DEF-MDL-05636.00001

Transmucosal Immediate-Release Fentanyl (TIRF) REMS

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

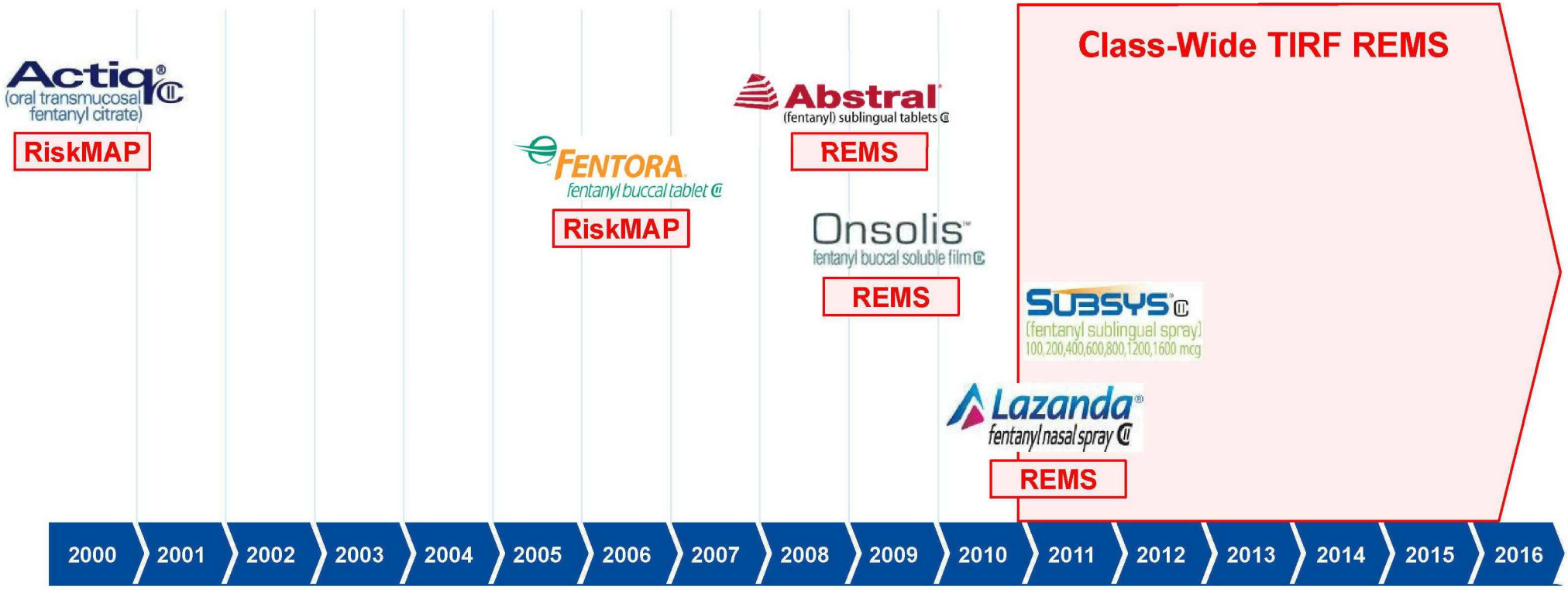
August 3, 2018

TIRF REMS ACCESS

DEF-NY-00022403

CCSF v Purdue Pharma, et al.
3:18-CV-7591
DEF-MDL-05636
Admitted:

History of TIRF Risk Mitigation Programs



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Goals of TIRF REMS

- The goals of the TIRF REMS Access program are to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors
- The TIRF REMS helps balance the access to these products to ensure that practitioners do not under treat breakthrough cancer pain while ensuring that TIRFs do not contribute to the opioid epidemic

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Elements of the TIRF REMS

- Medication Guide
- Prescriber certification
- Pharmacy certification
- Patient education and enrollment
- Distributors enrollment

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TIRF REMS Industry Group (TRIG) Sponsors and Partners

- **Sponsors**
  - BioDelivery Sciences International, Inc.
  - Insys Therapeutics, Inc.
  - SpecGx LLC (a wholly owned subsidiary of Mallinckrodt Inc.)
  - Mylan, Inc.
  - Par Pharmaceutical, Inc.
  - Sentynl Therapeutics, Inc.
  - Teva Pharmaceuticals USA, Inc.
  - West Therapeutic Development, LLC
- **Partners**
  - McKesson
  - UBC
  - Relay Health

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TIRF Medicines

- ABSTRAL® (fentanyl) citrate sublingual tablets
- ACTIQ® (fentanyl citrate) oral transmucosal lozenge and its authorized generic
- FENTORA® (fentanyl) buccal tablet
- LAZANDA® (fentanyl) nasal spray
- ONSOLIS® (fentanyl) buccal soluble film
- SUBSYS® (fentanyl) sublingual spray
- Fentanyl citrate oral transmucosal lozenge
- Fentanyl citrate buccal tablet

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TIRF REMS Is a Collaboration with FDA

- Design of the TIRF REMS Access program was a collaborative process with FDA and continues to be today
- TRIG (TIRF REMS Industry Group) and FDA are in constant dialogue about potential improvements to the TIRF REMS
- Continuous evaluation of effectiveness through use of new data sources
- Assessments are based on extensive annual reports

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Annual Assessment Reporting

Assessment Report	Reporting Period	Submission Date
6-Month	28 December 2011 – 27 April 2012	28 June 2012
12-Month	28 April 2012 – 28 October 2012	28 December 2012
24-Month	29 October 2012 – 28 October 2013	28 December 2013
36-Month	29 October 2013 – 28 October 2014	28 December 2014
48-Month	29 October 2014 – 28 October 2015	28 December 2015
60-Month	29 October 2015 – 28 October 2016	28 December 2016
72-Month	29 October 2016 – 28 October 2017	28 February 2018

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Modifications to the TIRF REMS

- **Modification 1 (2013) – edits to Patient-Prescriber Agreement form, addition of the Closed System Pharmacy Enrollment form**
- **Modification 2 (2013) – revised processes for outpatient pharmacies, revised attestations for physicians and patients to address concerns of patient access, revised program overview and frequently asked questions**
- **Modification 3 (2014) – revised assessment metrics, revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information**
- **Modification 4 (2017) – revised education materials and knowledge assessment to align with safety data requested by FDA for TIRF class product labeling**

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TIRF REMS Access Program Activities

- **The TIRF REMS is designed to educate healthcare prescribers, pharmacists, and patients about the appropriate use of TIRF medicines**
- **Ongoing activities**
  - Making sure healthcare providers who prescribe and use TIRF products know the risks and benefits of using the drug
  - Reinforcing to healthcare providers to adequately assess on a patient-by-patient basis if the benefits outweigh the risks
  - Reinforcing to healthcare providers to have conversations with the patient about the risk of a TIRF
  - Evaluating the effectiveness of the TIRF REMS Access program
  - Ensuring patients who need these products have access to them

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Agenda

Breakthrough Cancer Pain and the Public Health Impact of the TIRF Medicines	**Joseph Pergolizzi, MD** Naples Anesthesia and Pain Associates
Overview of TIRF REMS Access Program	**Kyle Irwin, MBA** Teva Pharmaceuticals
TIRF REMS Access Program Evaluation Results	**Annette Stemhagen, DrPH, FISPE** UBC
RADARS Data	**Richard C. Dart, MD, PhD** RADARS® System Denver Health and Hospital Authority University of Colorado School of Medicine
Effectiveness of the TIRF REMS Access Program	**Dean Mariano, DO** Insys Therapeutics
Planned Changes and Proposed Action Items	**Stephen Sherman, JD, MBA** Insys Therapeutics
Conclusions	**Stephen Sherman, JD, MBA** Insys Therapeutics

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Breakthrough Cancer Pain and the Public Health Impact of the TIRF Medicines

Joseph Pergolizzi, MD

Senior Partner and Director of Research
Naples Anesthesia and Pain Associates, Naples, Florida

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Cancer and Cancer Pain

- **In 2015, there were an estimated 15,112,098 people living with cancer of any site in the United States**
- **Pain is one of the most feared symptoms of cancer**
- **May be caused by the cancer itself, diagnostic procedures, or treatment**
- **Four categories**
  - Somatic
  - Visceral
  - Neuropathic
  - Mixed
- **Correlates with quality-of-life (QOL) indicators**
- **There is a moral imperative to treat cancer pain**

2018 Paice JA, et al. *Journal of Clinical Oncology* 2016;34(27):3325-334 PDQ® Supportive and Palliative Care Editorial Board. *PDQ Cancer Pain.* Bethesda, MD: National Cancer Institute. Updated 30 August 2017. Scarborough BM, et al. *CA Cancer J Clin* 2018;68:182-196. van den Beuken-van, et al. *Journal of Pain and Symptom Management* 2016;51(6):1070; NIH: https://seer.cancer.gov/statfacts/html/all.html

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Persistent Cancer Pain

- **Moderate to severe pain, greater than 12 hours per day**
- **Typically managed with around-the-clock opioids**
  - Administered at regular intervals throughout the day

NCCN Guidelines Version 1.2018 Adult Cancer Pain
PDQ® Supportive and Palliative Care Editorial Board. *PDQ Cancer Pain*. Bethesda, MD: National Cancer Institute. Updated 30 August 2017.

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Breakthrough Cancer Pain (BTCP)

- Severe or intense pain that "breaks through" maintenance pain medicine
- Character: rapid onset and short duration of pain
- Causes: cancer, diagnostic procedures, treatment, or activity
- Median time to peak intensity: 10 minutes (range: 0 to 60 minutes)
- Median duration (untreated): 60 to 90 minutes (range: 1 to 360 minutes)
- Episodic, frequency: 1 to 7 times per day
- Severity: moderate to severe
- Prevalence: approximately two third of cancer patients

Mercadante S, et al. *Value in Health* 2016;19:531-536.
Mercadante S, et al. *Pain* 2016;157(12) 2657 2663.
Vellucci R, et al. *Journal of Pain Research* 2017:10 2147–2155.

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Impact of BTCP

- **May affect patients in every area of their lives**
- **May limit activities of daily living**
  - Sleep, work, social activities, relationships, self care
- **Disability and decreased physical function**
- **Psychological impact**
  - Anxiety, depression, lack of control, isolation
- **Healthcare utilization**
  - Five times greater burden on the healthcare system due to pain-related hospitalizations, emergency room visits, and doctor's visits
- **Prognostic factor for mortality**

Hjermstad MJ, et al. *BMJ Supportive & Palliative Care* 2016;6:344–352. Katz NP, et al. *Postgraduate Medicine* 2017;129(1):32-39. Paice JA. *Cancer* 2018;124:2491-7. Vellucci R, et al. *Drugs* 2016;76:315–330; Scarborough BM, et al. *CA Cancer J Clin* 2018;68:182-196.

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Opioid Classes

	Long Acting Medications (LA)	Short Acting Medications (SA)	Transmucosal Immediate Release Fentanyl (TIRF)
Onset of action	1-12 hours	30-90 minutes	5-30 minutes
Effective duration	8-72 hours	3-6 hours	60-90 minutes

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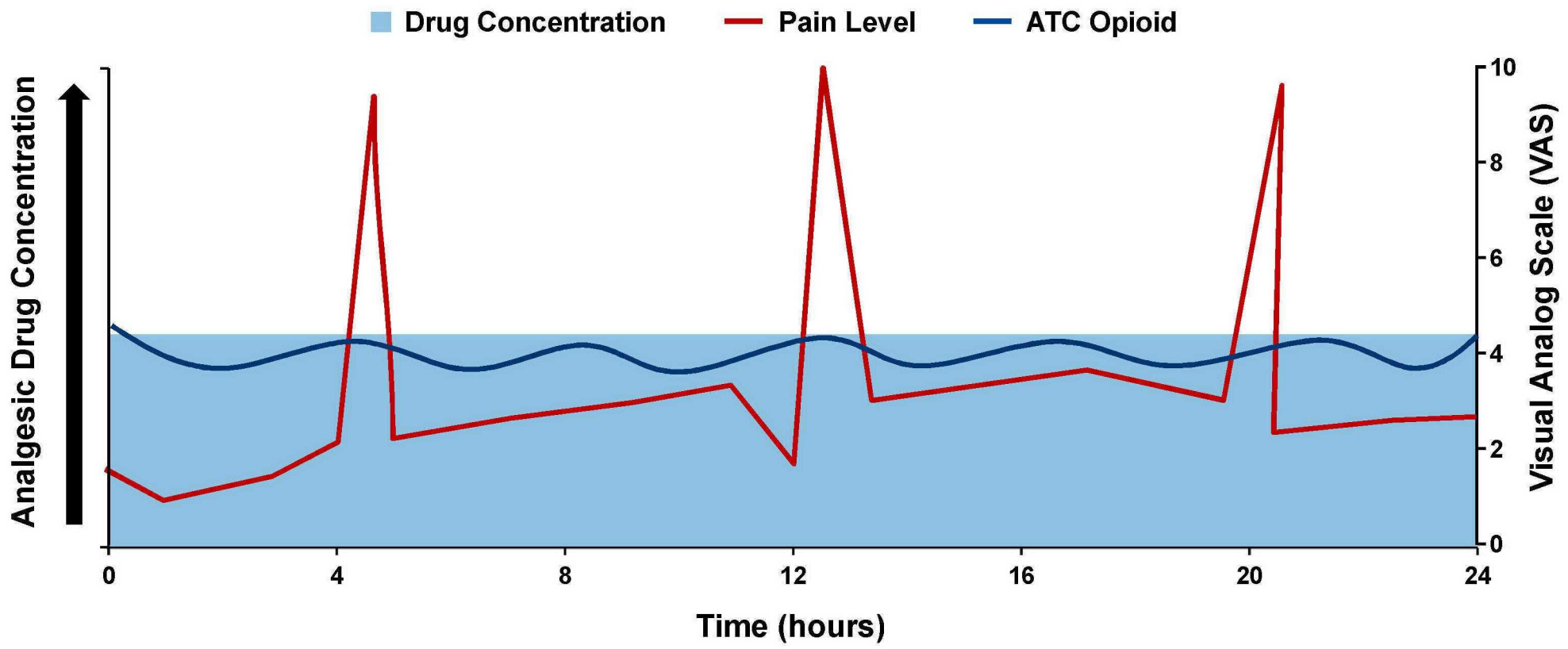
Untreated BTCP



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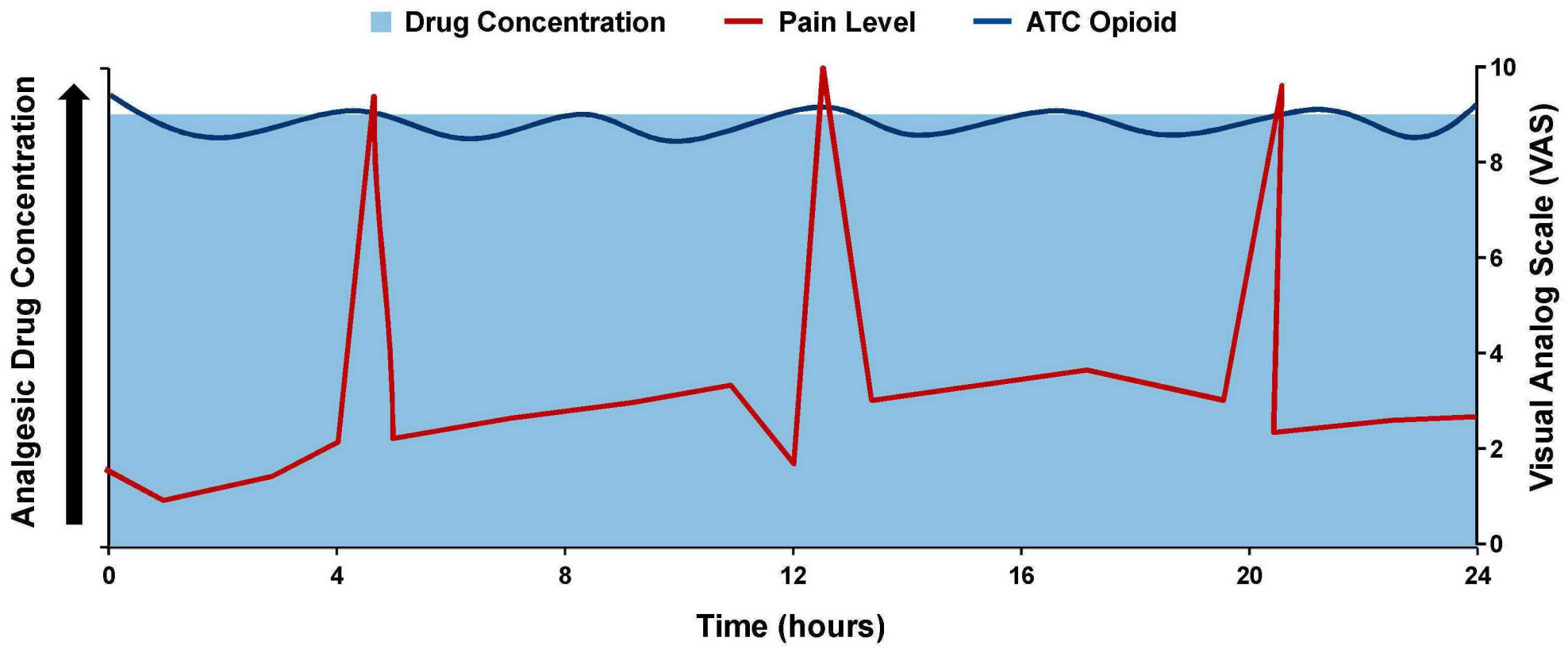
Overtreatment with ATC



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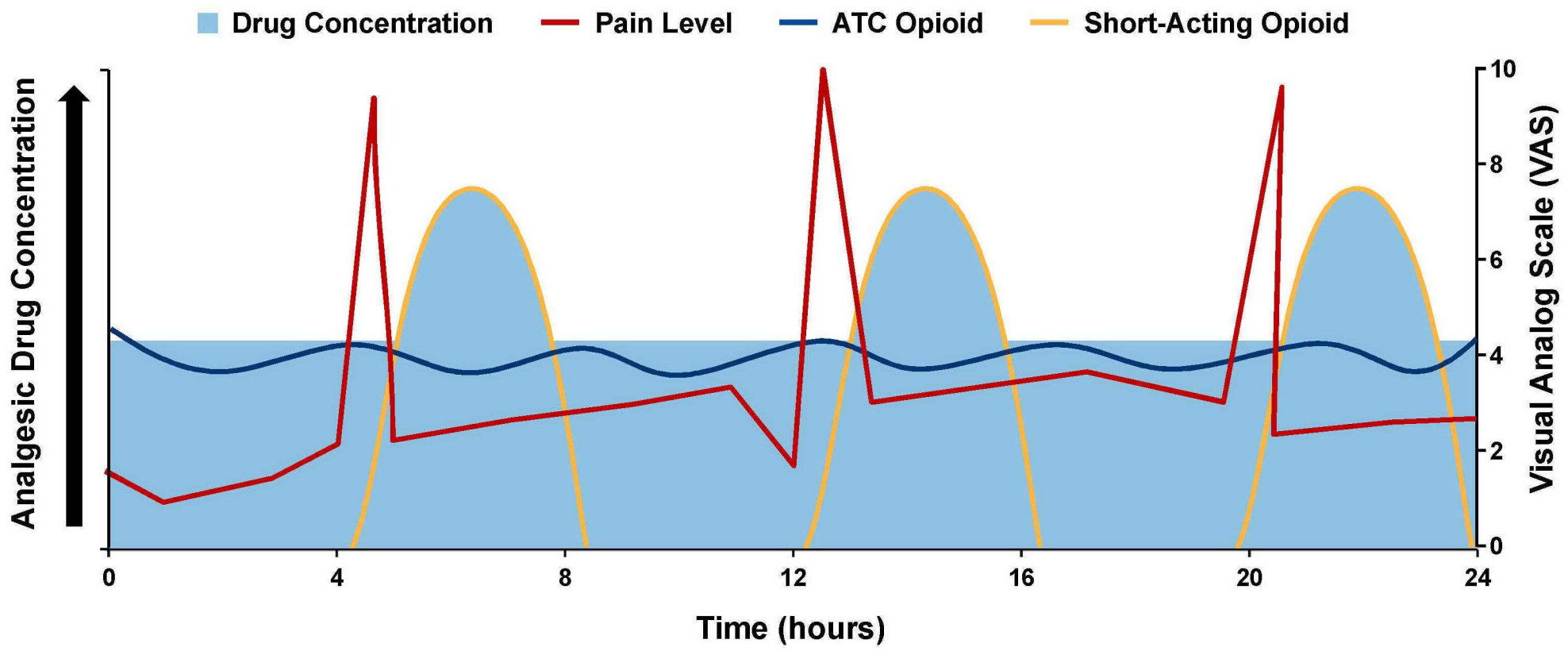
Short Acting Opioid – Suboptimal Timing of BTCP Episode



