SROM Past, Present and Future

Studies and Clinical Guidelines

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Disclosure Information

Slow-release oral morphine as MOUD: used internationally but why not the USA?

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- No Disclosures

Objectives

- Explore “the dilemma” in pursuing SROM for OUD in the US
- Review available research on slow-release oral morphine
- Discuss recently published clinical guidelines for OUD

The SROM Dilemma

- Why bother?
- Do benefits outweigh the risks?
- Misuse? Diversion?
- Tolerance?
- Who/where prescribe it?

Alternative Evidence-Based Treatment Options for OUD are Needed

- National and international authorities recommend opioid agonist treatment (OAT) as first-line OUD treatment
- Nearly 87% of individuals with OUD living in the US are not receiving treatment
- Less than 50% who initiate OAT continue treatment at six months
- Buprenorphine and Methadone May Not Be Effective for All Patients

Krawczyk N, Rivera BD, Jent V, Keyes KM, Jones CM, Cerdá M. “Has the treatment gap for opioid use disorder narrowed in the U.S.?: A yearly assessment from 2010 to 2019". Int J Drug Policy. 2022 Jul 19:103786. doi: 10.1016/j.drugpo.2022.103786. Epub ahead of print. PMID: 35934583.
Timko C, Schultz NR, Cucciare MA, Vittorio L, Garrison-Diehn C. Retention in medicationassisted treatment for opiate dependence: a systematic review. J Addict Dis. 2016; 35:22–35. DOI: 10.1080/10550887.2016.1100960

1941
FDA Approval

1998

1998: First Use of SROM for OUD Austria

Food & Drug Administration. (2016). Kadian Presribing Information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/020616s057lbl.pdf

European Monitoring Centre for Drugs & Addiction. (2016). *Year of introduction of MMT, HDBT, Heroin-Assisted Treatment, SROM*. https://www.emcdda.europa.eu/stats09/hsrtab1

2005: First RCT

- Crossover RCT comparing 7-weeks SROM vs 7-weeks methadone
- Primary outcome: retention, use, cravings, withdrawal, quality of life (QoL)
- Results: Similar efficacy, tolerability, no QoL difference, improved mood with SROM

Eder, H., Jagsch, R., Kraigher, D., Primorac, A., Ebner, N., & Fischer, G. (2005). Comparative study of the effectiveness of slow-release morphine and methadone for opioid maintenance therapy. Addiction, 100(8), 1101-1109.

Winklbaur, B., Jagsch, R., Ebner, N., Thau, K., & Fischer, G. (2008). Quality of life in patients receiving opioid maintenance therapy. A comparative study of slow-release morphine versus methadone treatment. *Eur Addict Res*, *14*(2), 99-105.

2005-2006: Expanded Use SROM for OUD

- Slovakia (2005), Slovenia (2005), Bulgaria (2006) and Luxembourg (2006)

2008: Saskatchewan Guideline

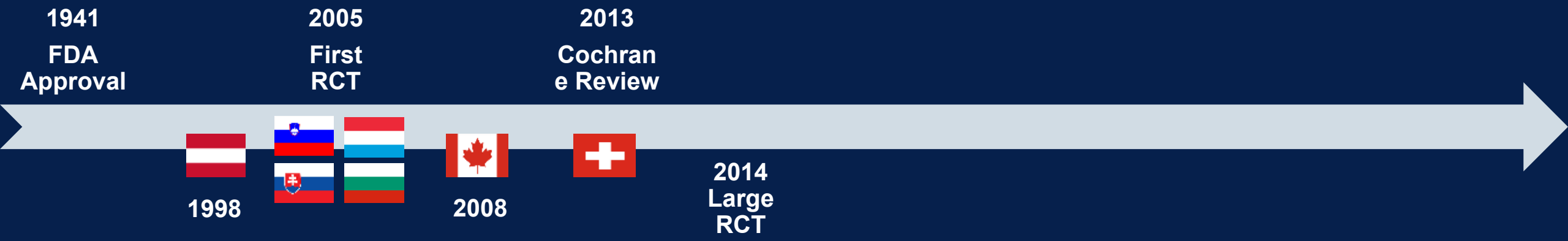
- First explicit guideline for use in North America
- Used since 1997 to supplement methadone initiations
- Continued until withdrawal symptoms and cravings are controlled
- “In most cases, the combination leads to immediate discontinuation of illegal drug use and a decrease in illegal activity necessary to obtain drugs”

