominal	laparoscopic adhesiolysis	<i>Analyzed Separately</i> Benefits: *Reduction in pain Risks: None
Monticone et al. [29]	Neck	rehabilitation program exercises, cognitive-behavioral therapy	<i>Analyzed Separately</i> Benefits: *Reduction in disability Risks: None
Persson et al. [30]	Neck	Chinese medicine Qigong	<i>Analyzed Separately</i> Benefits: Reduction in pain intensity Risks: None
Petersen et al. [31]	Low back	McKenzie method/physical therapy	<i>Analyzed Separately</i> Benefits: Reduction in disability Risks: None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Saner et al. [32]	Low back	tailored exercise program	<i>Analyzed Separately</i> Benefits: *Improved function Risks: None
Sanga et al. [33]	Chronic osteoarthritis	subcutaneous fulranumab (<i>Analyzed Separately</i> Benefits: *Reduction in pain Risks: AEs
Sieper et al. [34]	Spondylo-arthritis	golimumab	<i>Analyzed Separately</i> Benefits: *20% improvement in SpondyloArthritis International Society criteria Risks: AEs
Stahlschmidt et al. [35]	Various (pediatric population)	interdisciplinary pain treatment	<i>Analyzed Separately</i> Benefits: Treatment satisfaction Risks: None
Takahashi et al. [36]	Neck	laser therapy	<i>Analyzed Separately</i> Benefits: Pain Risks: None
Tan et al. [37]	Low back	self-hypnosis trainings	<i>Analyzed Separately</i> Benefits: Pain intensity, pain interference, and sleep quality Risks: None
Tchivileva et al. [38]	TMDs	propranolol	<i>Analyzed Separately</i> Benefits: *Pain intensity Risks: AEs
Thompson et al. [39]	Neck	interactive behavioral modification therapy	<i>Analyzed Separately</i> Benefits: *Disability Risks: None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Valenza et al. [40]	Low back	pilates exercise	<i>Analyzed Separately</i> Benefits: *Disability; *pain ratings Risks: None
Verra et al. [41]	Back	rehabilitation program	<i>Analyzed Separately</i> Benefits: *Disability Risks: None
Ware et al. [42]	Variety	herbal cannabis	<i>Analyzed Separately</i> Benefits: None Risks: *AEs
Wasan et al. [43]	Low back	oral morphine or oxycodone	<i>Analyzed Separately</i> Benefits: *percent pain improvement Risks: opioid misuse
Williams et al. [44]	Low back	telephone-based healthy lifestyle coaching	<i>Analyzed Separately</i> Benefits: *pain intensity Risks: AEs
Wilson et al. [45]	Shoulder	peripheral nerve stimulation	<i>Analyzed Separately</i> Benefits: *worst pain last week Risks: AEs
Yoon et al. [46]	Musculo-skeletal	transdermal buprenorphine	<i>Analyzed Separately</i> Benefits: *pain reduction Risks: AEs

Note: Asterisk* represents primary outcome(s) in associated publication. AE (adverse event); TMDs (temporomandibular disorders); Overall, 39 of the studies in the table were randomized (85%) and types of interventions included (study counts in parentheses): pharmacological (18), physical activity or physical/occupational therapy (13), cognitive-behavioral therapy (8 studies), mindfulness (8), psychosocial support (8), manual therapy/chiropractic (4), acupuncture (2), and mind-body (2). The following interventions were represented in 1 study each: biofeedback, laser therapy, peripheral nerve stimulation, radiofrequency, and surgery. The chronic pain conditions examined across studies included (most to least frequent): back/lower back pain (12), neck pain (8), arthritis-related pain

(4), knee pain (3), prostatitis/pudendal neuralgia/pelvic pain (3), and abdominal pain (2). Angina, cancer-related pain, migraine headache, hidradenitis suppurativa (a painful skin condition), musculoskeletal pain, shoulder pain, spinal cord injury-related pain, and temporomandibular disorders were each evaluated in 1 study. Six studies various types of chronic pain conditions in the same study. The only criteria for inclusion in this review is that the study was a clinical trial. Therefore, a portion of the studies reviewed reported no risk outcomes and one study reported no benefit outcome.