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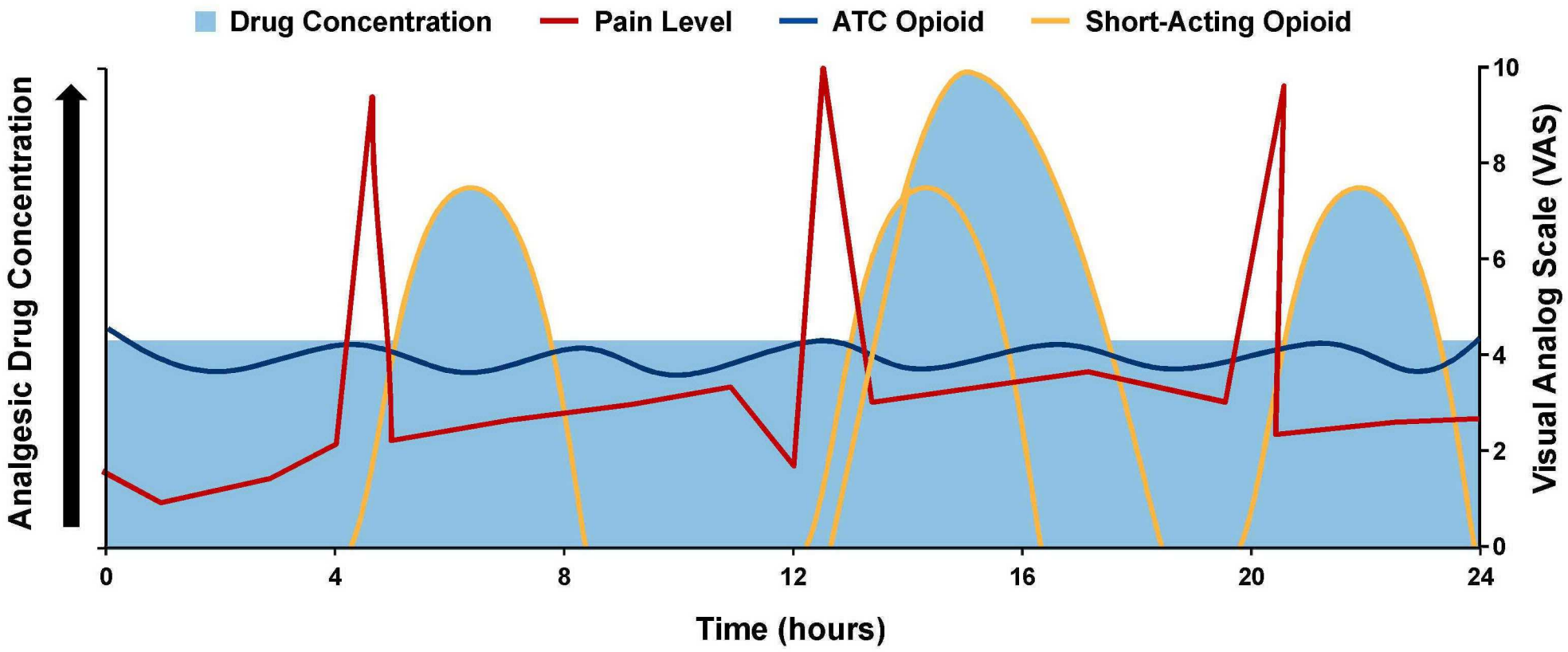
Short Acting Opioid Double Dosing



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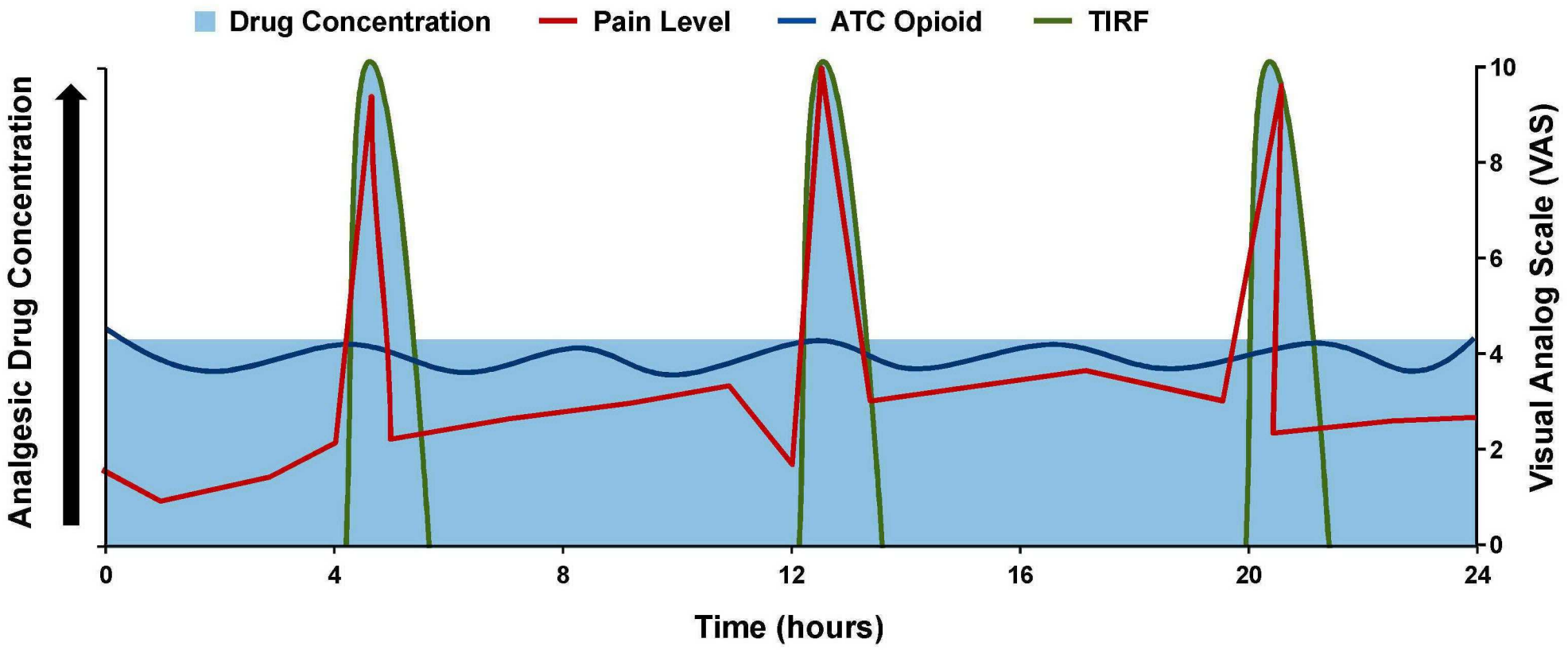
TIRF for BTCP Episode



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TIRF Medicines for BTCP

- Routes of TIRF administration include oral, buccal, sublingual, and intranasal
- Rapid onset of action of fentanyl with transmucosal route of administration (5 to 30 minutes)
- Short duration of action (1 to 2 hours)
- Potency (90 to 100 times that of morphine)
- Effect matches the BTCP episode
- Self-administered or by caregiver
- Non-injection, does not require swallowing
- Bypass first-pass metabolism

Chang A, et al. *J Pain Palliat Care Pharmacother* 2015;29(3):247-260. Janknegt R, et al. *Eur J Hosp Pharm* 2018;25:e2. Mercadante S. *Curr Opin Anesthesiol* 2015;28:559–564. Stanley TH. *J Pain*. 2014;15(12):1215-1226.

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Undertreatment of BTCP

- **About 1/3 of patients with BTCP did not receive any kind of rescue therapy, even in the cases of patients with at least 3 attacks per day**
  - The most common non-pharmacologic option is rest (81.2%)
- **1/3 received a WHO level I drug (non-opioid ± adjuvant)**
- **When opioids are prescribed, morphine is more frequently administered (71.2%) than a TIRF product (18.3%)**
  - TIRF provide superior pain relief vs. oral morphine in the first 30 and 45-60 minutes post-dosing
  - In the first 30 minutes after dosing oral morphine performed little better than placebo
- **Only 24.1% reported that their BTCP treatment worked every time**
- **Patients misuse prescribed opioids with the primary motivation to relieve physical pain (63.4%)**

Greco MT, et al. *Clin J Pain* 2011;27:9–18.
Jandhyala R, et al. *J Pain Symptom Manage* 2013;46:573e580.
Katz NP et al. *Postgraduate Medicine* 2017;129(1):32-39.
Paice JA. et al. *Cancer* 2018;124:2491-7

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Barriers to Cancer Pain Management

- **Barriers related to patients and family members**
  - Reluctance to report pain
  - Fears relating to addiction and side effects
  - Inadequate training or misunderstanding instructions for use of pain medications
  - Socioeconomic limitations to accessing treatment
  - Cognitive and affective factors, most critical for patients with severe dementia
- **Barriers related to healthcare professionals**
  - Inadequate training and expertise
  - Insufficient pain assessment due to competing priorities and time limitations
  - Concerns of opioid dependence and drug-seeking behaviors cause a reluctance to prescribe opioids
- **Barriers related to healthcare systems and payors**
  - Reduced access to and payment for opioids, non-opioids, and non-pharmacologic therapies
  - Shortages of opioids in retail and hospital pharmacies

Drageset J, et al. *Journal of Pain and Symptom Management* 2014;48(4):699-710.
Odonkor CA, et al. *Pain Medicine* 2017; 18: 363–373
Paice JA. et al. *Cancer* 2018;124:2491-7

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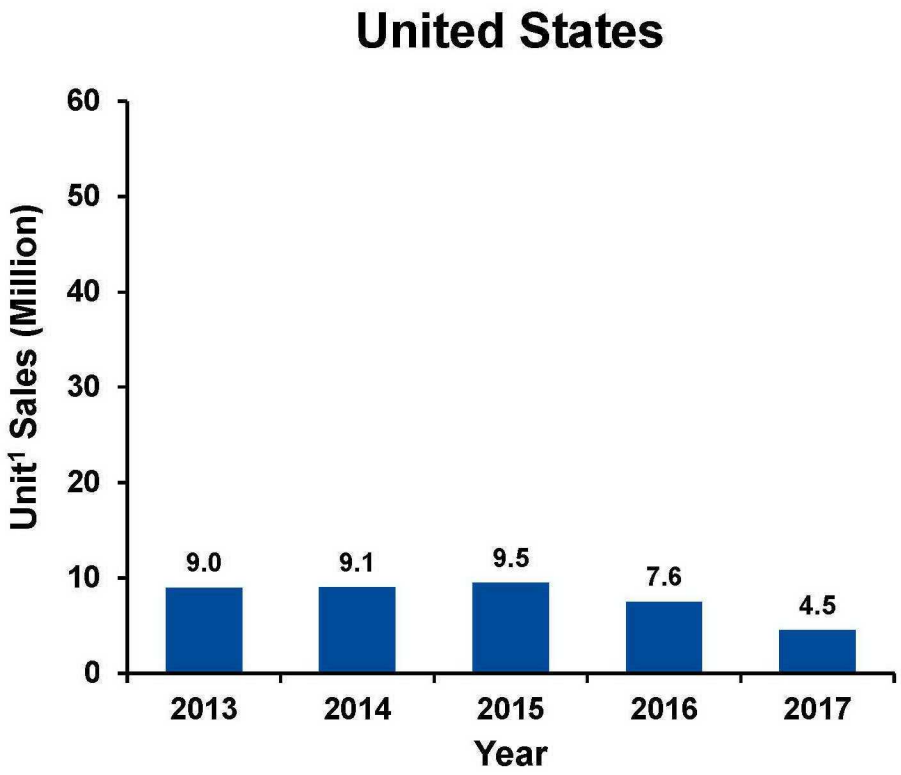
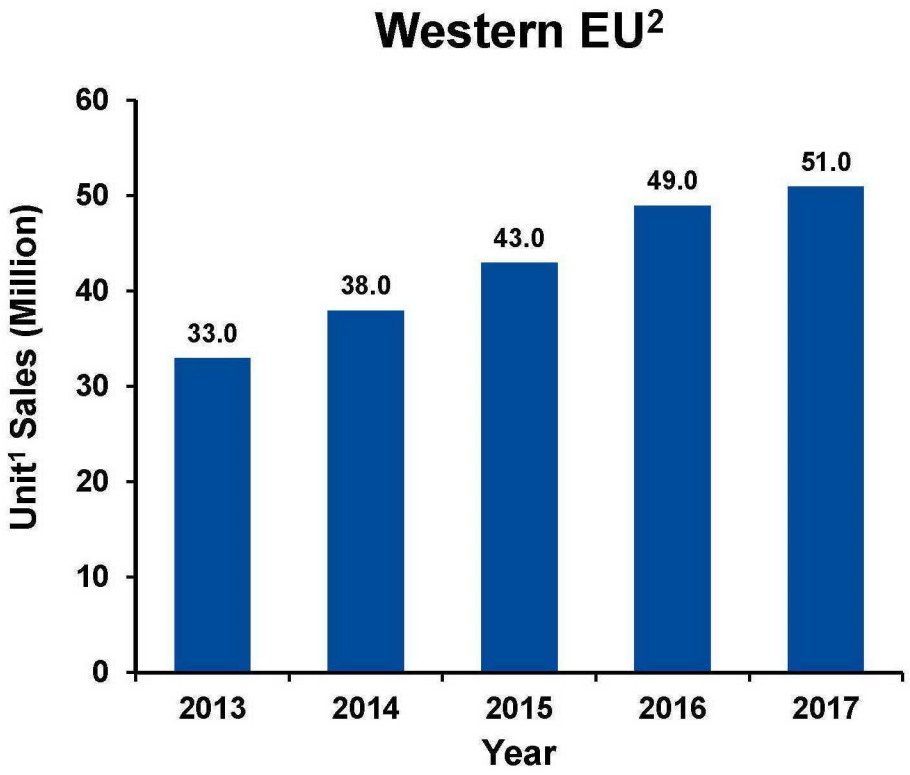
TIRF Prescriptions Over Time





1. Unit sales defined as number of individual doses
2. Includes 14 countries: Germany, France, Spain, Italy, UK, Finland, Norway, Sweden, Denmark, Belgium, Austria, Switzerland, Portugal, Ireland

Symphony Health (Moving Annual Total thru Sep); IMS (Moving Annual Total through Sep)

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Public Health Benefits of TIRF Products and REMS

- **TIRF products effectively manage BTCP**
  - Maintain daily functioning and ability to contribute to society
  - Minimize risk of adverse effects due to unwarranted dosage increases
  - Minimize risk of opioid misuse by serial dosing due to delayed onset of action
  - Lower total exposure to opioids compared to PRN use of short-acting opioids
- **TIRF REMS Access program mitigates risks**
  - Controlled prescribing, distribution, and dispensing
  - Prescriber, pharmacist, distributor, and patient: mandatory participation
  - Prescriber, pharmacist, and patient: mandatory education

Vellucci R, et al. *Drugs* 2016;76:315–330.
Vellucci R, et al. *Journal of Pain Research* 2017:10 2147–2155.

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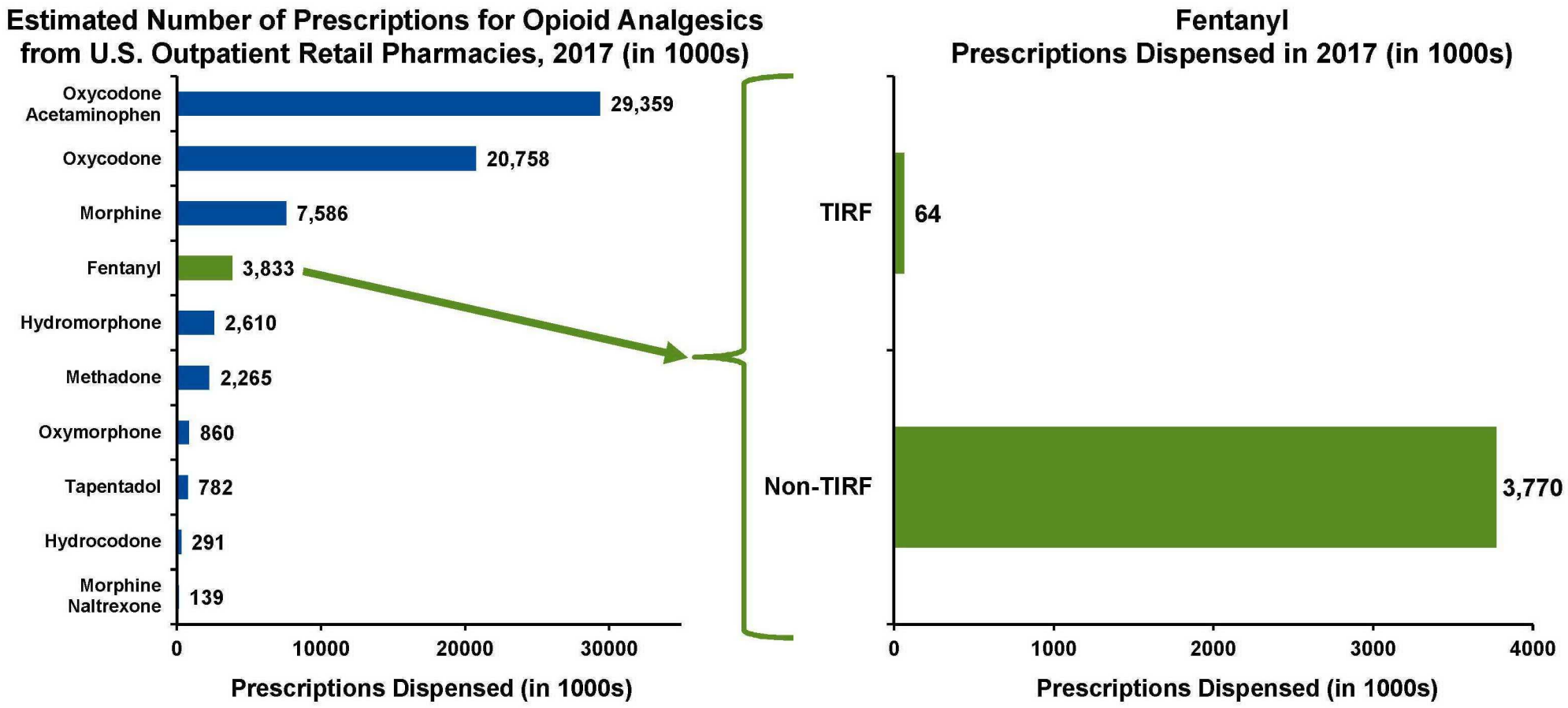
Utilization of TIRF Products



IQVIA, National Prescription Audit™, 2017.

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Public Health Considerations of Prescription Non-TIRF Fentanyls

- **3.8 million non-TIRF fentanyl prescriptions in the US**
  - 98.3% of US fentanyl prescriptions are not TIRF products
  - IV and transdermal
- **Small amount diverted from healthcare facilities in US**
  - Personal use
  - Street sales
- **Abusers can extract from patches to smoke or ingest**
- **Fentanyl solution, IV or extracted, can be injected**
- **Small factor in the opioid crisis**

US Department of Justice Drug Enforcement Administration: *2017 National Drug Threat Assessment*
IQVIA, National Prescription Audit™, 2017.

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Potential Public Health Considerations of TIRF Products

- Highly potent and high risk of overdose and death
- Desirable for abuse
- Hard to obtain
- Only available in small volumes
- Low rate of utilization
- Low rate of diversion and abuse
- Very small factor in the opioid crisis

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Public Health Risks of Illicitly Manufactured Fentanyl (IMF)

- **Illicitly produced fentanyl responsible for US fentanyl problem**
- **Vast global market (produced mostly in China)**
  - Fentanyl
  - Fentanyl derivatives
  - Fentanyl-laced counterfeit prescription-type pills
  - Fentanyl-laced street drugs
- **Easily purchased online**
  - Paid with cryptocurrency and delivered by USPS and other shippers
  - Directly linked to overdose deaths
- **Biggest driver of fentanyl overdose and death**
  - Illicit fentanyl dwarfs the entire prescription fentanyl market
- **Major contributor to US opioid crisis**

Drug Enforcement Administration, U.S. Dep't of Justice, DEA-DCT-DIR-040-17, *National Drug Threat Assessment* (2017).

Gottlieb S. *Statement by FDA Commissioner Scott Gottlieb, M.D., on balancing access to appropriate treatment for patients with chronic and end-of-life pain with need to take steps to stem misuse and abuse of opioids.* July 9, 2018.

United States Senate. Committee on Homeland Security and Governmental Affairs Permanent Subcommittee on Investigations. *Combatting the OPIOID Crisis: Exploiting the Vulnerabilities in International Mail* January 25, 2018.

