Supplementary Information

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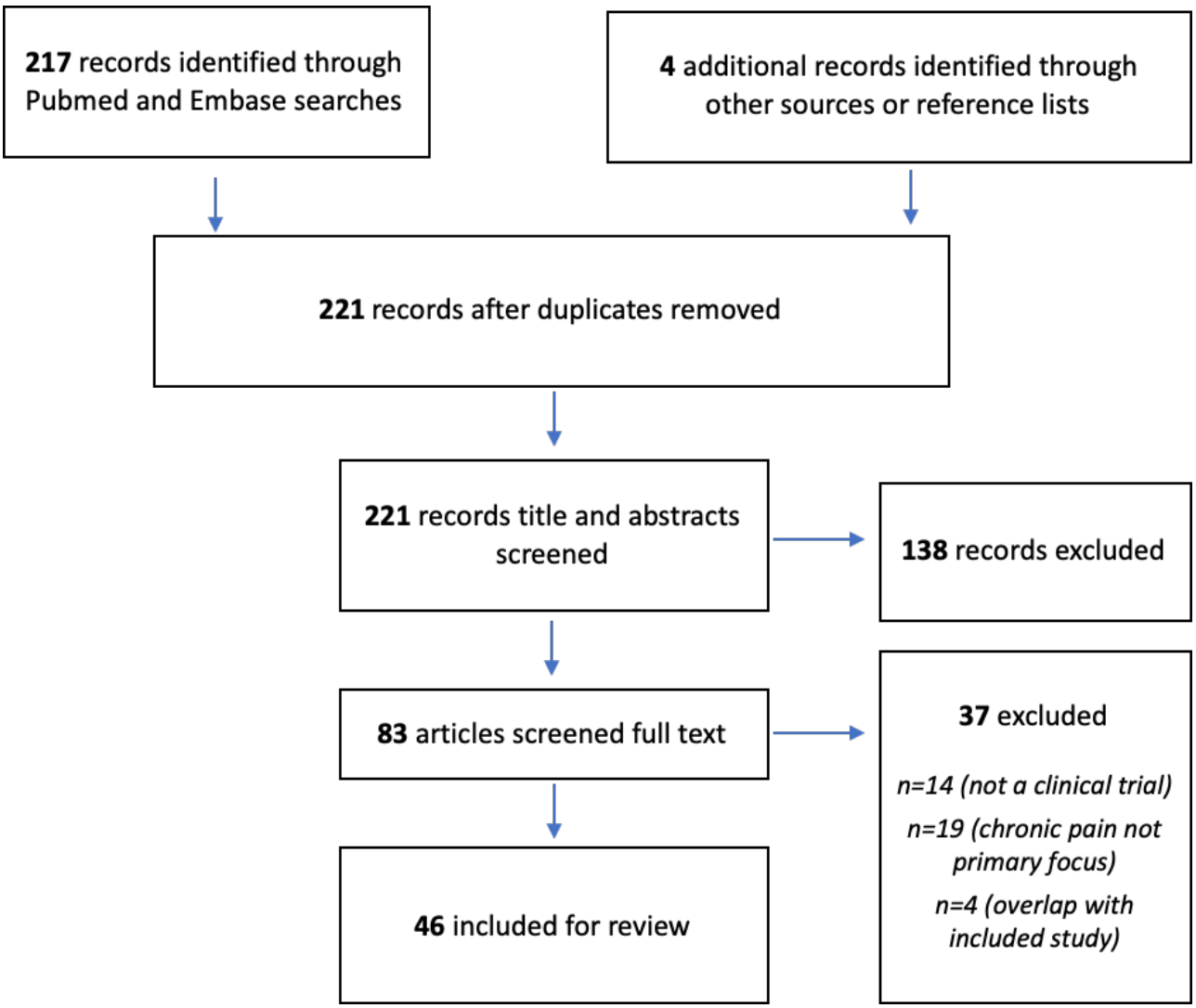
Appendix A. PRISMA Flow Diagram



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

Objective. The review's goal was to provide a “snapshot” of whether formal, structured, or systematic approaches to benefit-risk assessment are being used in clinical trials of chronic pain treatments.