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Appendix C - Food and Drug Administration and Benefit-Risk Assessment

Title	Date	FDA Organization	Topic	URL
<p>Structured Approach to Benefit Risk Assessment in Drug Regulatory Decision-Making PDUFA V Implementation Plan</p>	<p>01-July-13</p>	<p>Center for Drug Evaluation and Research</p>	<p>Medicinal Product</p>	<p>https://www.fda.gov/media/84831/download</p>
<p>Periodic B/R Evaluation Report (PBRER)</p>	<p>18-July-16</p>	<p>Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research</p>	<p>Periodic B/R Evaluation Report (PBRER)</p>	<p>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2cr2-periodic-B/R-evaluation-report-pbrer</p>
<p>Periodic B/R Evaluation Report – Questions and Answers</p>	<p>18-July-16</p>	<p>Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research</p>	<p>Periodic B/R Evaluation Report</p>	<p>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2cr2-periodic-B/R-evaluation-report-questions-and-answers</p>

Title	Date	FDA Organization	Topic	URL
			questions/ answers	
<p>Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)</p>	28-Nov-16	Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research	Postmarket Periodic Safety Reports	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-postmarket-periodic-safety-reports-ich-e2cr2-format-periodic-benefit-risk-evaluation
<p>Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions: Guidance for Industry and</p>	27-Dec-16	Center for Devices and Radiological Health	Medical Device	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and

Title	Date	FDA Organization	Topic	URL
Food and Drug Administration Staff				
Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions: Guidance for Investigational Device Exemption Sponsors, Sponsor-Investigators and Food and Drug Administration Staff	13-Jan-17	Center for Devices and Radiological Health	Medical Devices	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device

Title	Date	FDA Organization	Topic	URL
Benefit-Risk Assessment in Drug Regulatory Decision-Making PDUFA VI Implementation Plan	10-March-18	Center for Drug Evaluation and Research	Medication	https://www.fda.gov/media/112570/download
Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics: Guidance for Industry and Food and Drug Administration Staff	25-Sept-18	Center for Devices and Radiological Health	510(k) Premarket Notification	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k
Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment	20-June-19	Center for Drug Evaluation and Research	Medication/ Opioids	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-

Title	Date	FDA Organization	Topic	URL
<p>Framework Guidance for Industry</p>				<p><u>considerations-benefit-risk-assessment-framework-guidance-industry</u></p>
<p>Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions: Guidance for Industry and Food and Drug Administration Staff</p>	<p>30-Aug-19</p>	<p>Center for Devices and Radiological Health</p>	<p>Medical Devices</p>	<p><u>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de</u></p>

Title	Date	FDA Organization	Topic	URL
<p>Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications: Guidance for Industry and Food and Drug Administration Staff</p>	<p>30-Aug-19</p>	<p>Center for Devices and Radiological Health</p>	<p>Medical Device</p>	<p>https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de</p>

Appendix D - European Medicines Agency and Benefit-Risk Assessment

Title	Date	Topic	URL
Guidance document for full implementation of the EMA Benefit Risk Assessment (includes a report template)	last updated Oct-17	Medicinal Products	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/d80-assessment-report-overview-guidance-rev1017_en.pdf
Benefit-risk methodology project	12-Mar-09	Project overview	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project_en.pdf
Benefit-risk methodology project: Work package 1 report: Description of the current practice of benefit-risk assessment for centralised procedure products in the European Union regulatory network	25-May-11	Current practices	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-1-report-description-current-practice-benefit-risk_en.pdf