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Public Health Conclusions

- **TIRF products effectively manage BTCP**
  - Lower total exposure to opioids and reduced risk of misuse of extended-release or immediate-release opioids
- **TIRF REMS Access program mitigates risks**
  - Controlled prescribing, distribution, and dispensing
  - Prescriber, pharmacist, and patient education and participation mandatory
- **Small subset of total opioid prescriptions**
- **Very small factor in opioid crisis**
- **Majority of fentanyl-related events of abuse, overdose, and death involve illicitly produced fentanyl**

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Overview of TIRF REMS Access Program

W. Kyle Irwin, MBA

Associate Director, REMS Operations
Teva Pharmaceuticals

DEF-NY-00022435

DEF-MDL-05636.00034

Goals of TIRF REMS Access Program

- **Mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by**
  - Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients
  - Preventing inappropriate conversion between TIRF medicines
  - Preventing accidental exposure to children and others for whom it was not prescribed
  - Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

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Elements of TIRF REMS

- **Medication Guide**
- **Elements to Assure Safe Use (ETASU)**
  - Prescriber certification
  - Pharmacy certification
  - Dispensing to outpatients with evidence of safe use conditions
- **Implementation System**
- **Timetable for Submission of Assessments**

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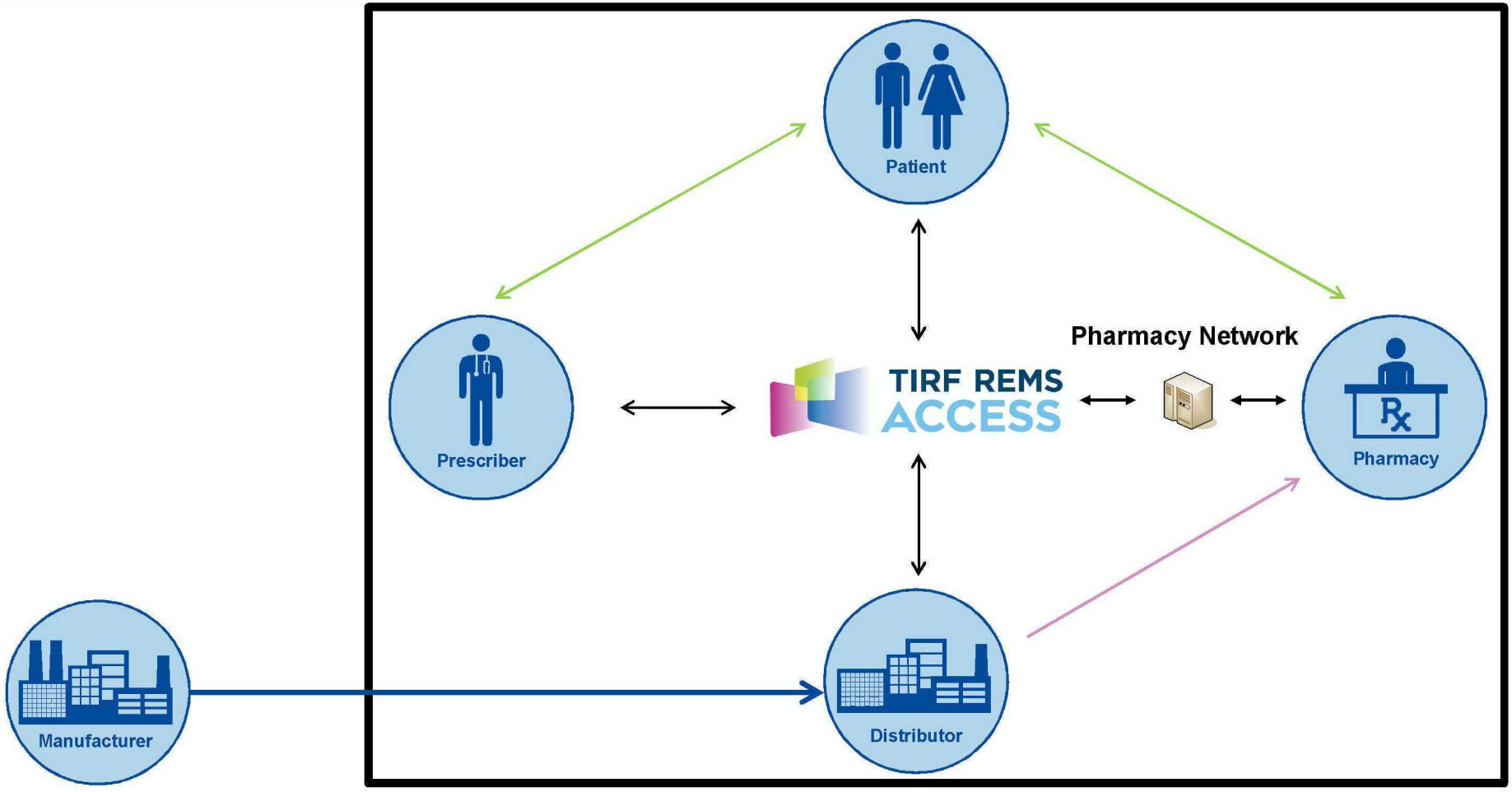
TIRF REMS Access Program: Restricted Distribution



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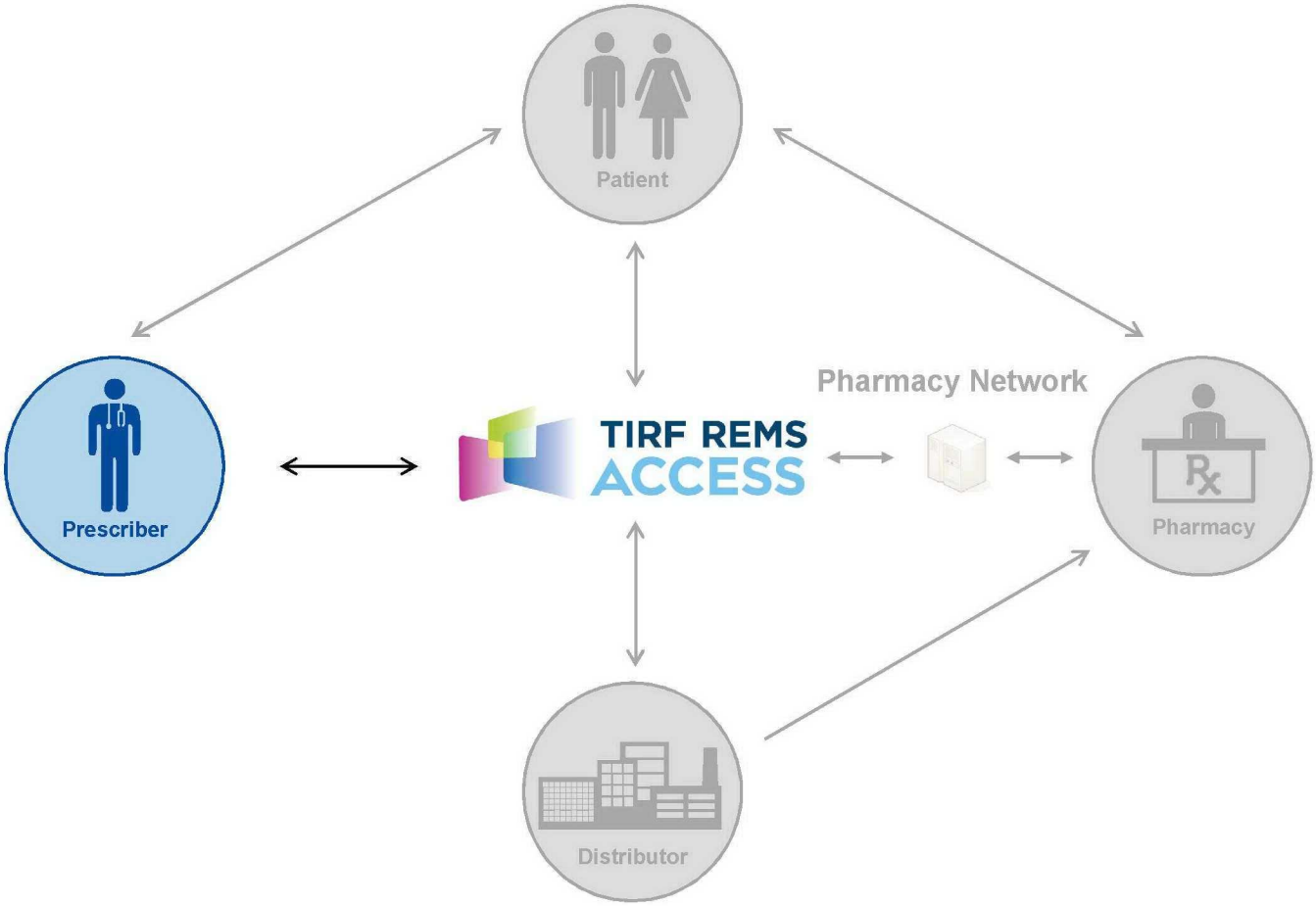
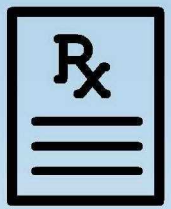
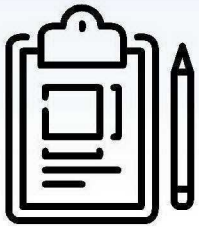
Prescriber – Certification





Prescribing Info

Knowledge Assessment



Prescriber Enrollment Form

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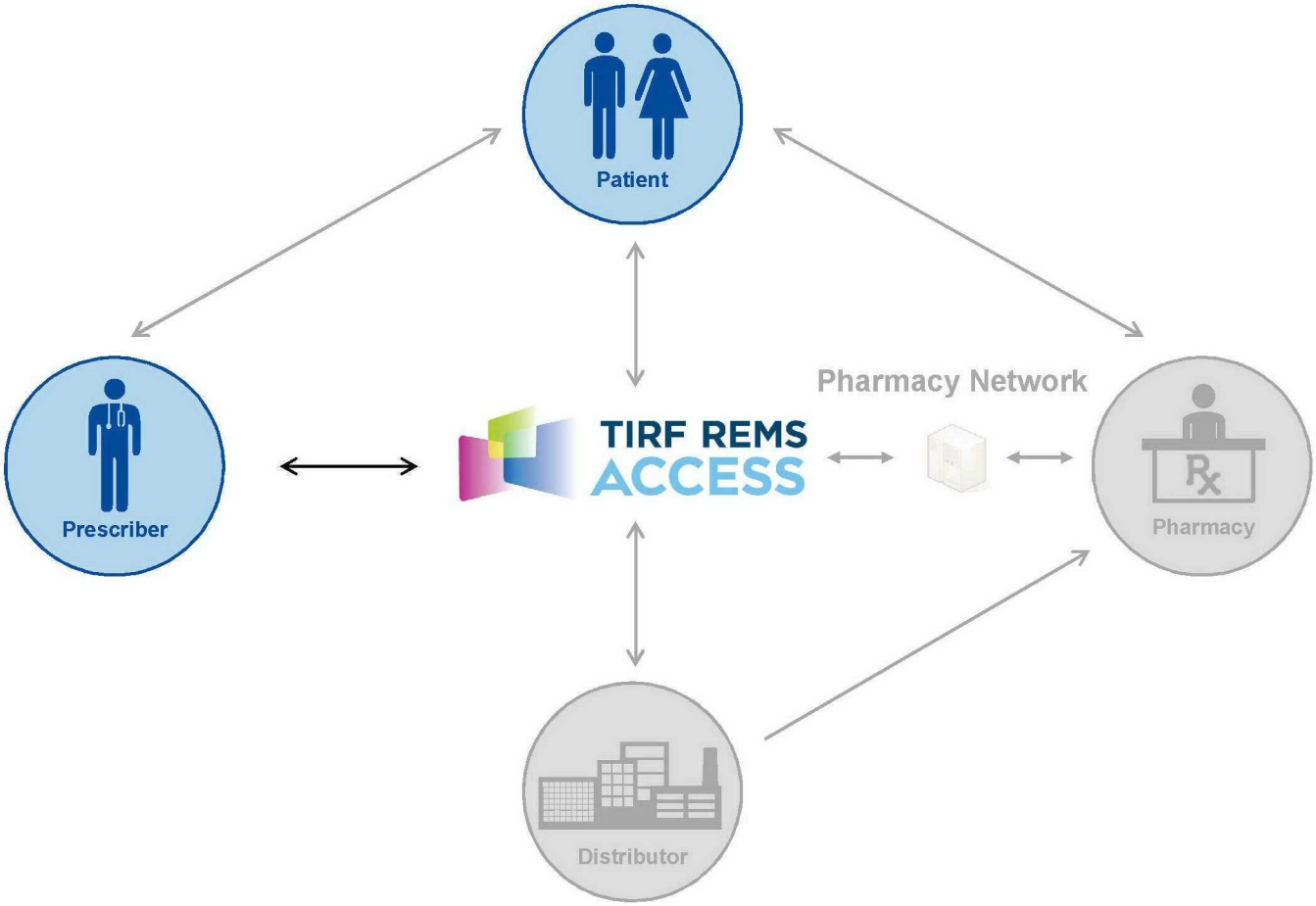
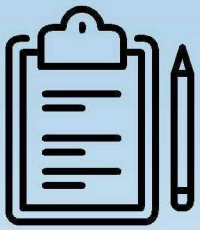
Prescriber – Counseling





Patient-Prescriber Agreement Form (PPAF)

Med Guide

DEF-NY-00022440

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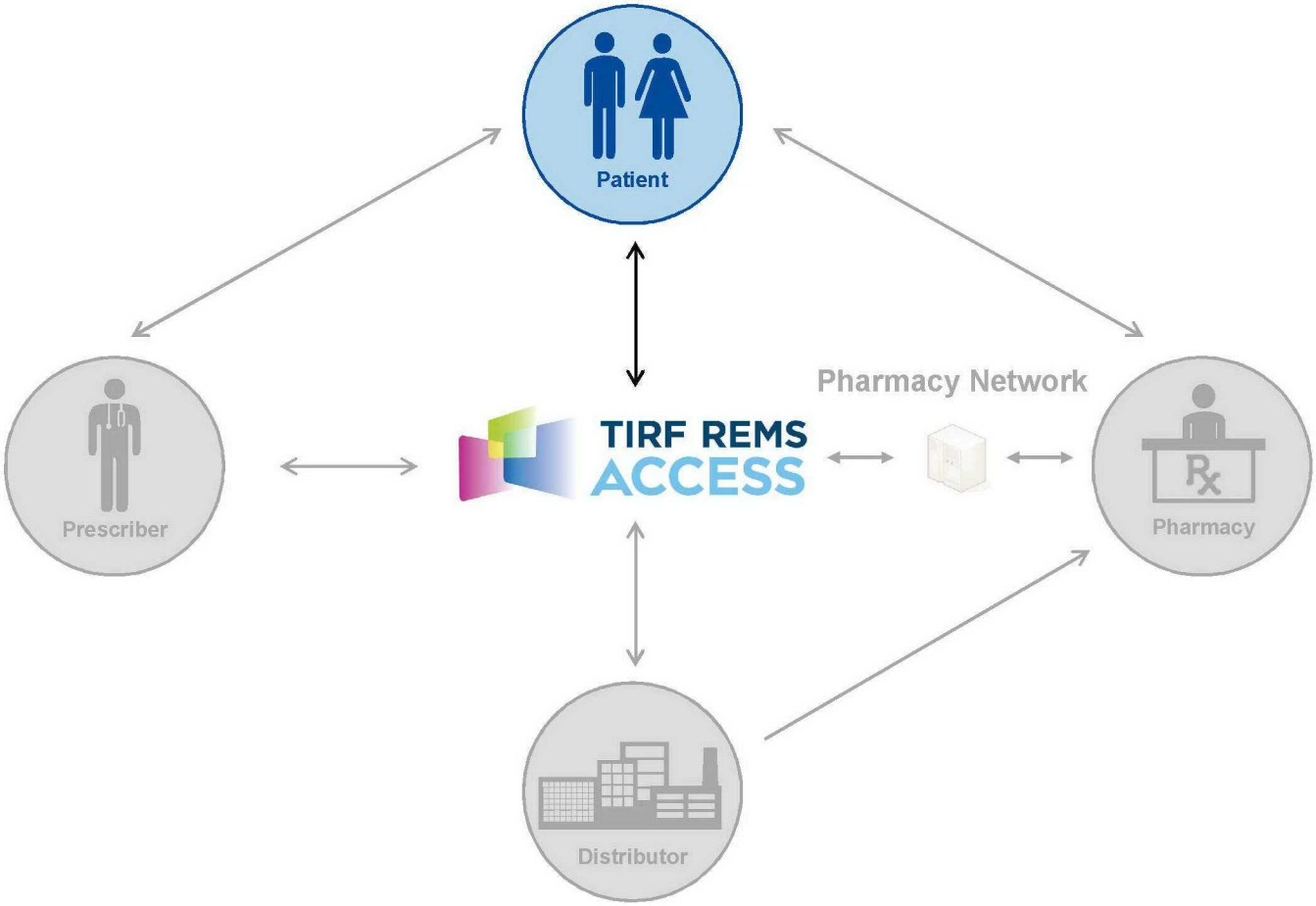
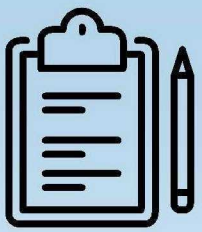
Patient





Patient-Prescriber Agreement Form (PPAF)

Medication Guide

Patient and Caregiver Overview

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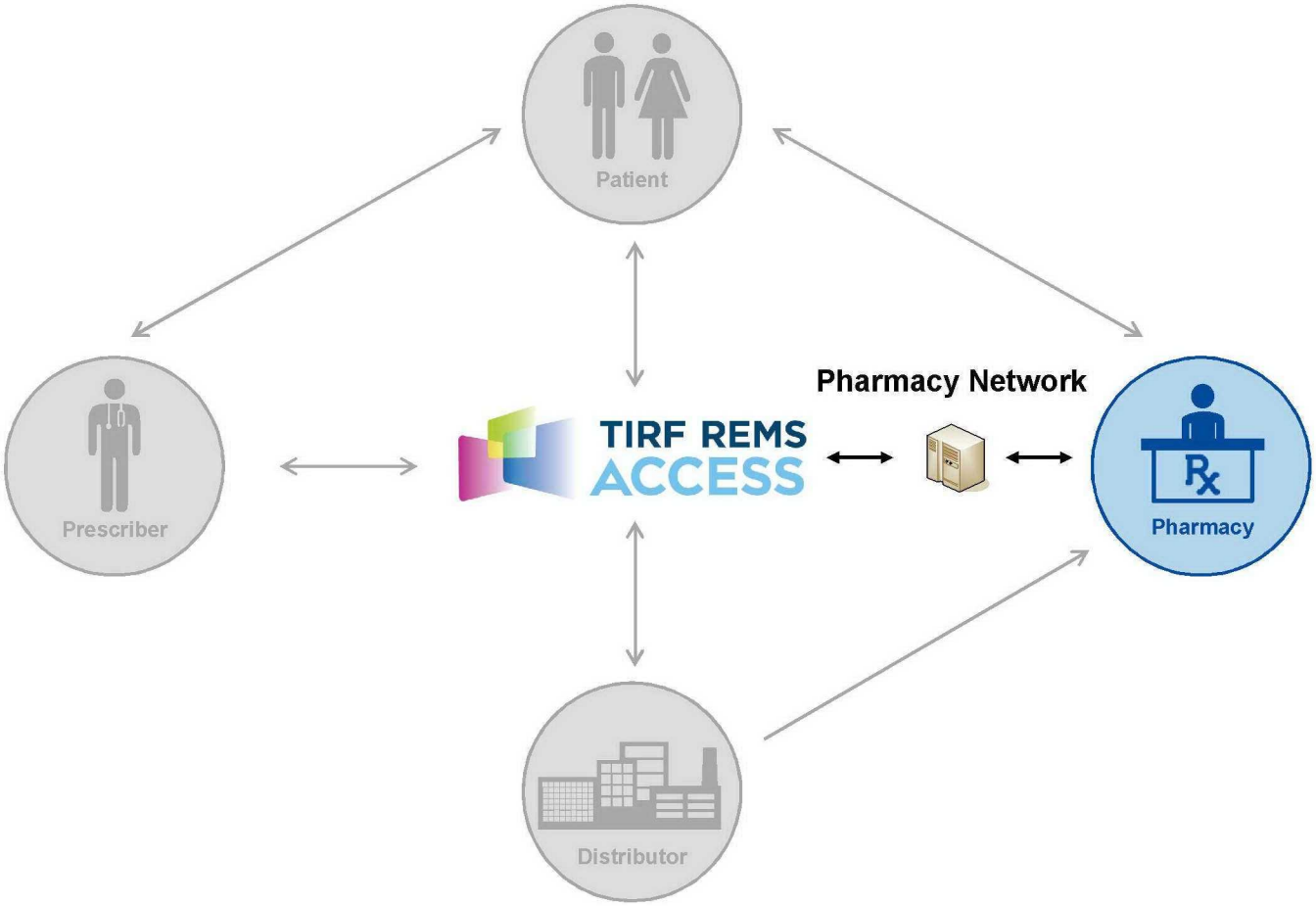
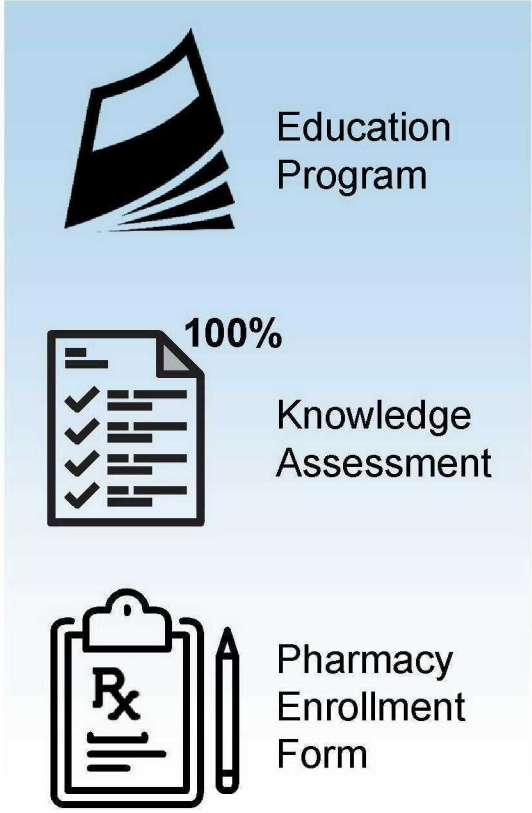
Pharmacy – Certification