Literature Search and Data Extraction. The literature search was limited to trials published between January 2010 to December 2019 and was conducted in PubMed, PsychInfo, and Embase databases with the following search string (modified for each database and using various combinations of the following search terms): ((benefit and risk) or (risk-benefit or benefit-risk)) and (method* or analys* or assessment or appraisal or ratio or model or framework) and (chronic pain) and (clinical trial or randomized controlled trial). All eligible studies and documents from the searches were reviewed and data were extracted by the first author (BAK), who developed a narrative summary. Extracted data included sample size and patient characteristics (age, gender, duration of primary diagnosis), chronic pain diagnosis (method of diagnosis and conditions), study design (i.e., treatment type, comparators), methods and results of benefit-risk analysis (types of data and/or statistical analyses), and funding source.

Evidence Summary. Forty-six clinical trials of chronic pain treatments published between 2010 and 2019 were identified for review (Supplementary Information). None of these 46 peer-reviewed publications reported a planned analysis that combined benefit and risk outcomes into an integrated, benefit-risk outcome. Five of the studies descriptively discussed benefits related to risks [4; 72; 90; 108; 156], but only as isolated statements in the text of the publication rather than through a formal evaluation. Two examples of such statements were as follows: (1) “The safety profile was similar for patients receiving weekly therapy and those receiving EOW [every other week] therapy. Given the apparent increase in efficacy achieved with the higher dose, the risk–benefit balance seems to favor weekly dosing.” [90]; (2) "These results indicate that the benefit and risk considerations in CLBP [chronic low back pain] patients with high vs. low NA [negative affect] are distinctly different.…Thus, negative affect is an important phenotypic variable to characterize at baseline, prior to deciding whether to prescribe opioids for CLBP." [156]. Most of the primary outcomes across studies focused on the benefits of treatment, not risks, including reductions in pain severity, functional improvements, reduction in anxiety or depression, and opioid misuse and craving (Supplementary Information). In contrast, a subset of studies focused on harms, rather than benefits, as the primary outcome of interest (e.g., AEs, opioid misuse) [56; 64; 155]. These studies were designed to evaluate treatments with abuse potential, including cannabis and hydrocodone extended-release, which prompted a focus on risks rather than benefits in the study analyses. An additional 10 studies declared no primary outcomes.

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Abdely-Meguid, 2018 [1]	Chronic prostatitis/ pelvic pain syndrome	onabotulinum-toxin-A	*Analyzed Separately* **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 [3]	Knee osteoarthritis	autologous platelet lysate percutaneous injection.	*Analyzed Separately* **Benefits**: *Knee Osteoarthritis and Disability Outcome Score **Risks:** Complications including infection and hospitalization
Alev, 2017 [4]	Low back	duloxetine	*Analyzed Separately* **Benefits**: *Proportion of patients with ≥30% reduction in pain **Risks:** AEs
Asbury, 2012 [7]	Refractory angina	cardiac rehabilitation	*Analyzed Separately* **Benefits:** *Anxiety and depression. **Risks:** None
Blumenfeld, 2018**[10]**	Chronic migraine	onabotulinum-toxin-A	*Analyzed Separately* **Benefits**: *Reduction in headache days **Risks**: AEs
Brage et al. [14]	Neck	pain education/ training (neck-shoulder exercises, balance and aerobics)	*Analyzed Separately* **Benefits**: Reduction in neck pain, function and global perceived effect; no primary outcomes declared **Risk**s: None
Burmester et al. [17]	Rheumatoid arthritis	tofacitinib	*Analyzed Separately* **Benefits**: *American College of Rheumatology response rate, *disability, *rates of disease activity score **Risk**: AEs
Buvanendran et al. [19]	Knee	pregabalin	*Analyzed Separately* **Benefits**: *Reduction in neuropathic pain **Risk**s: AEs