College of Physicians and Surgeons of Saskatchewan. (2008). *Saskatchewan Methadone Guidelines for the Treatment of Opioid Addiction/Dependence* . https://www.cps.sk.ca//imis/Documents/Programs%20and%20Services/Methadone/Methadone%20for%20Pain%20Guidelines%20-%20Sask(2).pdf

2013: Cochrane Review

- 3 randomized trials (n=195) comparing SROM to methadone or buprenorphine/naloxone
- Similar efficacy:
  - Retention, medication adherence, non-medical opioid use
- Possibly more SROM adverse events (minor)
  - Toothache, headache, stomach cramps, sleep disturbance
- Overall, insufficient evidence

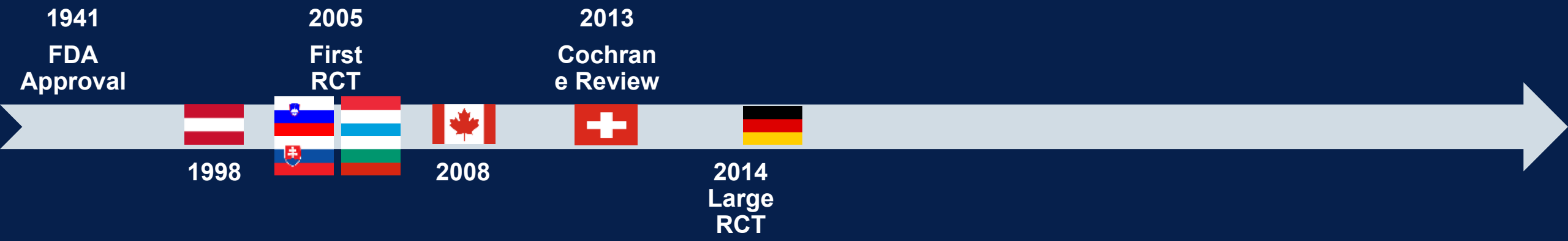
Ferri M, Minozzi S, Bo A, Amato L. Slow-release oral morphine as maintenance therapy for opioid dependence. *Cochrane Database Syst Rev.* Jun 5 2013;(6):CD009879. doi:10.1002/14651858.CD009879.pub2he



2014: Large RCT

- Provided additional safety and efficacy evidence
- Multi-site comparing 11-weeks methadone vs 11-weeks SROM, n = 157
- Inclusion: Adults, methadone dose ≥50 mg/day for > 6 months
- Results: SROM non-inferior to methadone
  - No differences in retention rates, heroin use, adverse events

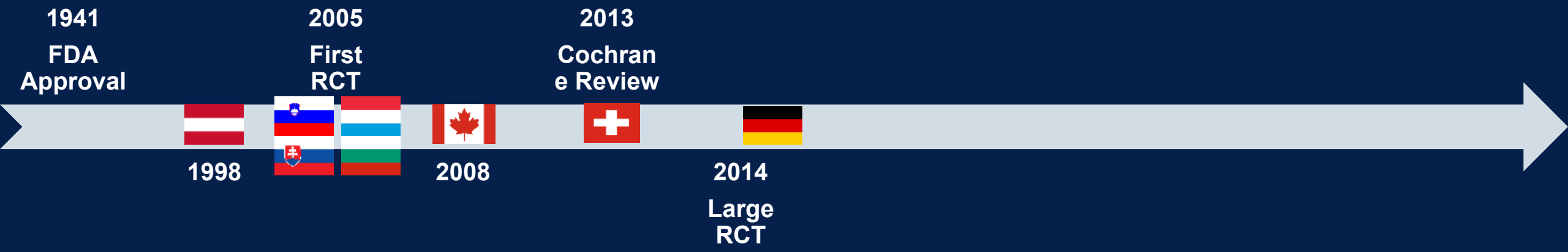
Beck T, Haasen C, Verthein U, et al. Maintenance treatment for opioid dependence with slow-release oral morphine: a randomized cross-over, non-inferiority study versus methadone.