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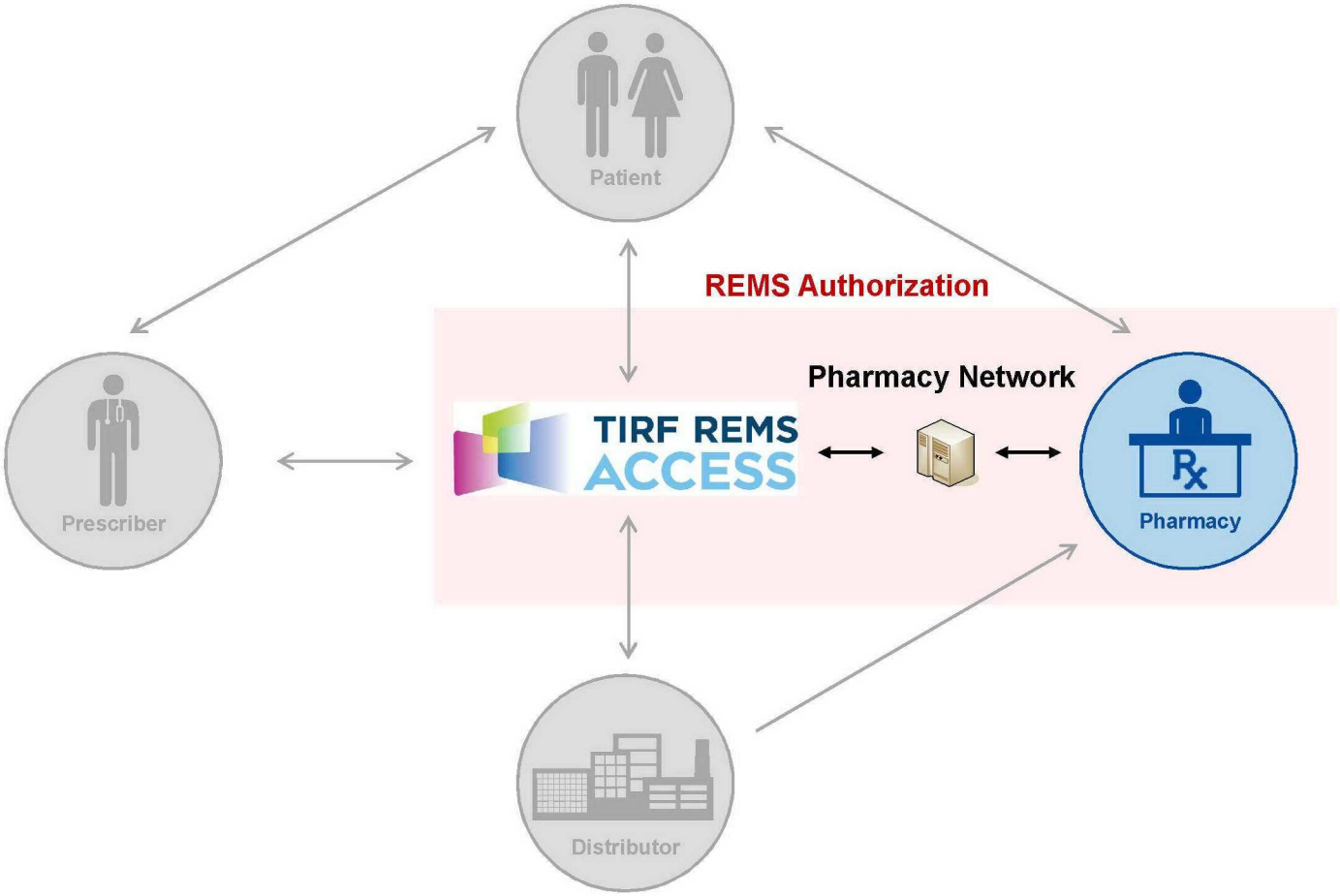
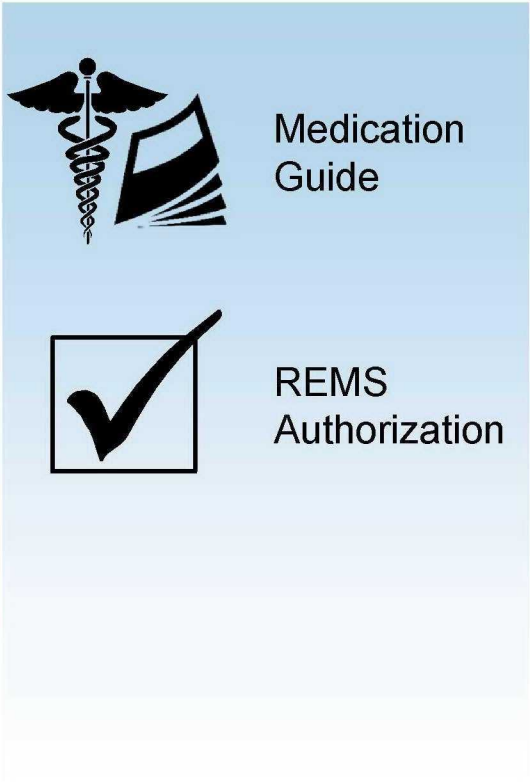
Pharmacy – Dispensing Requirements





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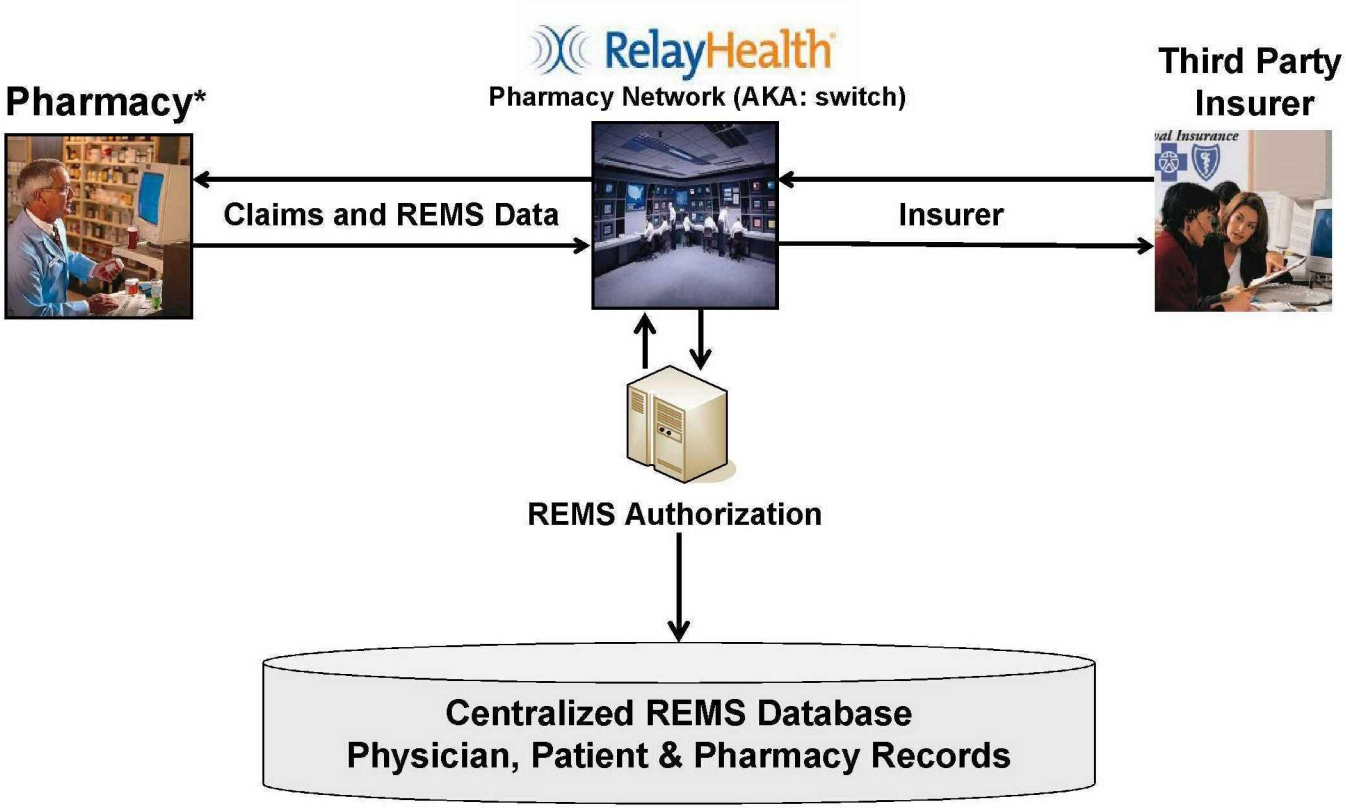
REMS Pharmacy Network Process



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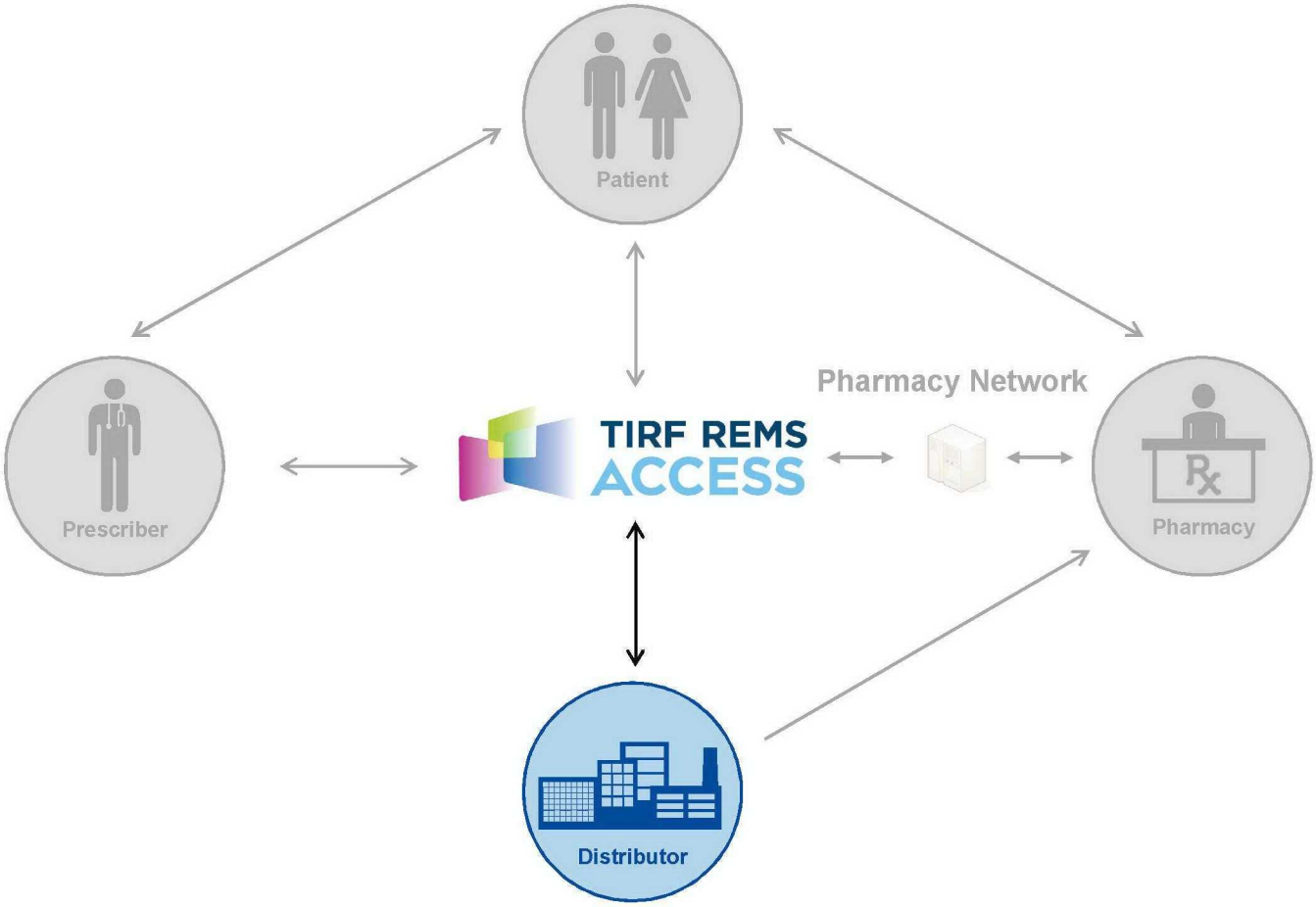
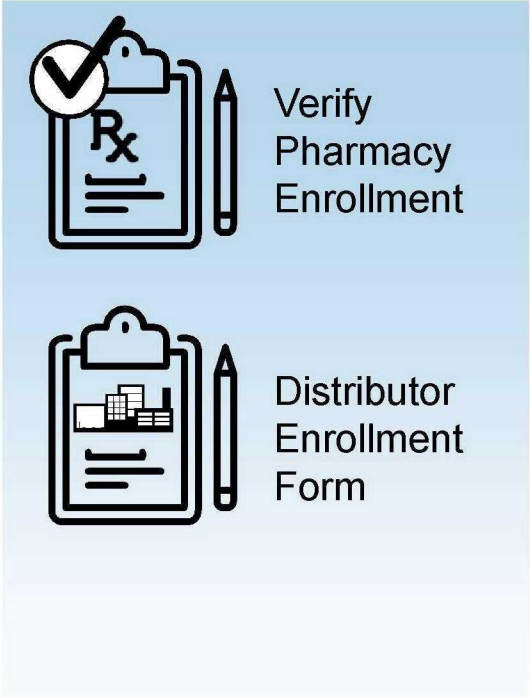
Distributor





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Conclusions

- The restricted distribution system prevents prescribing and dispensing outside of the TIRF REMS Access program
- Mandatory education, knowledge assessment, and enrollment of pharmacies and prescribers provides a baseline understanding of the risks and appropriate use of TIRF medicines
- Medication Guide, PPAF, and other education materials facilitate risk/benefit discussions between prescribers and patients/caregivers
- Use of the Pharmacy Network for the REMS authorization reduces the burden on the pharmacies

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TIRF REMS Access Program Evaluation Results

Annette Stemhagen, DrPH, FISPE

Senior Vice President and Chief Science Officer
UBC

DEF-NY-00022447

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REMS Assessments

- **Program and Product Utilization**
- **Dispensing Data**
- **Noncompliance**
- **Studies conducted to assess the REMS**
  - Opioid Tolerance Study
  - Persistency Analysis
- **Safety Surveillance**
- **Knowledge, Attitude, and Behavior (KAB) Surveys**
- **Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System**

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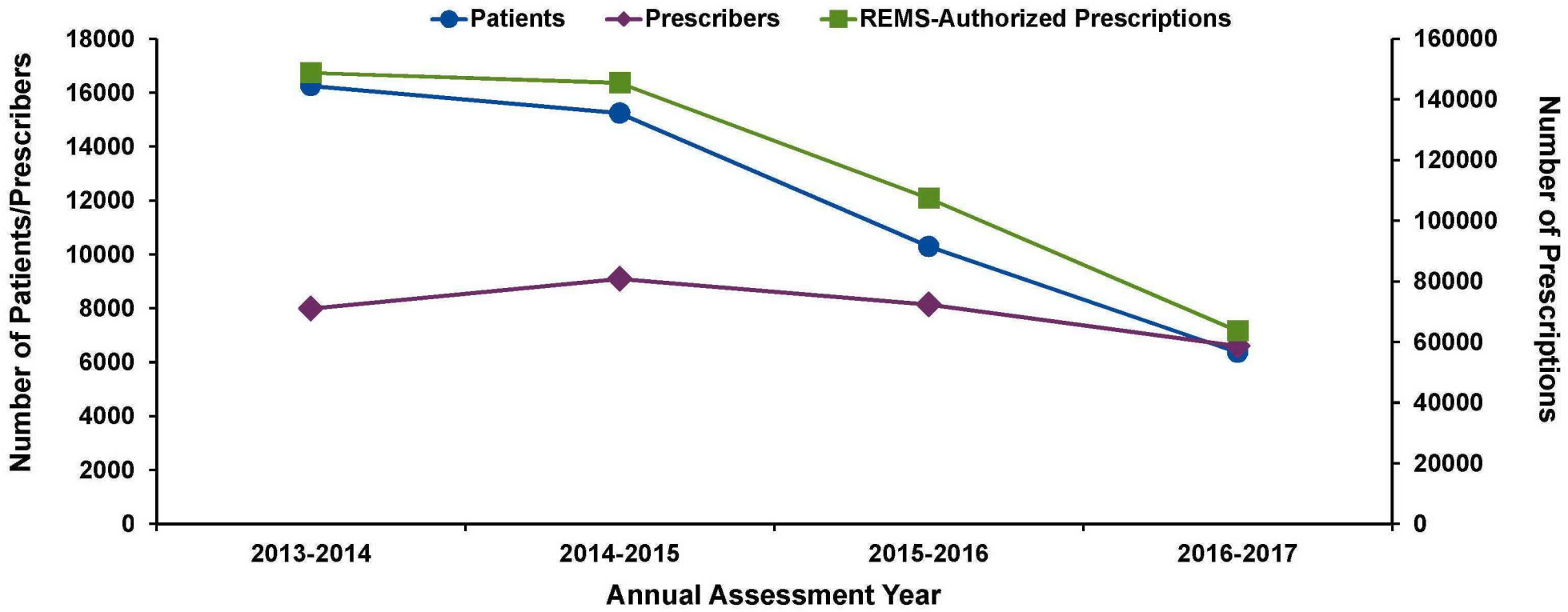
Trend in Active Patients and Prescriptions Authorized

Total Number of REMS-Authorized Prescriptions and Patients Receiving a TIRF During the Reporting Period



TIRF REMS Access program annual assessment reports: 36-month report (October 2013-October 2014); 48-month report (October 2014-October 2015); 60-month report (October 2015-October 2016); 72-month report (October 2016-October 2017).

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Why Are the Numbers Declining?