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Chen et al. [24]	Knee	acupuncture and exercise-based physical therapy	*Analyzed Separately* **Benefits**: *Proportion with at least 36% improvement in Western Ontario and McMaster Universities Osteoarthritis Index score **Risk**s: AEs
Choi and Huang [26]	Functional abdominal pain	dietary supplement	*Analyzed Separately* **Benefits**: *Presence of recurrent abdominal pain and reductions in pain; *quality of life **Risk**s: Drug toxicity and psychiatric outcomes
Dear et al. [32]	Variety	internet-delivered pain management program	*Analyzed Separately* **Benefits**: *Disability; *health outcomes including anxiety **Risk**s: None
Garland et al. [56]	Non-cancer pain	Mindfulness-Oriented Recovery	*Analyzed Separately* **Benefits**: *Reduction in pain severity and interference **Risk**s: *Opioid craving and misuse
Garland et al. [55]	Bone cancer pain	Mindfulness-Oriented Recovery Enhancement	*Analyzed Separately* **Benefits**: Reduction in pain severity **Risks:** Opioid misuse
Hale et al. [64]	Variety	hydrocodone extended release	*Analyzed Separately* **Benefits**: None **Risks** *AEs
Hardy et al. [66]	Cancer pain	ketamine	*Analyzed Separately* **Benefits**: *Pain improvement **Risks**: AEs
Hearn and Finlay [69]	Spinal cord injury	internet-delivered mindfulness	*Analyzed Separately* **Benefits**: Reduction in depression symptom severity **Risks**: none

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Hofmann et al. [72]	Osteoarthritis and low back	tapentadol prolonged release	*Analyzed Separately* **Benefits**: *Reduction in pain intensity **Risks**: AEs
Izquierdo Perez et al. [80]	Neck	manual therapy	*Analyzed Separately* **Benefits**: *Reduction in pain intensity **Risks**: AEs
Jay et al. [83]	Variety	physical, cognitive, and mindfulness group-based training	*Analyzed Separately* **Benefits**: *Pain intensity **Risks** None
Kendall et al. [89]	Neck	instrument-assisted cervical and thoracic spine manipulation plus massage/mobilization/ exercises/heat	*Analyzed Separately* **Benefits**: *Reductions in dizziness handicap inventory and neck disability **Risks**: AEs
Kimball et al. [90]	Hidradenitis suppurativa	Adalimumab	*Analyzed Separately* **Benefits**: *Improvement in hidradenitis suppurativa severity score **Risks**: AEs
Kivitz et al. [91]	Low back	intravenous tanezumab	*Analyzed Separately* **Benefits**: *Pain intensity **Risks**: AEs
Lee et al. [98]	Prostatitis/ pelvic pain syndrome	acupuncture	*Analyzed Separately* **Benefits**: *Integrity of blinding **Risks**: None
Licciardone et al. [101]	Low back	osteopathic manual treatment and ultrasound therapy	*Analyzed Separately* **Benefits**: Pain ratings **Risks:** None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Lluch et al. [102]	Neck	assisted plus active cranio-cervical flexion exercise	*Analyzed Separately* **Benefits**: Cranio-cervical flexion test, cervical range of motion, and pain were assessed **Risks:** None
Masala et al. [104]	Pudendal neuralgia	computed tomography-guided percutaneous pulse-Dose radiofrequency	*Analyzed Separately* **Benefits**: Reduction in pain intensity **Risks**: None
Mecklenburg et al. [106]	Knee	Hinge Health digital care remotely delivered	*Analyzed Separately* **Benefits**: *Reduction in pain; *improved physical functioning **Risks**: AEs
Molegraaf et al. [108]	Abdominal	laparoscopic adhesiolysis	*Analyzed Separately* **Benefits**: *Reduction in pain **Risks**: None
Monticone et al. [109]	Neck	rehabilitation program exercises, cognitive-behavioral therapy	*Analyzed Separately* **Benefits**: *Reduction in disability **Risks**: None
Persson et al. [117]	Neck	Chinese medicine Qigong	*Analyzed Separately* **Benefits**: Reduction in pain intensity **Risks**: None
Petersen et al. [119]	Low back	McKenzie method/physical therapy	*Analyzed Separately* **Benefits**: Reduction in disability **Risks**: None
Saner et al. [128]	Low back	tailored exercise program	*Analyzed Separately* **Benefits**: *Improved function **Risks**: None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Sanga et al. [129]	Chronic osteoarthritis	subcutaneous fulranumab (	*Analyzed Separately* **Benefits**: *Reduction in pain **Risks**: AEs
Sieper et al. [133]	Spondylo-arthritis	golimumab	*Analyzed Separately* **Benefits**: *20% improvement in SpondyloArthritis International Society criteria **Risks**: AEs
Stahlschmidt et al. [140]	Various (pediatric population)	interdisciplinary pain treatment	*Analyzed Separately* **Benefits**: Treatment satisfaction **Risks**: None
Takahashi et al. [141]	Neck	laser therapy	*Analyzed Separately* **Benefits**: Pain **Risks**: None
Tan et al. [142]	Low back	self-hypnosis trainings	*Analyzed Separately* **Benefits**: Pain intensity, pain interference, and sleep quality **Risks**: None
Tchivileva et al. [143]	TMDs	propranolol	*Analyzed Separately* **Benefits**: *Pain intensity **Risks**: AEs
Thompson et al. [145]	Neck	interactive behavioral modification therapy	*Analyzed Separately* **Benefits**: *Disability **Risks**: None
Valenza et al. [150]	Low back	pilates exercise	*Analyzed Separately* **Benefits**: *Disability; *pain ratings **Risks**: None