Title	Date	Topic	URL
Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment	31-Aug- 10	Applicability of current practices	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-2-report-applicability-current-tools-processes_en.pdf
Benefit-risk methodology project: Work package 3 report: Field tests	31-Aug- 11	Field Tests	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-3-report-field-tests_en.pdf
Benefit-risk methodology project: Work package 4 report: Benefit-risk tools and processes	9-May- 12	Tools and Processes	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-work-package-4-report-benefit-risk-tools-processes_en.pdf
Benefit-risk methodology project: Update on work package 5: Effects table pilot (Phase I)	6-Feb- 14	Effects table	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-update-work-package-5-effects-table-pilot-phase-i_en.pdf

Title	Date	Topic	URL
Benefit-risk methodology project - Report on risk perception study module	24-Jan- 12	Risk Perception	https://www.ema.europa.eu/en/documents/report/benefit-risk-methodology-project-report-risk-perception-study-module_en.pdf
Report of the CHMP working group on benefit-risk assessment models and methods	19-Jan- 07	Models and Methods	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/report-chmp-working-group-benefit-risk-assessment-models-methods_en.pdf
Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use	19-Mar- 08	Marketing Authorisation Applications	https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-benefit-risk-assessment-methods-context-evaluation-marketing-authorisation_en-0.pdf
Benefit-risk methodology project: Comments received from Dr William Holden on the work package 2 report	2-Nov- 10	Researcher comments	https://www.ema.europa.eu/en/documents/other/benefit-risk-methodology-project-comments-received-dr-william-holden-work-package-2-report_en.pdf

Title	Date	Topic	URL
Benefit-risk methodology project: Reply to the comments received from Dr William Holden on the work package 2 report	6-May- 11	Comments	https://www.ema.europa.eu/en/documents/other/benefit-risk-methodology-project-reply-comments-received-dr-william-holden-work-package-2-report_en.pdf

Appendix E - National Academies of Science, Engineering, and Medicine (including Institute of Medicine) and Benefit-Risk Assessment

Title	Date	Topic	URL
<p>The Future of Drug Safety: Promoting and Protecting the Health of the Public</p>	<p>22-Sept-06</p>	<p>Medicinal Products</p>	<p>http://www.nationalacademies.org/hmd/Reports/2006/The-Future-of-Drug-Safety-Promoting-and-Protecting-the-Health-of-the-Public.aspx</p>
<p>Understanding the Benefits and Risks of Pharmaceuticals. Workshop Summary</p>	<p>15-Aug-07</p>	<p>Medicinal Products</p>	<p>http://www.nationalacademies.org/hmd/Reports/2007/Understanding-the-Benefits-and-Risks-of-Pharmaceuticals-Workshop-Summary.aspx</p>
<p>Ethical and Scientific Issues in Studying the Safety of Approved Drugs</p>	<p>1-May-12</p>	<p>Medicinal Products</p>	<p>http://www.nationalacademies.org/hmd/Reports/2012/Ethical-and-Scientific-Issues-in-Studying-the-Safety-of-Approved-Drugs.aspx</p>
<p>Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products: Workshop Summary</p>	<p>26-Sept-14</p>	<p>Medicinal Products</p>	<p>http://nationalacademies.org/hmd/Reports/2014/Characterizing-and-Communicating-Uncertainty-in-the-Assessment-of-Benefits-and-Risks-of-Pharmaceutical-Products.aspx</p>

Pain Management and the Opioid Epidemic: Balancing Societal and Individual Benefits and Risks of Prescription Opioid Use	1-July-17	Medicinal Products/Opioids	https://www.ncbi.nlm.nih.gov/pubmed/2902308 3
Public Health Consequences of E-cigarettes	23-Jan-18	Electronic Cigarettes	http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx
The Role of Nonpharmacological Approaches to Pain Management: A Workshop	4-Dec-18	Non-drug Interventions	http://nationalacademies.org/hmd/Activities/Global/InnovationHealthProfEducation/2018-DEC-5.aspx
Framing Opioid Prescribing Guidelines for Acute Pain: Developing the Evidence	19-Dec-19	Medicinal Products/Opioids	http://www.nationalacademies.org/hmd/Reports/2019/framing-opioid-prescribing-guidelines-for-acute-pain-developing-the-evidence.aspx