- **Decline is primarily due to enrollment expiration without re-enrollment**
- **Outreach is done to remind stakeholders to re-enroll in order to continue to prescribe or dispense**
- **Additional outreach to subset of prescribers and pharmacists is done to understand why they did not re-enroll**
  - No patients to dispense product
  - Change of prescribing

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Stakeholders Are Following REMS

- **As of October 2017, a total of 747,383 prescriptions have been submitted for authorization**
  - 89.2% did not encounter any REMS-related rejection prior to being authorized
  - 3.1% encountered at least one REMS-related rejection prior to being authorized
  - 7.7% encountered at least one REMS-related rejection prior to being authorized and were never dispensed

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REMS Assessments

- Program and Product Utilization
- Dispensing Data
- **Noncompliance**
- Studies conducted to assess the REMS
  - Opioid Tolerance Study
  - Persistency Analysis
- Safety Surveillance
- Knowledge, Attitude, and Behavior (KAB) Surveys

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Noncompliance Monitoring

- **Potential incidents of noncompliance identified through routine monitoring**
- **Noncompliance is identified by**
  - Standard program reporting
  - Reports to the program's call center
  - Vendor/sponsor reported events
  - Outreach to relevant stakeholders to validate data/information
  - Pharmacy audits
- **Process**
  - Notice → Warning → Suspension → Deactivation

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Noncompliance Events

- **Noncompliance events have been declining over the time period of the REMS**
- **Cumulatively, there have been 471 confirmed instances of stakeholder noncompliance**
- **Most common noncompliance events**
  - Prescriber failure to submit PPAF to the program in a timely manner
  - Pharmacy dispensed TIRF medication without obtaining REMS authorization
- **11 prescribers have been deactivated for unresolved noncompliance**
- **No pharmacies have been deactivated**

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Noncompliance Events – Audits

- **Yearly audits of closed system pharmacies and inpatient pharmacies to confirm compliance with the REMS**
- **Monitor closed system pharmacy dispensing activity to ensure compliance**
- **Monitor adherence to REMS requirements in inpatient pharmacies**
- **Audit results for 72 month assessment**
  - No inpatient pharmacies were found to be non-compliant
  - 18% of the prescriptions evaluated in closed system pharmacies were found to have been dispensed without obtaining REMS authorization

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REMS Controls

- No more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF
- No prescriptions dispensed after ten days without a PPAF in place
- Neither of these scenarios occurred during the 60 month or the 72 month assessment reporting period

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REMS Assessments

- Program and Product Utilization
- Dispensing Data
- Noncompliance
- **Studies conducted to assess the REMS**
  - Opioid Tolerance Study
  - Persistency Analysis
- Safety Surveillance
- Knowledge, Attitude, and Behavior (KAB) Surveys

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Prescribing and Dispensing TIRF Medicines Only to Opioid Tolerant Patients

- **Opioid tolerance cannot be assessed using data from the REMS database**
  - Only data on dispensed TIRF medications are collected
- **Other databases are difficult to use for studying PRN medications**
  - TIRF medicines used PRN
  - Track prescribing or dispensing, but not actual use
  - TIRF product may not be used for weeks after initial dispensing

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Opioid Tolerance Study

- **Retrospective cohort study using pharmacy claims from the IQVIA Longitudinal Prescriptions Database (LRx)**
  - February 2012 to October 2015
- **Represents 86% of the outpatient retail pharmacy channel**
- **Data from hospitalized patients are not included**
  - Could underestimate opioid tolerance
- **Because prescribing patterns are changing, TRIG is updating the study**

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Definition of Opioid Tolerance

- **Patients are considered opioid tolerant if, for one week or longer immediately preceding the initial TIRF prescription, they took at least**
  - 60 mg oral morphine/day
  - 25 mcg transdermal fentanyl/hour
  - 30 mg oral oxycodone/day
  - 8 mg oral hydromorphone/day
  - 25 mg oral oxymorphone/day
  - 60 mg oral hydrocodone/day

    OR
  - An equianalgesic dose of another oral opioid

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Opioid Tolerance Study Results

- **21,286 patients were dispensed an initial TIRF medicine**
- **86% had an outpatient prescription for an opioid analgesic in the 30 days prior to their TIRF prescription**
- **Approximately 42% of patients were considered opioid non-tolerant following the strict definition used in the study**
  - Misclassification can occur since TIRF products are used PRN

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Persistency Analysis

- **Study objective:**
  - Quantify switches from one TIRF medicine to another
  - Does not assess inappropriate conversions
- **Analysis began with patient's first prescription after REMS initiation**
- **Only outpatient prescriptions are included**

[1] Based on paid claims as of the end of the reporting period; data on file

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Persistency Analysis Results

- **Observational retrospective cohort study using data collected from all patients enrolled in the REMS program**
- **18,160 unique patients received more than one prescription and were included in the persistency analysis**
  - 81% remained on their index TIRF regimen
  - 19% had conversions from one TIRF regimen to another
  - Study did not evaluate whether any of the conversions were inappropriate

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REMS Assessments

- Program and Product Utilization
- Dispensing Data
- Noncompliance
- Studies conducted to assess the REMS
  - Opioid Tolerance Study
  - Persistency Analysis
- **Safety Surveillance**
- Knowledge, Attitude, and Behavior (KAB) Surveys

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Spontaneous Reports of Events of Special Interest

- **Standard approach for safety surveillance**
  - Spontaneous reports are used by most REMS to evaluate AEs
- **Identifies trends and potential safety signals**
  - Addiction
  - Overdose
  - Death
  - Pediatric exposure
- **Manufacturers follow standard protocol with MedDRA codes and text string searches to identify relevant cases**
- **Annually, independent healthcare professional (UBC) reviews and aggregates data from sponsors**

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Limitations of Spontaneous Reporting

- Cannot be used to calculate incidence rates
- Causality cannot be determined
- Incomplete reporting and limited ability for follow-up
- Could be affected by recall bias
- Possibility of duplicate cases
- Cannot always distinguish TIRF medicines from illicitly manufactured fentanyl, other fentanyl products, or other opioids
- Event may be related to an underlying condition or co-consumption of another product
- Focus on the opioid epidemic may be stimulating reports

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Aggregate Spontaneous Adverse Event Data of Interest

- **From October 2016 to October 2017: 568 unique case reports**
  - Death (549, 96.7%) – Many with no cause of death provided
  - Overdoses (34, 6.0%)
  - Addiction (10, 1.8%)
  - Pediatric exposure (1, 0.2%)

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Spontaneous AE Data for Deaths

- **Between August 2016 to August 2017 there was a total of 549 reports of death**
  - 355 cases had insufficient information to allow for an assessment of potential causality
  - 187 death cases were determined to be not related to the TIRF medication
  - 5 deaths possibly related to the TIRF product
  - 2 deaths related to the TIRF medication

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Spontaneous AE Data for Overdose and Addiction

- **10 reports of addiction from August 2016 to August 2017**
  - Most had insufficient information to determine outcome
  - One report had an outcome of death
- **34 reports of overdose from August 2016 to August 2017**
  - 24 reports had an outcome of death

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Surveillance Reports of Exposure to Children

- **Since October 2013, there have been 17 reports of children exposed to TIRF products**
  - 14 of the cases had no adverse event reported
  - Only outcome reported was 1 death
- **No reports of accidental exposure**
- **All reports were intentional prescribing**

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REMS Assessments

- Program and Product Utilization
- Dispensing Data
- Noncompliance
- Studies conducted to assess the REMS
  - Opioid Tolerance Study
  - Persistency Analysis
- Safety Surveillance
- **Knowledge, Attitude, and Behavior (KAB) Surveys**

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Annual Knowledge, Attitude, and Behavior (KAB) Surveys

- **Measure understanding of appropriate use of TIRF medicines and TIRF REMS Access program requirements**
- **Survey sample from the REMS database**
  - 300 prescribers
  - 300 pharmacists
  - 300 patients/caregivers

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Patient KAB Survey Results

- **Patient/caregiver knowledge and understanding of the key risk messages has remained stable**
  - High level of patient understanding: average knowledge score for 5 of the 6 key risk messages >86% (72 month report)
  - Patients/caregivers scored <80% on the following items
    - TIRF medicines should not be taken for
      - Pain after surgery (68.4%)
      - Long-lasting pain not from cancer (48.1%)
      - Headache pain (72.6%)
    - Stop taking a TIRF medicine if they stop taking their around-the-clock pain medicine (43.2%)

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Prescriber and Pharmacist KAB Survey Results

- **There is an overall trend over time toward maintenance or improvement in prescriber and pharmacist knowledge and understanding of the key risk messages**
  - Average knowledge score was >89.6% for prescribers and 85% for pharmacists for all key risk messages
  - Items scoring <80% include
    - Understanding that a cancer patient may not start a TIRF medicine and an around-the-clock opioid at the same time (Prescriber: 79.2%, Pharmacist: 66.2%)
    - A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (Prescriber: 74%, Pharmacist: 48.1%)
    - TIRF medicines are not indicated for chronic non-cancer pain (Prescriber: 79.2%, Pharmacist: 53.6%)

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Generalizability of Survey Respondent Populations

- Comparisons made with IQVIA and REMS data to determine generalizability of survey respondents
- When adjusted to the general population characteristics, the knowledge scores were similar

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REMS Assessment Conclusions

- **Patients and prescriptions have been declining**
  - Decline began 3 years after program began
  - Decline likely due to changes in prescribing environment
- **Low rate of noncompliance and usually corrected by outreach**
  - Few deactivations due to noncompliance
- **Opioid nontolerance rate hard to assess**
  - Planned validation study and opioid tolerance study will better assess
- **Persistency shows low rate of switching**
  - Did not assess rate of inappropriate conversion
  - Protocol to study inappropriate conversion under review
- **Few reports of pediatric exposure**
  - Most are intentional medical exposures; one death; no other outcome data

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RADARS Data

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Executive Director, RADARS® System
Denver Health and Hospital Authority
Professor, University of Colorado School of Medicine

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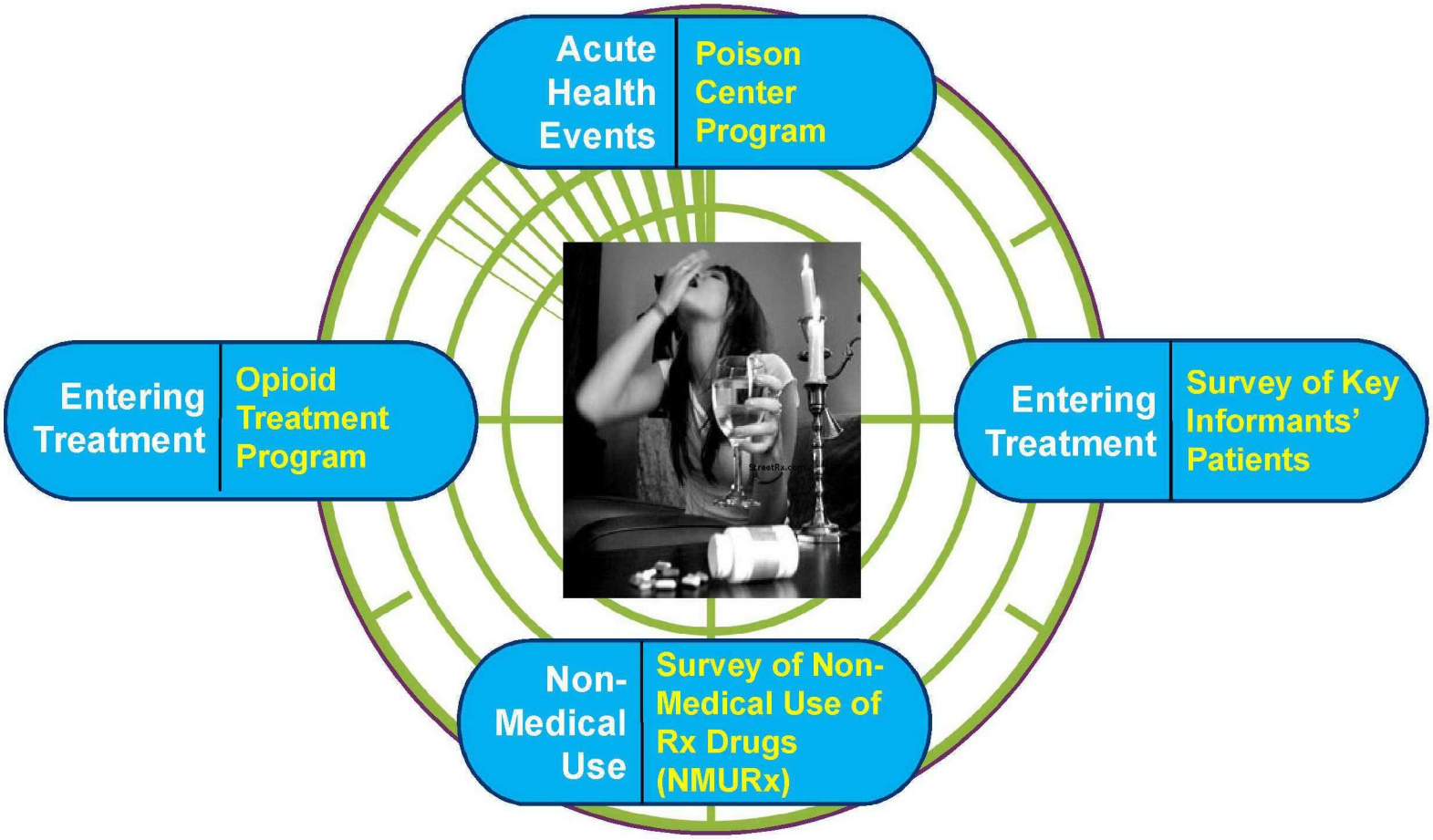
Mosaic Surveillance of Prescription Drug Abuse



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Licit (Prescription) vs Illicit Fentanyl

- RADARS System focuses on pharmaceutical products
- All programs identify the specific product involved
- Physical appearance of fentanyl products allows them to be differentiated
- Context and physical appearance of illicit fentanyl also reduces misidentification

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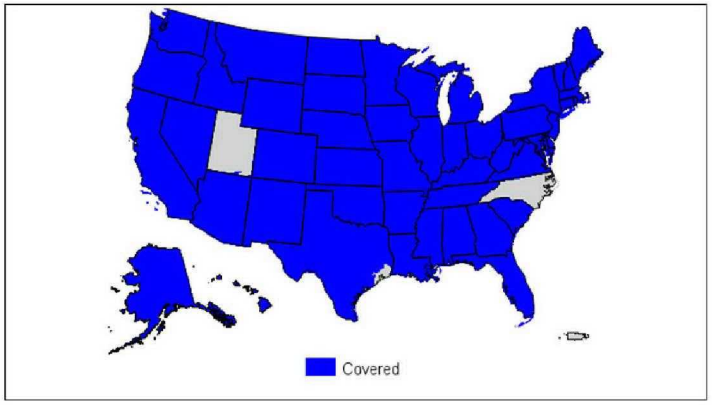
Acute Health Events
Poison Center Program



- **Surveillance period**
  - 3rd Quarter 2010 - 2nd Quarter 2017
- **Spontaneous contacts**
- **Covers over 94% of US population**
- **Population**
  - Children, adolescents, young adults, adults, elderly
- **Definition/Type of Cases**
  - Spontaneous reports of acute medical events associated with one or more prescription drugs of interest
  - **Intentional Abuse: An exposure resulting from the intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high, euphoric effect or some other psychotropic effect**

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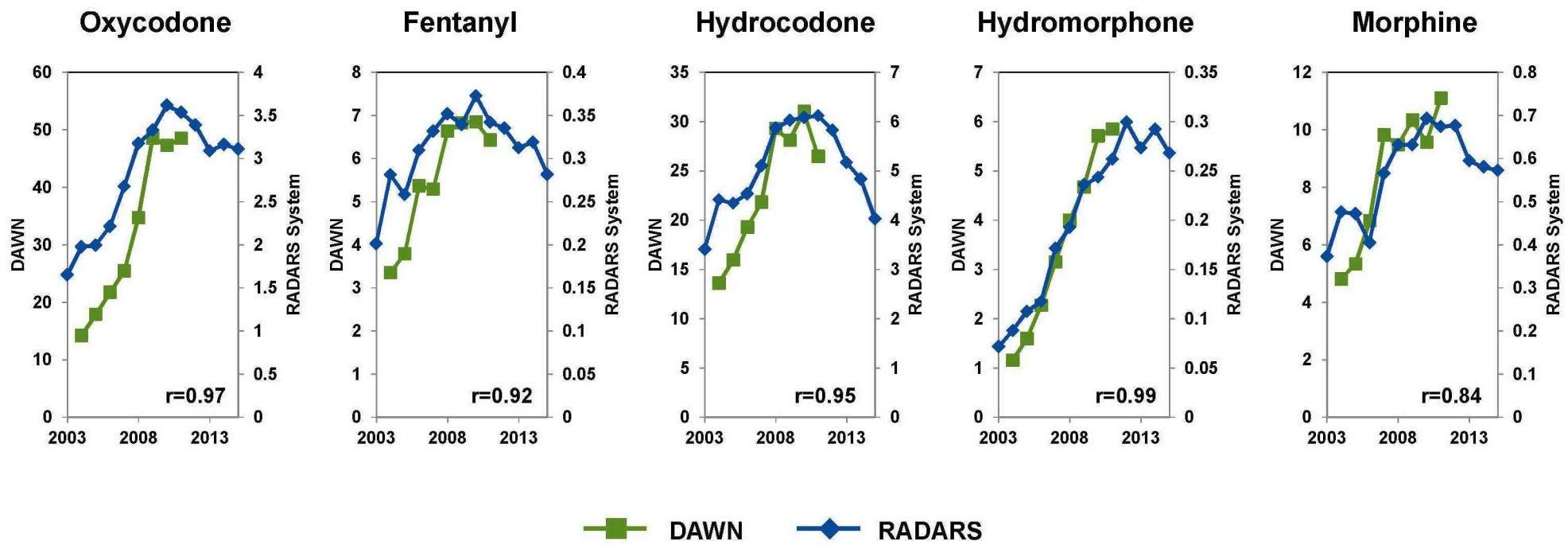
RADARS Poison Center Program Correlates Well With DAWN, 2003-2011



RADARS Systemic Technical Report 2016:
https://www.radars.org/system/publications/2016%204Q%20RADARS%20System%20QTR.pdf

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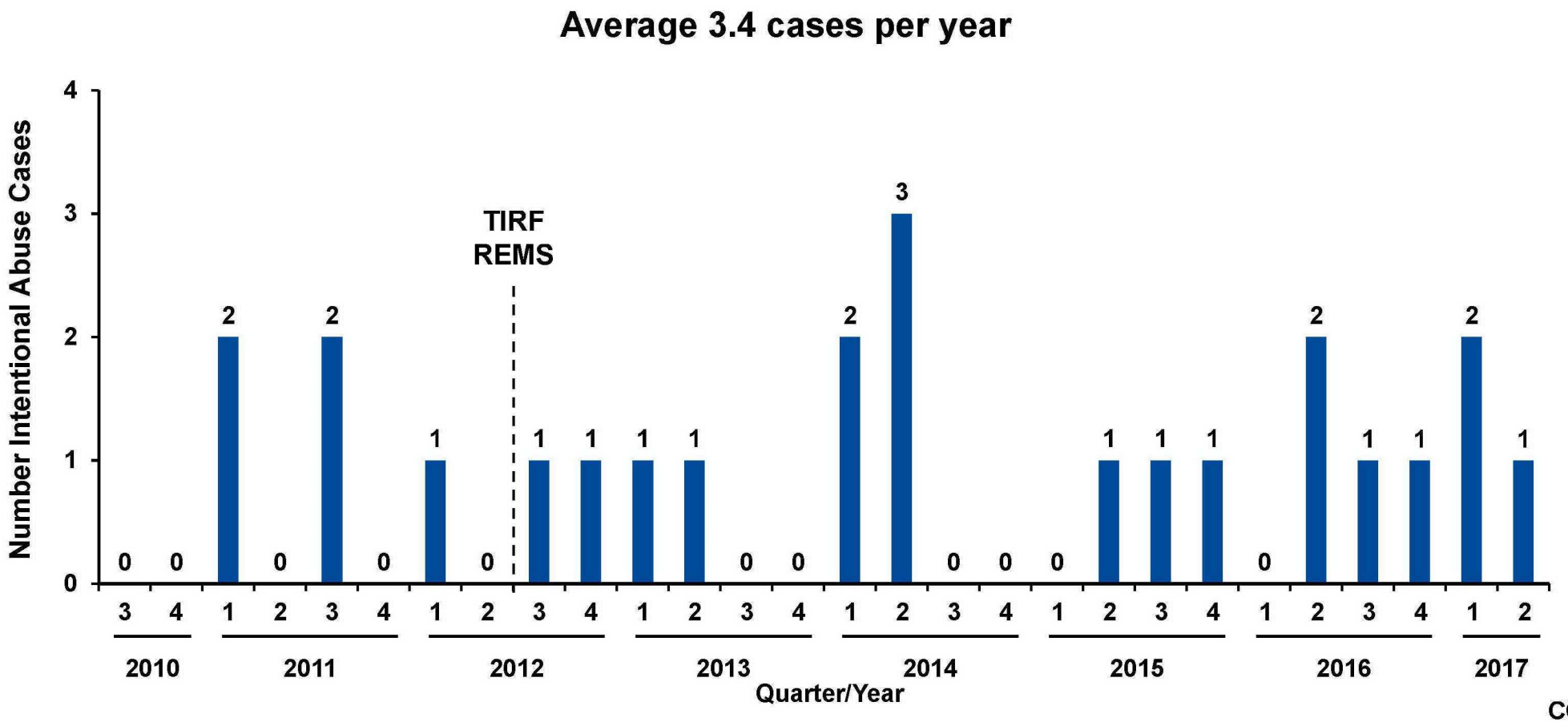
Intentional Abuse Cases Involving TIRF Products