Study	Pain Type	Intervention	Benefit and Risk Outcomes
Verra et al. [152]	Back	rehabilitation program	*Analyzed Separately* **Benefits**: *Disability **Risks**: None
Ware et al. [155]	Variety	herbal cannabis	*Analyzed Separately* **Benefits**: None **Risks**: *AEs
Wasan et al. [156]	Low back	oral morphine or oxycodone	*Analyzed Separately* **Benefits**: *percent pain improvement **Risks:** opioid misuse
Williams et al. [158]	Low back	telephone-based healthy lifestyle coaching	*Analyzed Separately* **Benefits**:*pain intensity **Risks:** AEs
Wilson et al. [160]	Shoulder	peripheral nerve stimulation	*Analyzed Separately* **Benefits**: *worst pain last week **Risks:** AEs
Yoon et al. **[162]**	Musculo-skeletal	transdermal buprenorphine	*Analyzed Separately* **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 (2Angina, 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.

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

Title	Date	FDA Organization	Topic	URL
Structured Approach to Benefit Risk Assessment in Drug Regulatory Decision-Making PDUFA V Implementation Plan	01-July-13	Center for Drug Evaluation and Research	Medicinal Product	https://www.fda.gov/media/84831/download
Periodic B/R Evaluation Report (PBRER)	18-July-16	Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research	Periodic B/R Evaluation Report (PBRER)	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2cr2-periodic-B/R-evaluation-report-pbrer
Periodic B/R Evaluation Report – Questions and Answers	18-July-16	Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research	Periodic B/R Evaluation Report questions/ answers	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e2cr2-periodic-B/R-evaluation-report-questions-and-answers
Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)	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

Title	Date	FDA Organization	Topic	URL
Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions: Guidance for Industry and Food and Drug Administration Staff	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
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
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

Title	Date	FDA Organization	Topic	URL
Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework Guidance for Industry	20-June-19	Center for Drug Evaluation and Research	Medication/ Opioids	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/opioid-analgesic-drugs-considerations-benefit-risk-assessment-framework-guidance-industry
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	30-Aug-19	Center for Devices and Radiological Health	Medical Devices	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/consideration-uncertainty-making-benefit-risk-determinations-medical-device-premarket-approvals-de
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	30-Aug-19	Center for Devices and Radiological Health	Medical Device	https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de

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
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

Title	Date	Topic	URL
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
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 Authorisatio 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
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
The Future of Drug Safety: Promoting and Protecting the Health of the Public	22-Sept-06	Medicinal Products	http://www.nationalacademies.org/hmd/Reports/2006/The-Future-of-Drug-Safety-Promoting-and-Protecting-the-Health-of-the-Public.aspx
Understanding the Benefits and Risks of Pharmaceuticals. Workshop Summary	15-Aug-07	Medicinal Products	http://www.nationalacademies.org/hmd/Reports/2007/Understanding-the-Benefits-and-Risks-of-Pharmaceuticals-Workshop-Summary.aspx
Ethical and Scientific Issues in Studying the Safety of Approved Drugs	1-May-12	Medicinal Products	http://www.nationalacademies.org/hmd/Reports/2012/Ethical-and-Scientific-Issues-in-Studying-the-Safety-of-Approved-Drugs.aspx
Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks of Pharmaceutical Products: Workshop Summary	26-Sept-14	Medicinal Products	http://nationalacademies.org/hmd/Reports/2014/Characterizing-and-Communicating-Uncertainty-in-the-Assessment-of-Benefits-and-Risks-of-Pharmaceutical-Products.aspx
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/29023083
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