2014: 6-month Outcomes

- 94% (n=198) continued or transitioned to SROM
- No signs of adaptation or loss of efficacy
- Treatment satisfaction, daily stress, and mental health scores remained stable
- Dysthymic symptoms significantly improved, decrease in QTc
- 71.2% (n=141) of patients were retained in treatment

Haemmig R, Koehler W, Bonorden-Kleij K, et al. Safety and tolerability of slow-release oral morphine versus methadone in the treatment…

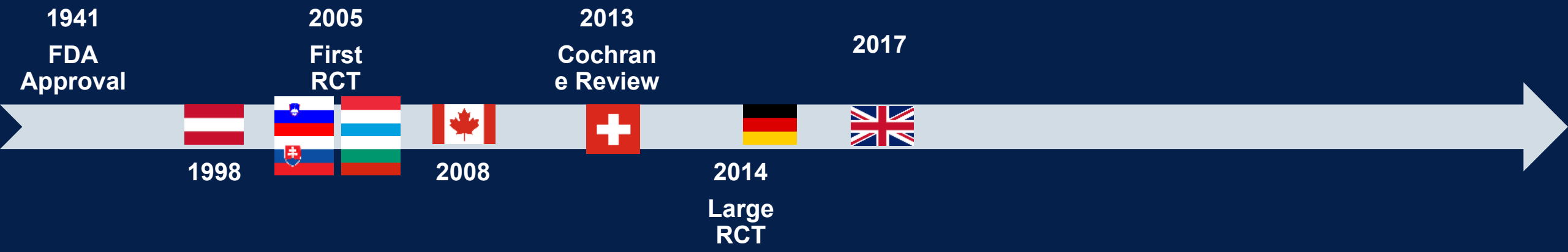


2015: Subsequent Analysis

- Compared to methadone, SROM:
  - Superior: patient satisfaction, improvements in mental health
  - No significant difference: overall physical health, alleviation of withdrawal symptoms, reduction of cravings

Verthein U, Beck T, Haasen C, Reimer J. Mental Symptoms and Drug Use in Maintenance Treatment with Slow-Release Oral Morphine Compared to Methadone: Results of a Randomized Crossover Study. *European Addiction Research.* 2015;21(2):97-104.

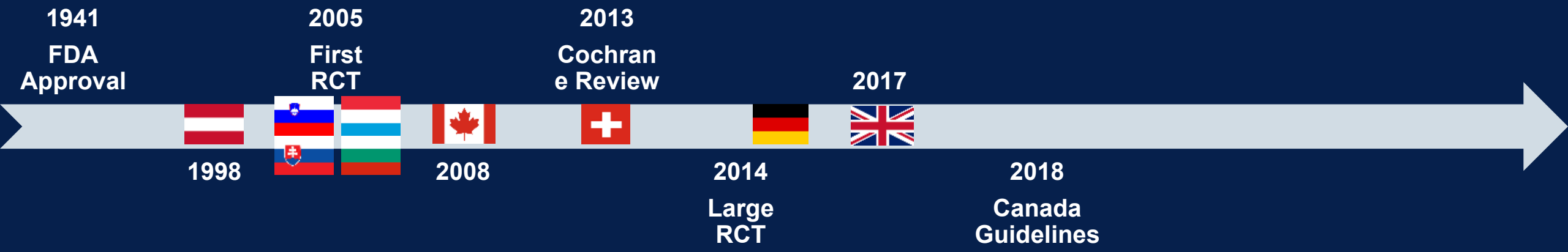
Falcato L, Beck T, Reimer J, Verthein U. Self-reported cravings for heroin and cocaine during maintenance treatment with slow-release oral morphine compared with methadone: a randomized, crossover clinical trial. *Journal of Clinical Psychopharmacology.* 2015;35(2):150-157.