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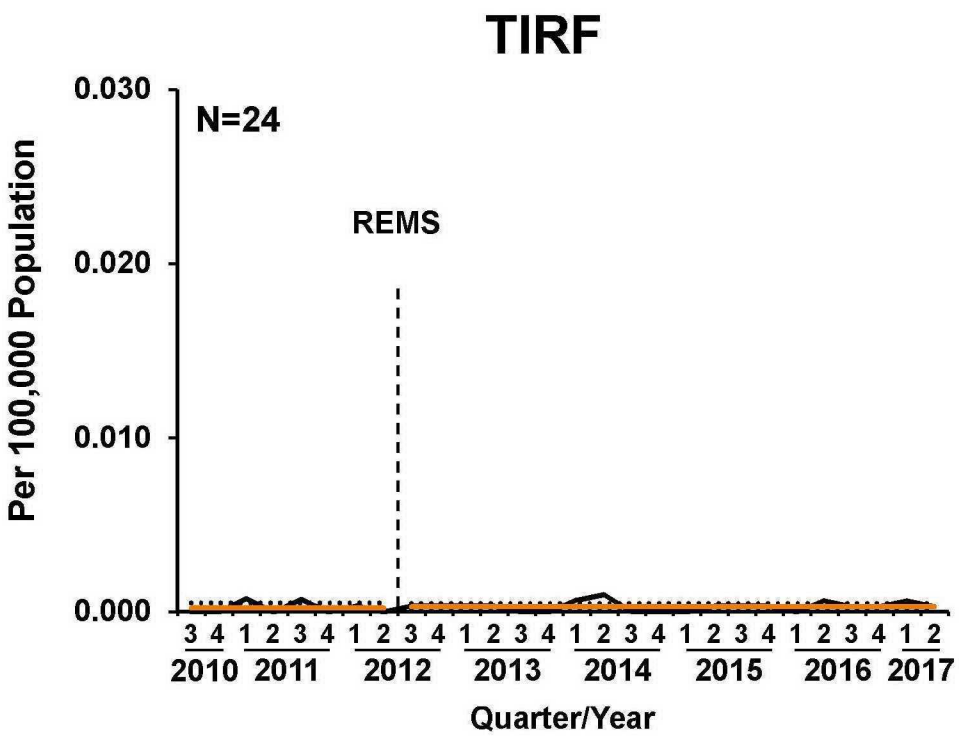
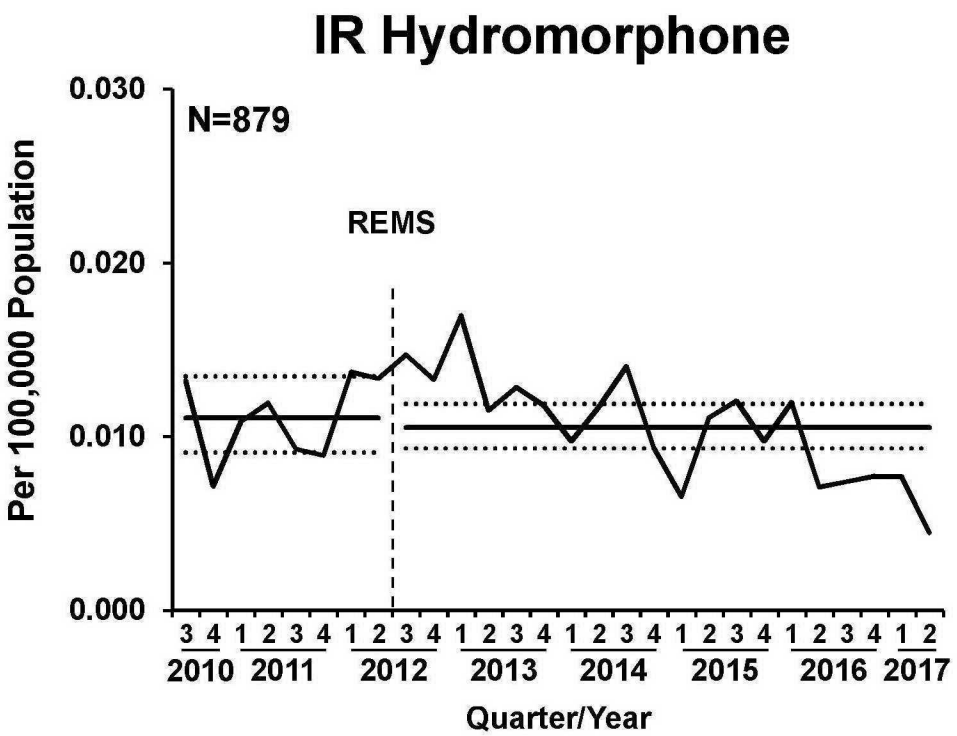
Intentional Abuse Population Rates Are Low and Decreasing





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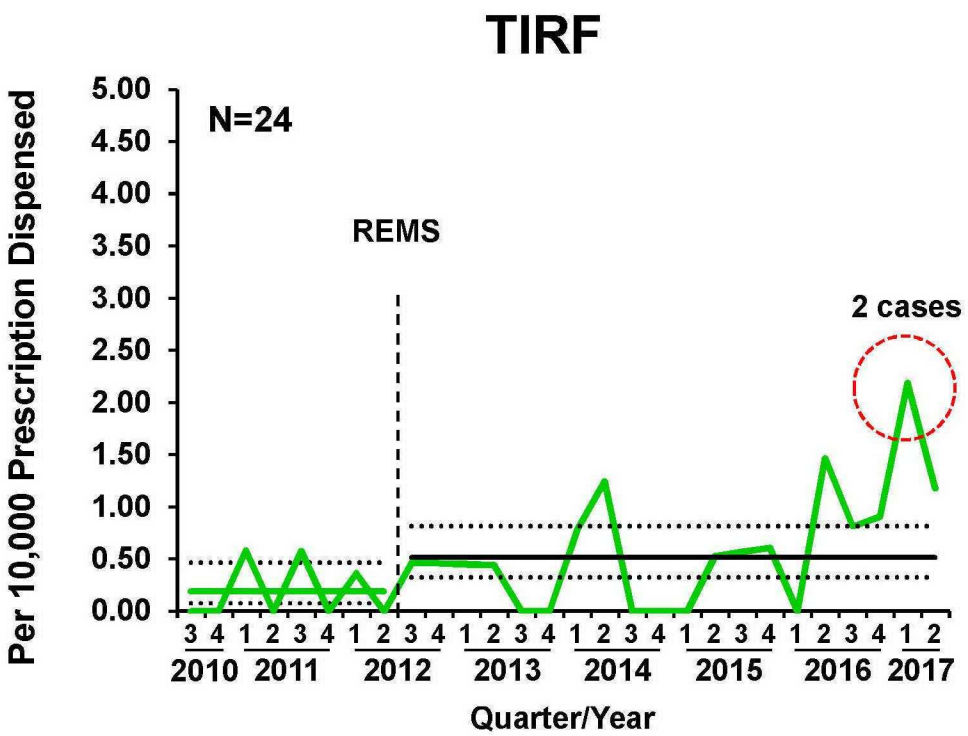
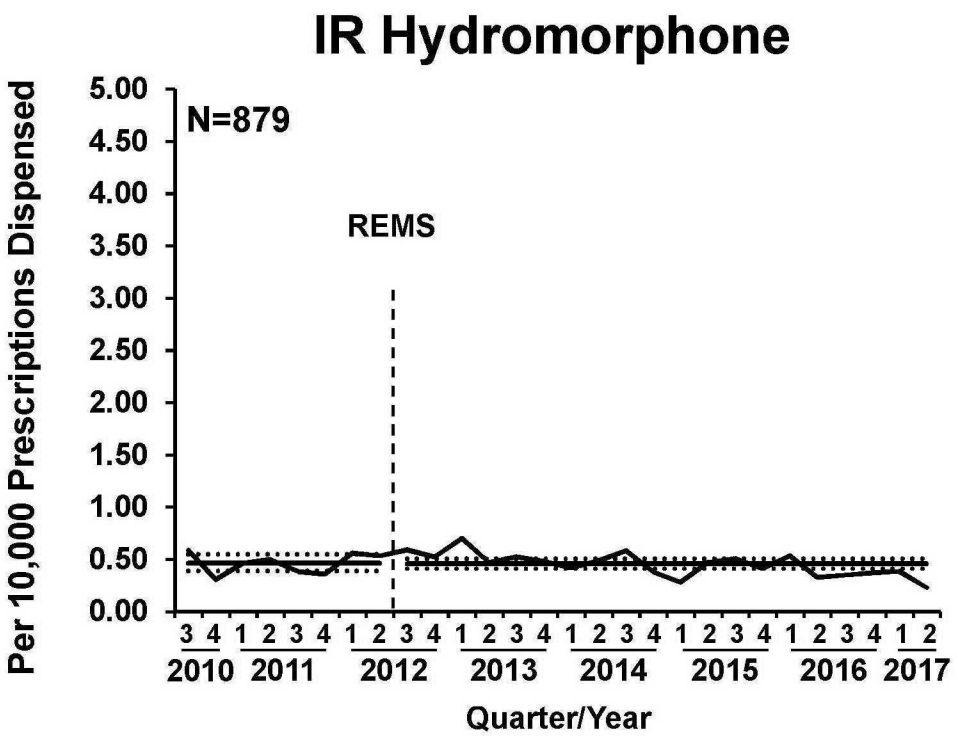
Intentional Abuse Utilization Rates Are Similar for TIRF and Comparator Drugs





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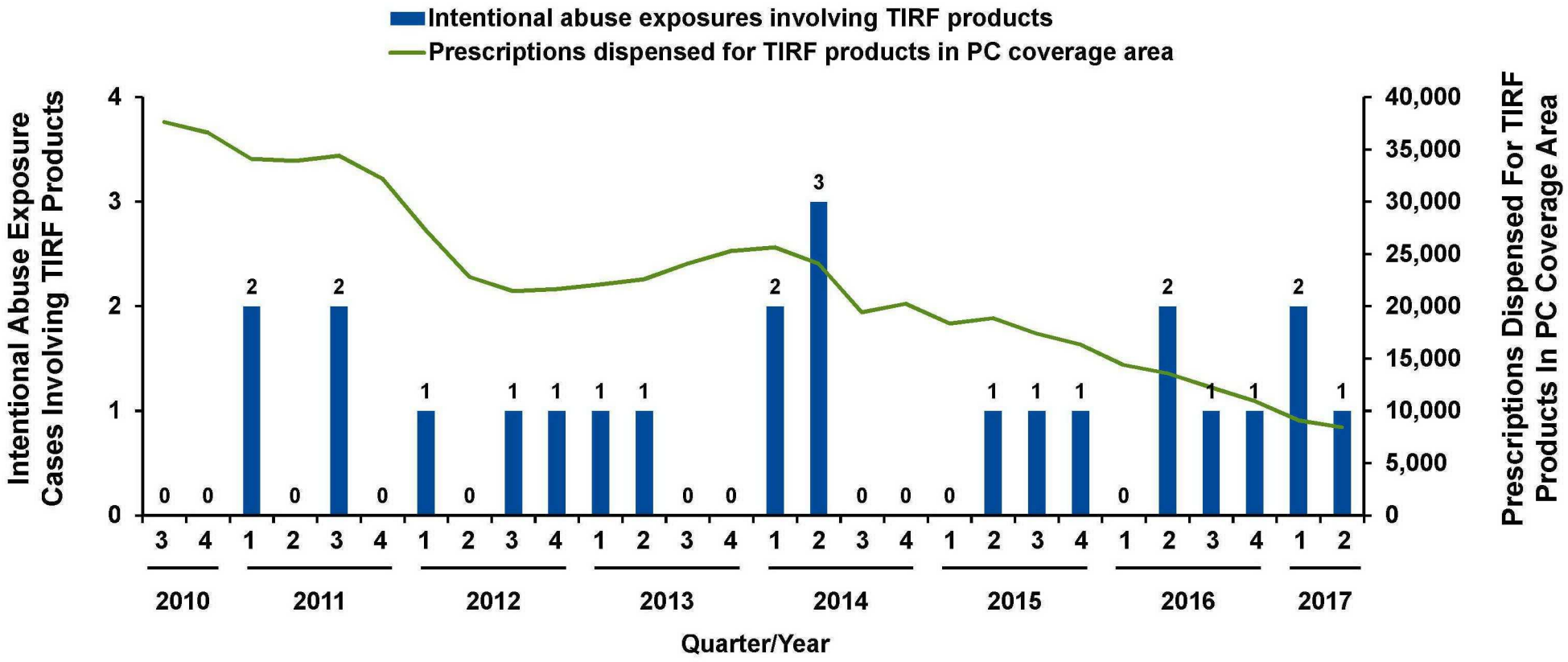
TIRF Rates of Abuse Are Driven by Decreasing Dispensing



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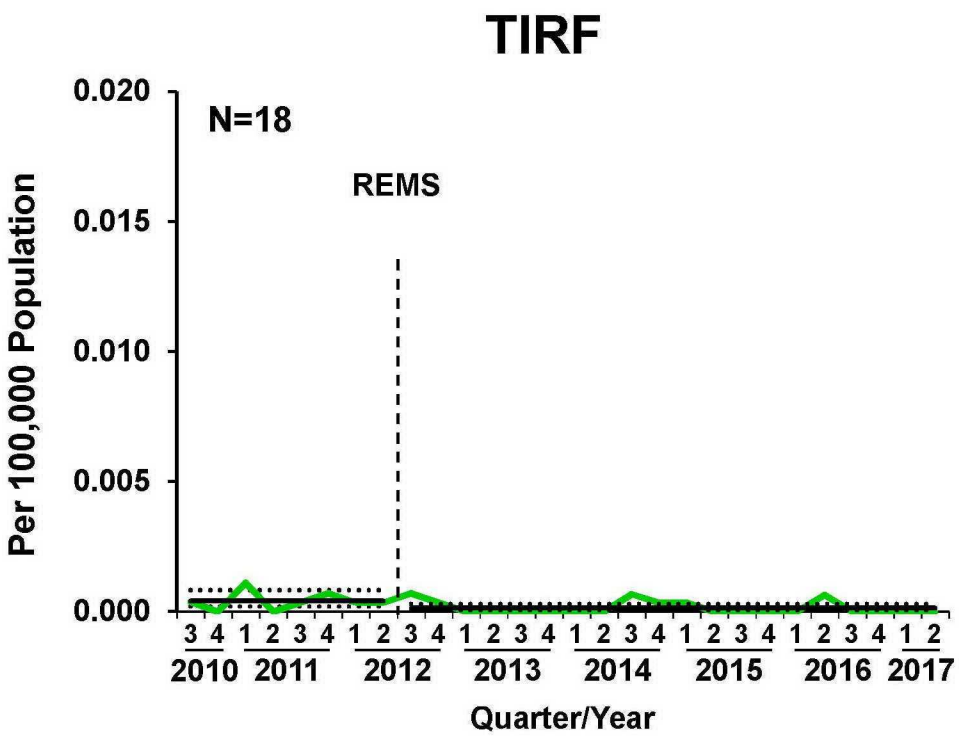
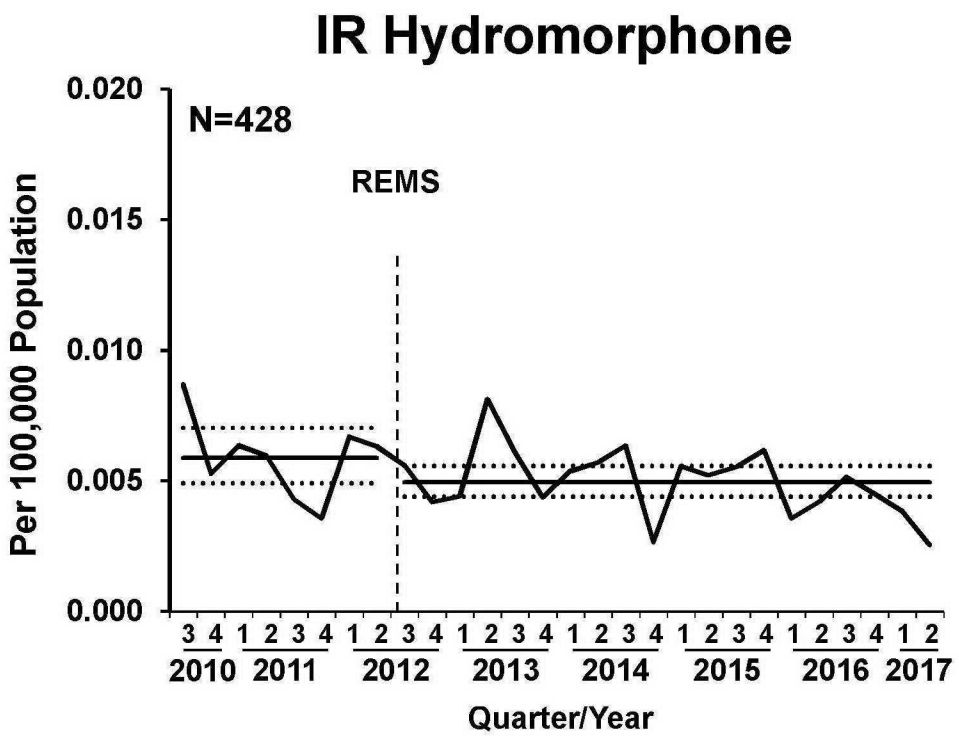
Unintentional General Population Rates Are Low and Decreasing





Unintentional - General: All unintended exposures that are not specifically defined elsewhere. Most unintentional exposures in children should be coded here. Never use this code if there is another code that fits the case.

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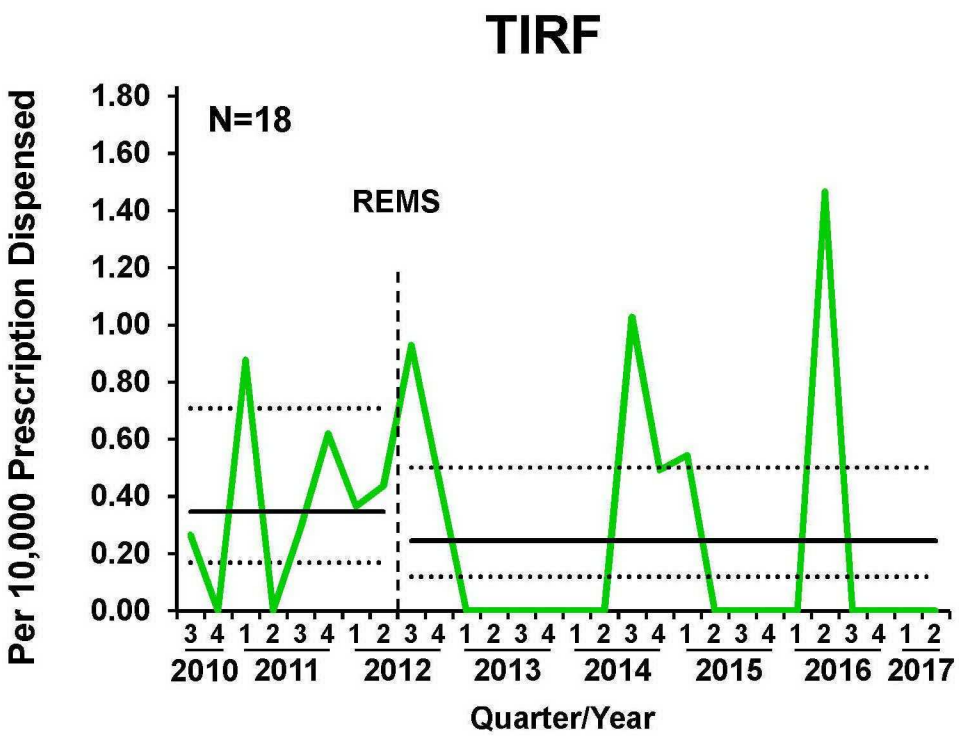
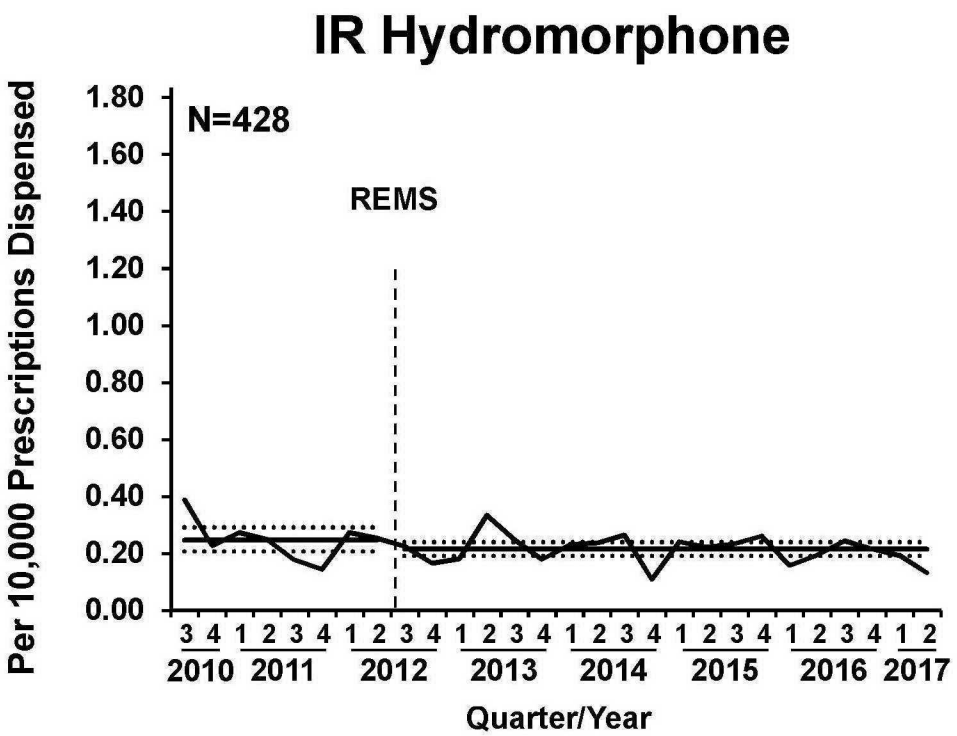
Unintentional General Utilization Rates Are Similar for TIRF and Comparators