2017: UK Clinical Guideline

- Methadone + buprenorphine/naloxone considered first-line therapy for **heroin driven** OUD
  - SROM considered second-line
- SROM may be used as first-line for OUD driven by opioids other than heroin
- SROM is considered “off label”
- Prescribed by specialist/seasoned clinicians with access to monitoring and support
- “Accountable officers” responsible for compliance and safe management

Expert CGoDMaDUI, Working Group. Drug misuse and dependence: UK guidelines on clinical management. 2017.



2018: Canadian National Practice Guideline

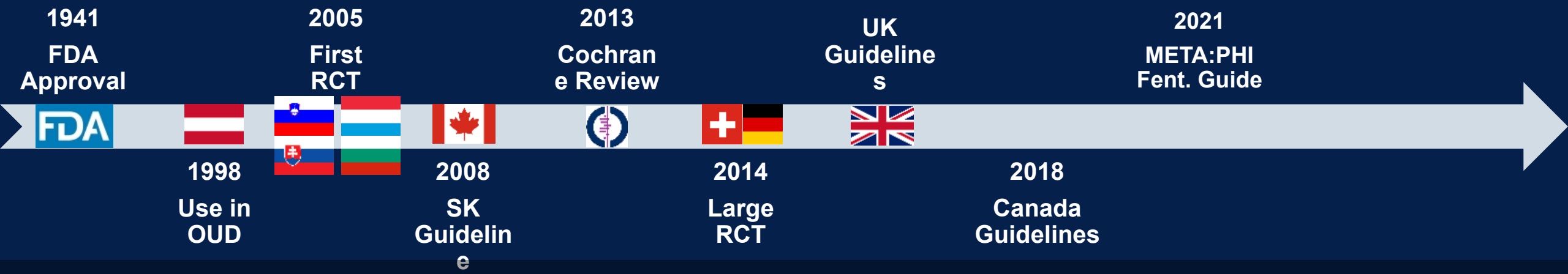
- Buprenorphine/naloxone considered first-line therapy due to safety profile
  - Methadone considered second-line
- Methadone may be used as a first-line when bup/nlx is contraindicated or not preferred
- SROM may be used as third-line if above ineffective or contraindicated
- SROM considered “off-label”
- Requires federal Section 56 exemption from the *Controlled Drugs and Substances Act* to prescribe methadone or prior consult with addiction medicine to Rx SROM

Bruneau J, Ahamad K, Goyer ME, et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ. Mar 5 2018;190(9):E247-E257.

2019: Systematic Review

- Included 4 RCTs, n = 471
- Conclusion: SROM generally equal to methadone in outcomes, possibly associated with less craving

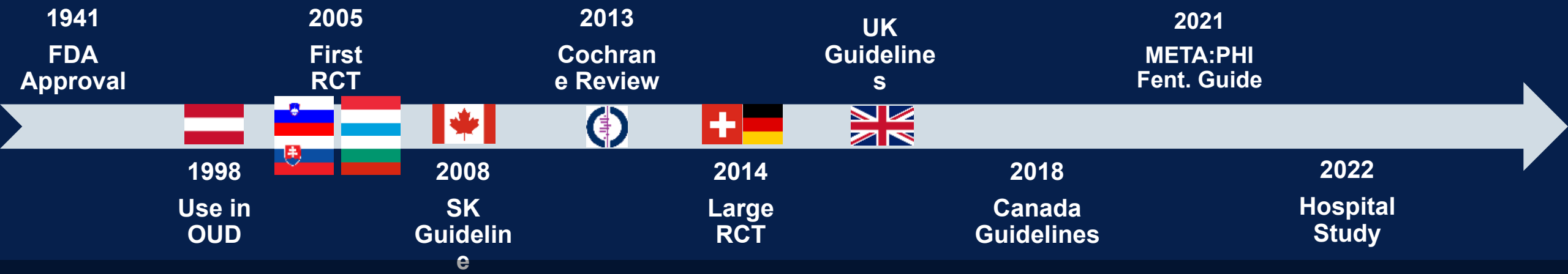
Klimas, J., Gorfinkel, L., Giacomuzzi, S. M., Ruckes, C., Socias, M. E., Fairbairn, N., & Wood, E. (2019). Slow release oral morphine versus methadone for the treatment of opioid use disorder. *BMJ Open*, *9*(4), e025799. https://doi.org/10.1136/bmjopen-2018-025799