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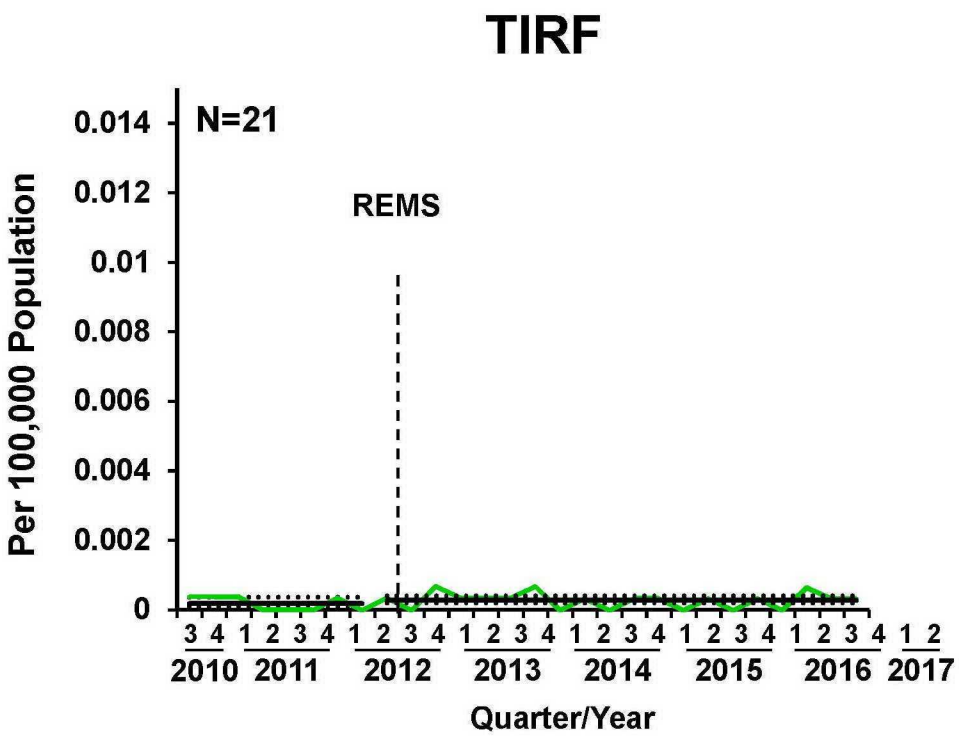
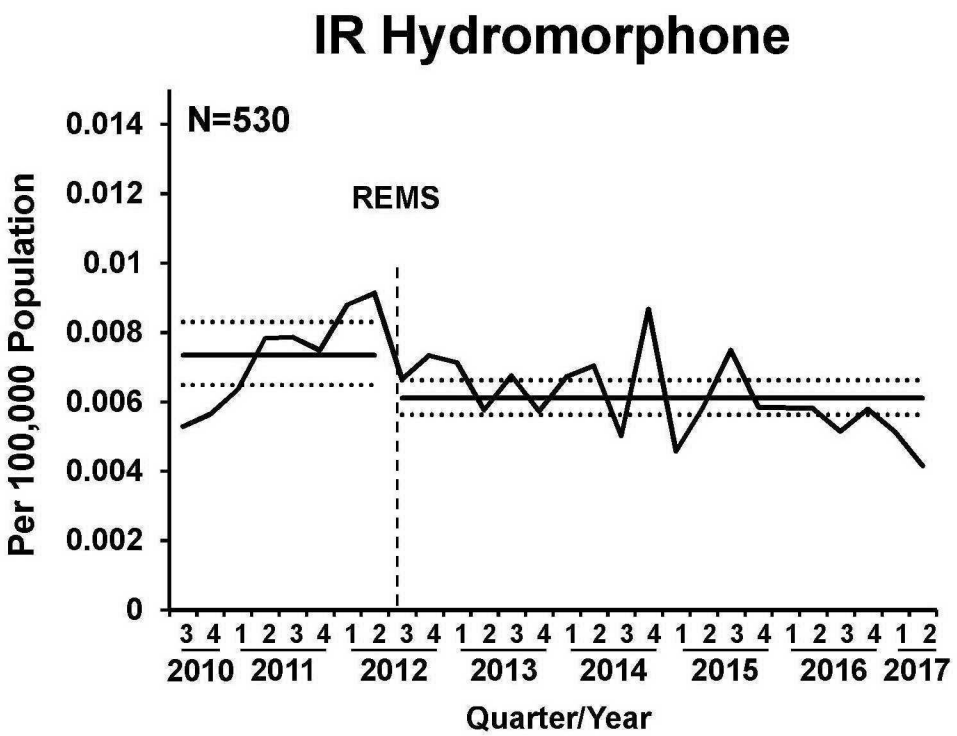
Combined Major Outcome + Death Population Rates Are Low and Decreasing





Major: The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement

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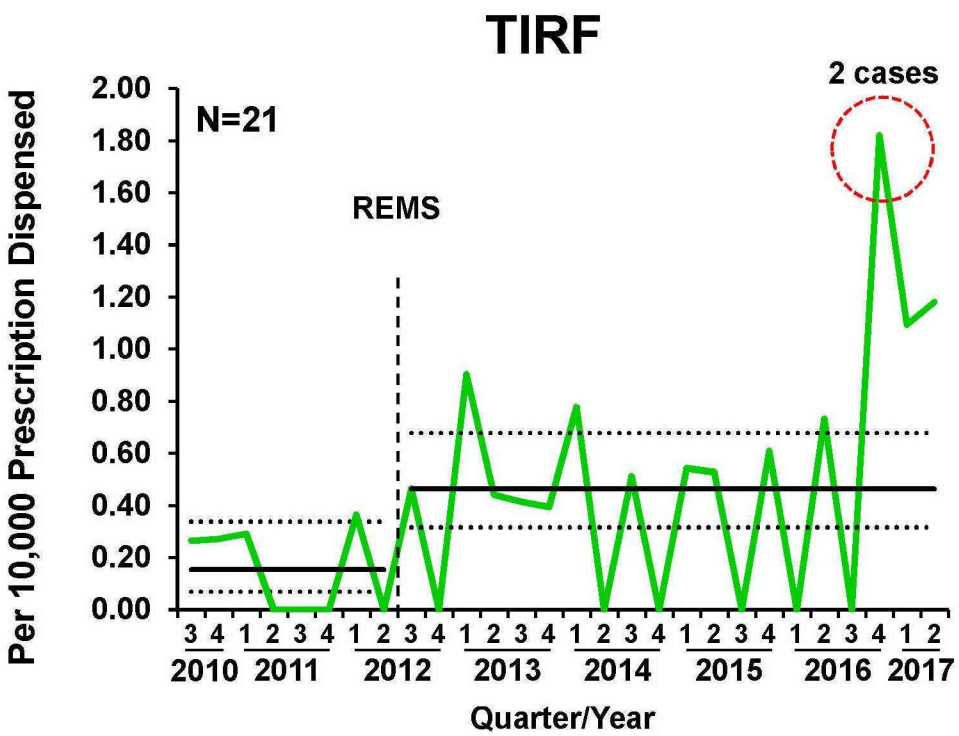
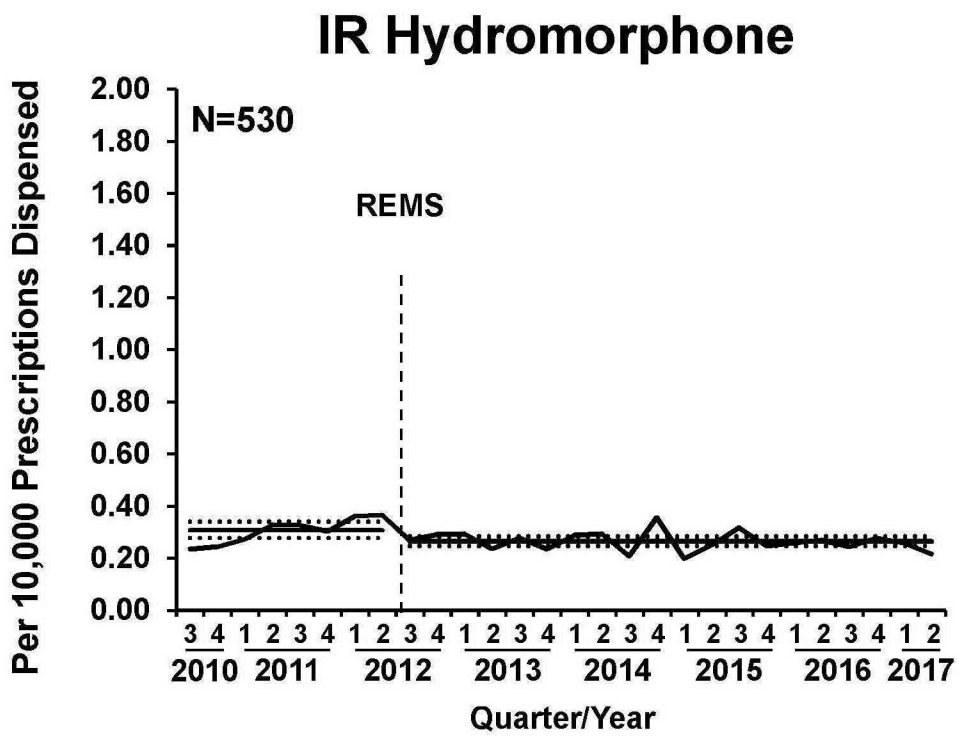
Combined Major Outcome + Death Utilization Rates Similar for TIRF and Comparators





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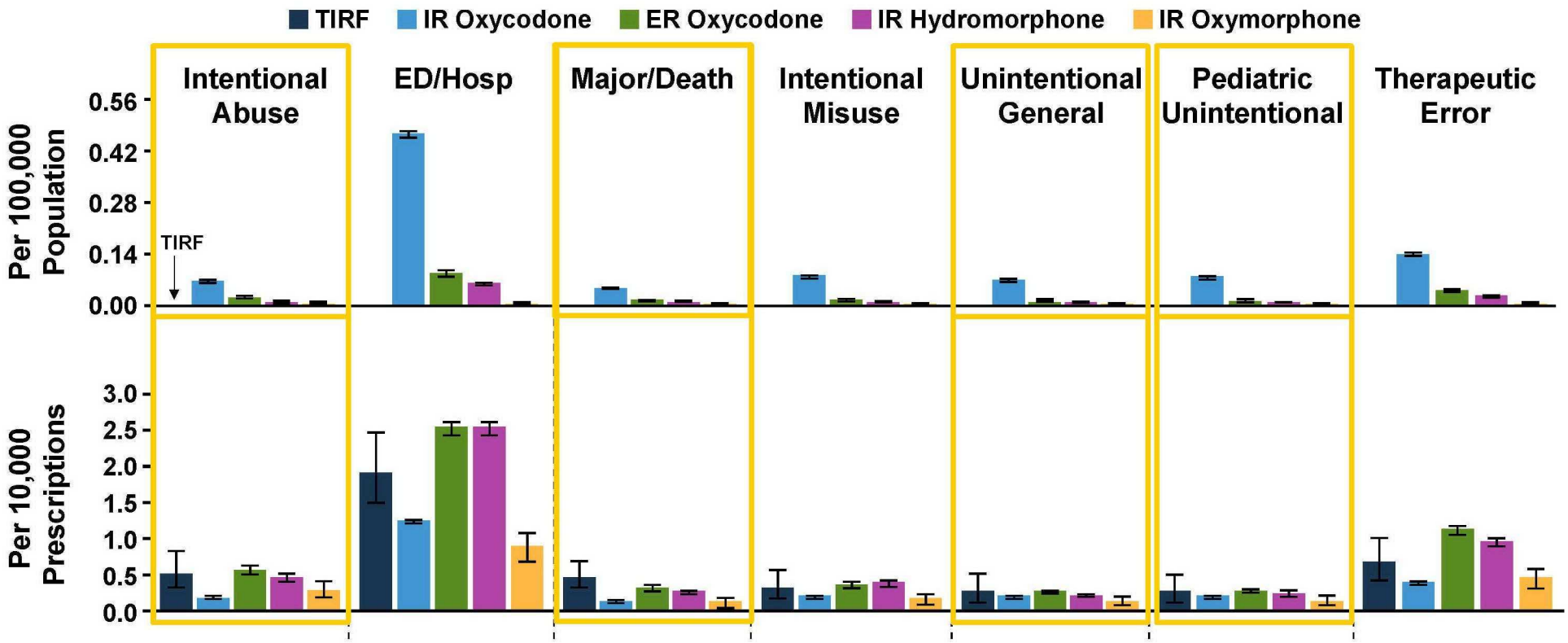
Poison Center Event Rates for TIRF Drugs and Comparators



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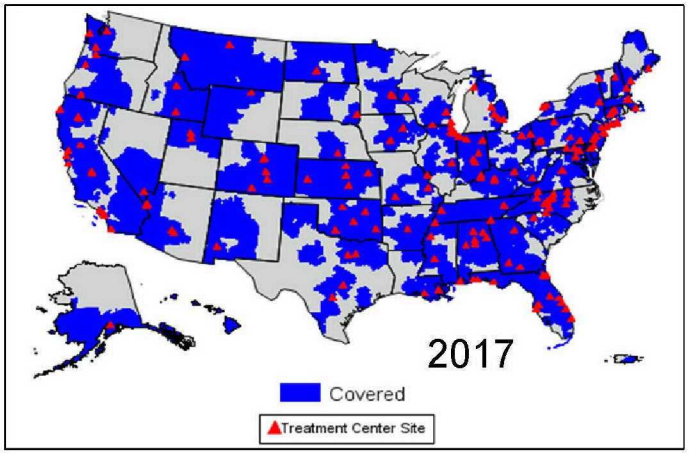
Entering Treatment

Survey of Key Informants' Patient and Opioid Treatment Program

- **Population**
  - Persons seeking treatment at public or private treatment programs
- **Definition/Type of Cases**
  - Self-reported past 30 day use of prescription or illicit opioids to "get high"



- **Coverage**
  - Opioid Treatment Programs - 65 programs across 31 states
  - Survey Key Informant Patients - 129 programs across 49 states

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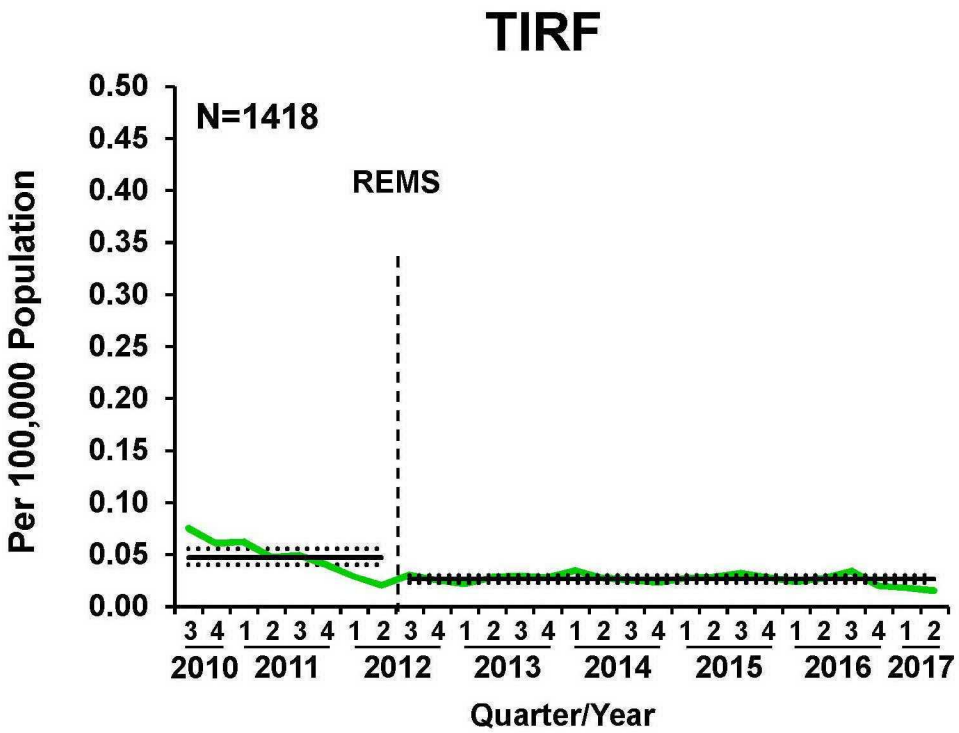
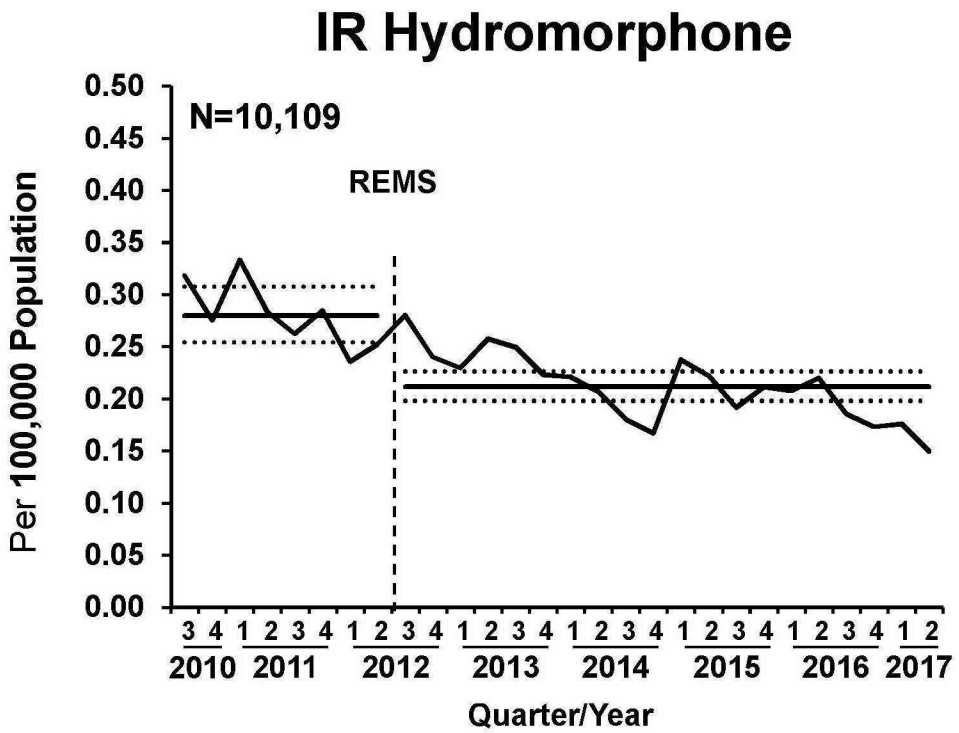
Abuse of TIRF Products in Treatment Centers Is Low and Decreasing





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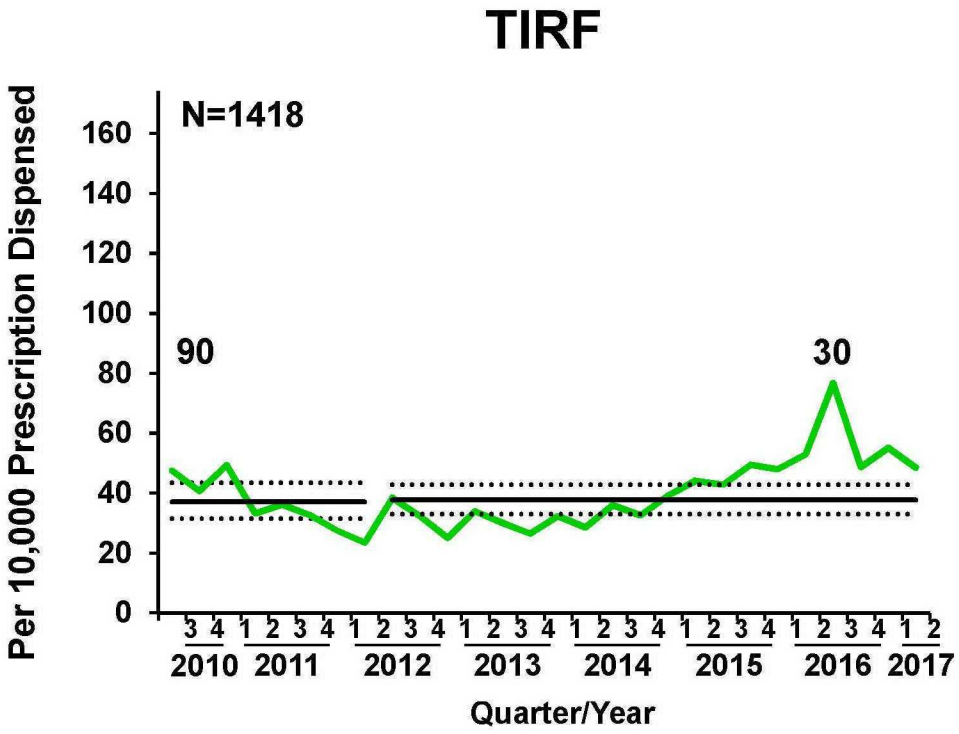
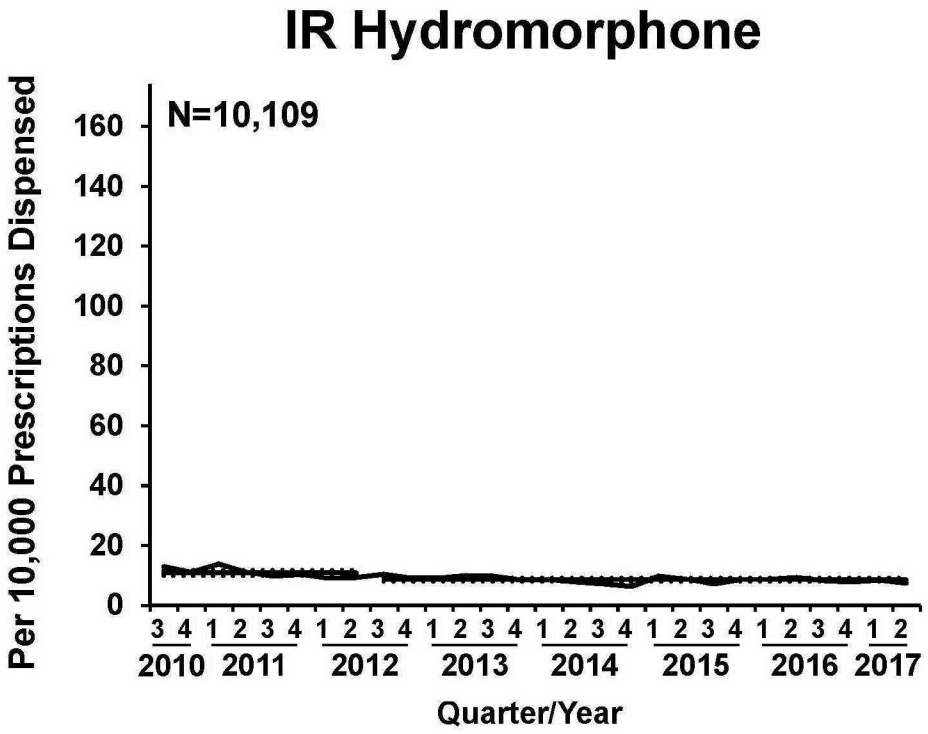
Abuse of TIRF Products Slightly Higher Than IR Hydromorphone