2021: Methadone Treatment for People Who Use Fentanyl

- SROM may be co-prescribed with methadone and can be maintained or tapered
  - Relieves withdrawal symptoms and cravings during methadone initiation
  - Serum levels don't accumulate
  - Once-a-day dosing safer than alternative short-acting opioids
- Patients who experience side effects at higher methadone doses or who do not achieve adequate control of withdrawal symptoms at full methadone doses may remain on combination therapy
- Dispensed as observed dosing along with methadone

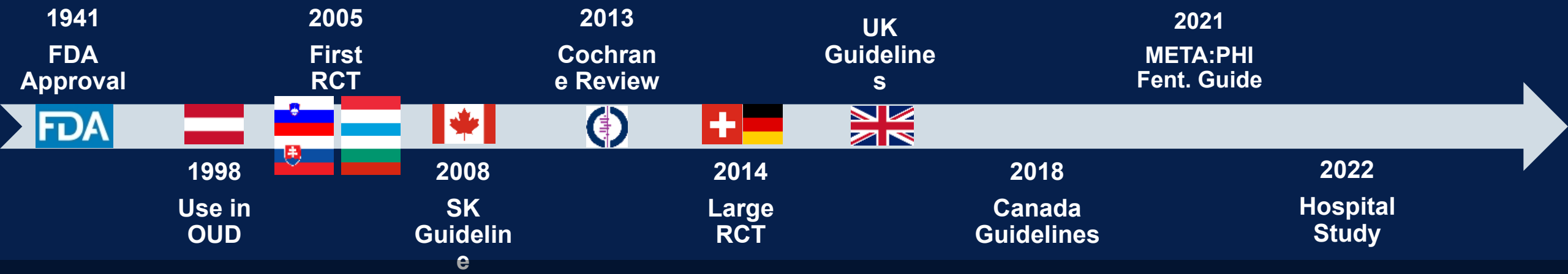
Bromley, L. K., M, Regenstreif, L, Srivastava, A, Wyman, J. (2021). *Methadone treatment for people who use fentanyl: Recommendations*. https://www.metaphi.ca/wp-content/uploads/Guide_MethadoneForFentanyl.pdf



2022: SROM for Hospitalized Patients

- Retrospective chart review of hospitalized patients who received addiction med consultation, n = 34
- 21 patients (62%) initiated first-line OAT (bup or methadone)
- 13 patients declined first-line OAT, and 7 initiated SROM
- SROM more common among **co-occurring chronic pain**

Brothers, T. D., Fraser, J., MacAdam, E., Morgan, B., & Webster, D. (2022). Uptake of slow-release oral morphine as opioid agonist treatment among hospitalised patients with opioid use disorder.



The Future: pRESTO Trial

- Ongoing 24-week RCT comparing SROM versus methadone
- Outpatient setting, Vancouver, Canada
- Primary outcome: bi-weekly urine drug screens
- Secondary outcomes: retention, safety, overdose events, QoL, and cost-effectiveness

Socias, M. E., Wood, E., Dong, H., Brar, R., Bach, P., Murphy, S. M., & Fairbairn, N. (2020). Slow release oral morphine versus methadone for opioid use disorder in the fentanyl era (pRESTO): Protocol for a non-inferiority randomized clinical trial. Contemp Clin Trials, 91, 105993.

The SROM Dilemma Revisited

- Why bother?
  - Limited OAT options, high potency contaminants
- Do benefits outweigh the risks?
  - Similar efficacy and tolerability
  - Superior patient satisfaction, mental health scores
  - Decrease in QTc potential safety advantage
  - Role in comorbid chronic pain
- Misuse? Diversion?
  - Mediate risk through observed administration, close monitoring, auditing agencies and regulations
- Tolerance?
  - No signs of adaptation or loss of efficacy
- Who/where prescribe it?
  - federal exemption requirement for prescriber's, addiction specialists federally regulated sites

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