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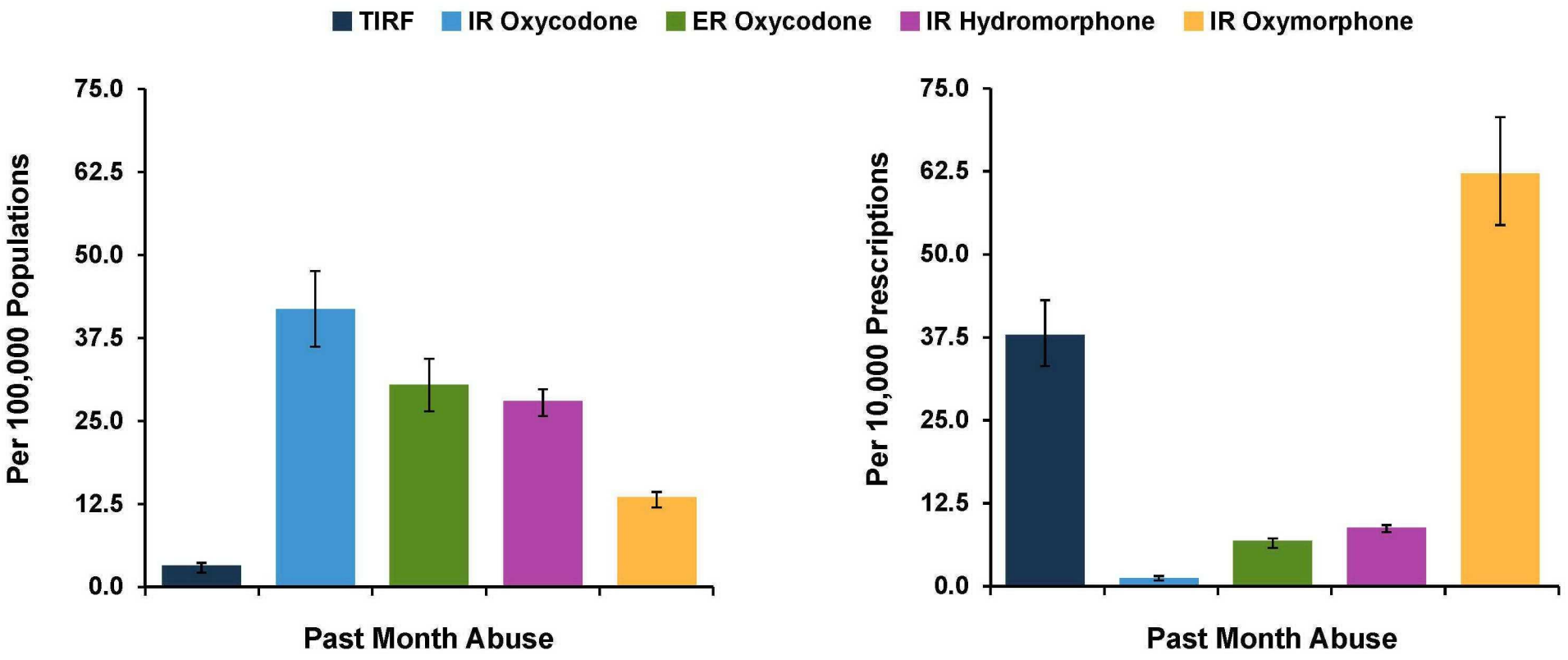
Abuse of Prescription Opioids for Abuse in Treatment Centers Combined



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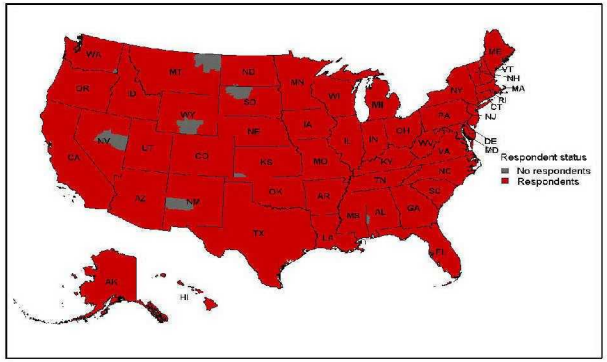
Non-Medical Use

Survey of Non-Medical Use of Prescription Drugs (NMURx)

- **Population**
  - General adult population survey recruited through online survey company
- **Definition/Type of Cases**
  - Self-reported non-medical use of prescription drugs
    - Non-medical use: without a doctor's prescription or for any reason other than what was recommended by your doctor
- **Coverage**
  - 30,000 respondents per launch – responses from all 50 states
- **Period of Data Collection**
  - 3Q 2016 - Present



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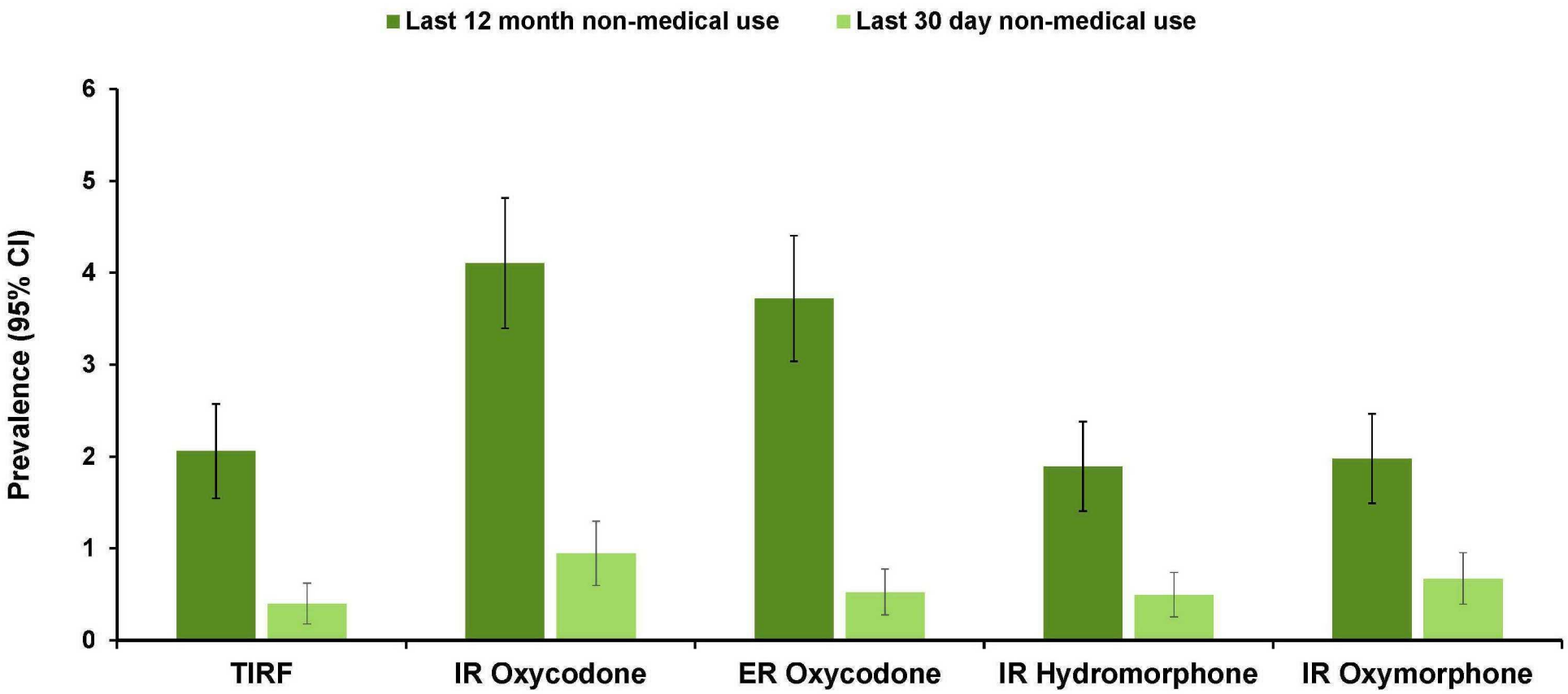
Nonmedical Use by College Students*, 3Q 2017



* Student attending any type of university or college within the last 3 months.

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Summary

- **TIRF REMS associated with similar findings in each program**
- **Poison Centers**
  - 3-4 cases of abuse involving a TIRF product annually
  - Intentional Abuse and Misuse TIRF rates lower than comparators by population
  - TIRF rates similar to comparators by utilization
    - Difference is driven by decreased rates of dispensing
  - Death cases are rare; none in last 4 years
- **Treatment Centers**
  - Fentanyl is a desired drug by abusers
  - Abuse of TIRF products is low and decreasing
- **College Students**
  - TIRF products are abused at a low rate

DEF-NY-00022497

DEF-MDL-05636.00096

Effectiveness of the TIRF REMS Access Program

Dean Mariano, DO

Senior Director Clinical Development and Medical Affairs
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DEF-NY-00022498

DEF-MDL-05636.00097

Prescriber Practices for All Opioid Products

- **Proper assessment of patients**
- **Safe prescribing practices**
- **Periodic re-evaluation of therapy**
- **Keeping detailed records of prescribing information**
- **Monitor for compliance**
  - Drug screening, pill counts, Prescription Drug Monitoring Program, etc.

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Additional Regulations Related to Opioids

- State prescription monitoring programs
- DEA requirements for controlled substances
- Diversion prevention

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Protecting Against Theft and Accidental Exposure

- **Secure in locked storage space so only patient has access**
  - Keep out of sight of anyone who enters the home and could look for medications, such as teenagers, neighbors, or guests
  - Some products have child safety kits to further reduce the risk of accidental exposure in children
  - Properly dispose of partially used or unneeded opioid pain medicine remaining from a prescription
- **Never give to anyone else, even if they have the same symptoms, because it may cause harm or even death**
- **It is against the law to sell or give away opioid pain medicine**

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DEF-MDL-05636.00100

Balancing the Benefits and Risks of the TIRF REMS Access Program

Benefits

- Maintain access to the TIRF medicines for the appropriate patients
- Educate all stakeholders
- Minimize and mitigate risks
- Reduces burden on healthcare system

Risks

- Potential risk of unduly limiting access to the TIRF medicines

DEF-NY-00022502

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Adverse Events of Interest

Prior to the TIRF REMS Access Program

- **Medication errors accounted for >2/3 reported adverse events associated with TIRF use**
- **SAEs, including death, were reported due to inappropriate prescribing**

Since the implementation of the TIRF REMS Access Program

- **Consistently low numbers of medication errors, overdose, and accidental exposure**
- **No reports of AEs due to Inappropriate conversion between TIRF products**

Clarivate Analytics Adcomm Bulletin; IDRAC Number 82127.

DEF-NY-00022503

DEF-MDL-05636.00102

Mandatory Requirements of the TIRF REMS Access Program

- **Mandatory participation for prescribers, patients, pharmacies, distributors, and manufacturers**
- **Mandatory education for prescribers, patients, and pharmacies**
- **100% scores required for certification of prescribers and pharmacies**
- **Mandatory re-enrollment and education every two years**
- **Signed agreement between prescriber and patient/caregivers (PPAF)**
  - Includes review of education and delivery of Medication Guide
  - Facilitates discussion between prescriber and patient/caregivers

DEF-NY-00022504

DEF-MDL-05636.00103

Strengths of the TIRF REMS Access Program

- **Designed as a closed system for all participants**
  - To prevent any prescribing, dispensing, and distribution outside the program
- **Continuous oversight, monitoring, and corrective actions**
  - Collaboration with FDA
  - Continuous improvement
- **Fits seamlessly into practice of medicine**
  - Matches opioid guidelines and best practices
  - Included in 2016 National Comprehensive Cancer Network guidelines
- **Integrated into pharmacy processes**
  - Switch system automatically linked into existing pharmacy network

DEF-NY-00022505

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TIRF REMS Access Program Effectiveness: Conclusions

- **Appropriate balance of access and restrictions**
- **Ensures safe and appropriate use of TIRF medications**
  - Very low numbers of events reported
  - Since implementation substantial decrease in medication errors resulting in SAEs and death
- **Multiple mandatory requirements**
- **No dispensing permitted outside program**
- **Continuous improvement**
  - Additional work is planned and ongoing to improve certain areas of education in collaboration with FDA

DEF-NY-00022506

DEF-MDL-05636.00105

Planned Changes and Proposed Action Items

Stephen Sherman, JD, MBA

Sr. Vice President of Regulatory Affairs and Clinical Development
Insys Therapeutics

DEF-NY-00022507

DEF-MDL-05636.00106

Proposed REMS Program Changes

- **Update educational materials based on low-scoring KAB concepts**
  - Prescriber understanding of opioid tolerance
  - To stop TIRF treatment if opioid maintenance therapy is discontinued
- **Upon making changes to the educational material, align the Knowledge Assessment and the KAB surveys with the proposed changes to the education materials**
- **Revision of the PPAF to include a prescriber attestation that the patient is opioid tolerant**

DEF-NY-00022508

DEF-MDL-05636.00107

Proposed REMS Program Changes

- Revising the pharmacy enrollment form to allow for process audits to increase the potential pool of inpatient pharmacies in the audit
- Updating the noncompliance protocol so that prescribers will be flagged at first occurrence of patient enrollment without a PPAF submitted within 10 days
- Contacting Healthcare Professionals concerning their change in prescribing behavior regarding TIRFs

DEF-NY-00022509

DEF-MDL-05636.00108

New and Updated Assessments

- **New studies to assess risk of accidental pediatric exposure**
  - Analysis of Drug Involved Mortality (DIM) data
  - Evaluation of medical records in Humedica database
- **New study to assess occurrence of prescribing to the opioid non-tolerant**
  - Updating the IQVIA Opioid Tolerance Study
  - Validating the algorithm for opioid tolerance across the inpatient and outpatient settings and comparing administrative claims data to EMR
- **New studies to analyze overdose in the opioid tolerant and non-tolerant**
  - Feasibility to identify an appropriate data source is underway

DEF-NY-00022510

DEF-MDL-05636.00109

Conclusions

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DEF-NY-00022511

DEF-MDL-05636.00110

Need for TIRF Medicines to Treat BTCP

- **Cancer pain that breaks through around-the-clock opioid treatment**
  - Abrupt onset
  - Severe
  - Short duration
- **BTCP represents a substantial burden to patients**
  - Debilitating
  - Disrupts activities
  - Diminishes quality of life
- **TIRF medicines meet the needs of patients with BTCP**
  - Immediate onset
  - Potently manage severe pain
  - Short duration
- **TIRF medicines are critical for the management of BTCP**

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DEF-MDL-05636.00111

Effectiveness of TIRF REMS Access Program

- **TIRF medicines have significant risks**
- **TIRF REMS is designed to help prescribers and patients use them safely**
- **Metrics of the TIRF REMS demonstrate it's effective and continually improving**
  - Before, there were medication errors and inappropriate conversions resulting in AEs and death
  - After, no AEs reported associated with inappropriate conversions
  - Continuous improvements to program in collaboration with FDA
- **TRIG data and RADARS surveillance show a very low incidence of overdose, and pediatric or other unintentional exposure to TIRF medicines**

DEF-NY-00022513

DEF-MDL-05636.00112

Improvements to Program and Assessments

- **New studies under development to complement data in the annual assessment reports**
  - Validation study of the algorithm of opioid tolerance in the Henry Ford Health System
  - Study of fatal versus non-fatal overdose in opioid tolerant versus opioid non-tolerant patients
  - Evaluation of pediatric exposures in Humedica data and pediatric exposures resulting in death through CDC DIM data
- **Proposed language to the pharmacy enrollment form, which allows for additional pharmacy auditing, pending FDA approval**
- **Revising educational materials based on low-scoring KAB questions**
- **PPAF revision to add prescriber attestation that patient is opioid tolerant**

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Conclusions

- **Patients with BTCP need TIRFs to adequately treat their fast onset, severe, and short duration pain**
- **TIRFs are the only treatments specifically approved for the indication of BTCP**
  - BTCP can be debilitating, life limiting, and cause high healthcare utilization without appropriate treatment
- **TIRF REMS Access program reduces the risk of TIRF medicines without restricting access for appropriate patients**

DEF-NY-00022515

DEF-MDL-05636.00114

Additional Responders

Vickie Andros, PharmD	Product Manager RelayHealth
Amanda Bulkley	Sr. Customer Manager McKesson Specialty Health
Syd Phillips, MPH	Director, Epidemiology and Drug Safety IQVIA

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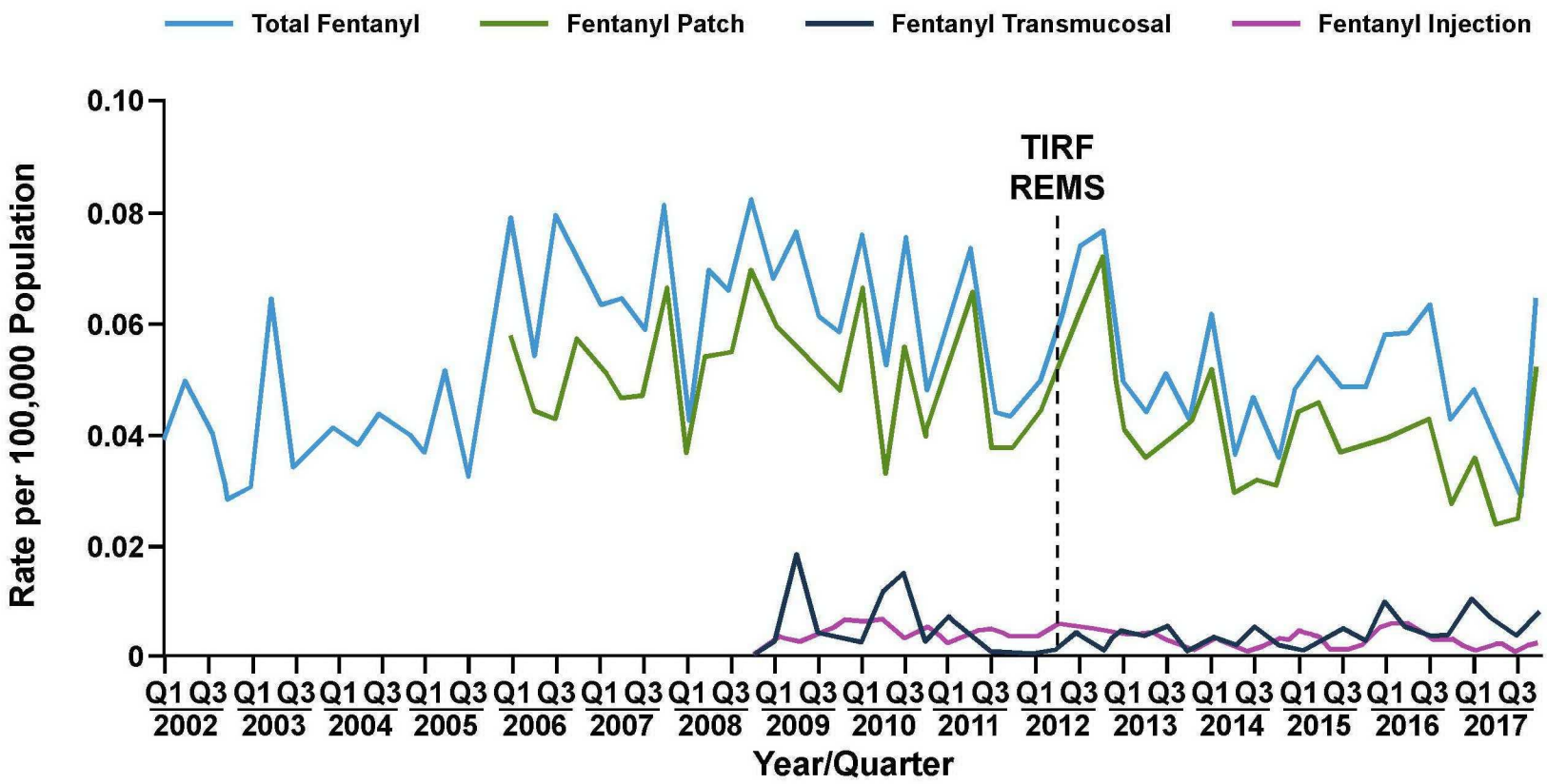
DEF-MDL-05636.00115

Backup Slides Shown

TIRF REMS ACCESS

DEF-NY-00022517

Rate of Fentanyl Abuse in Poison Center Progam



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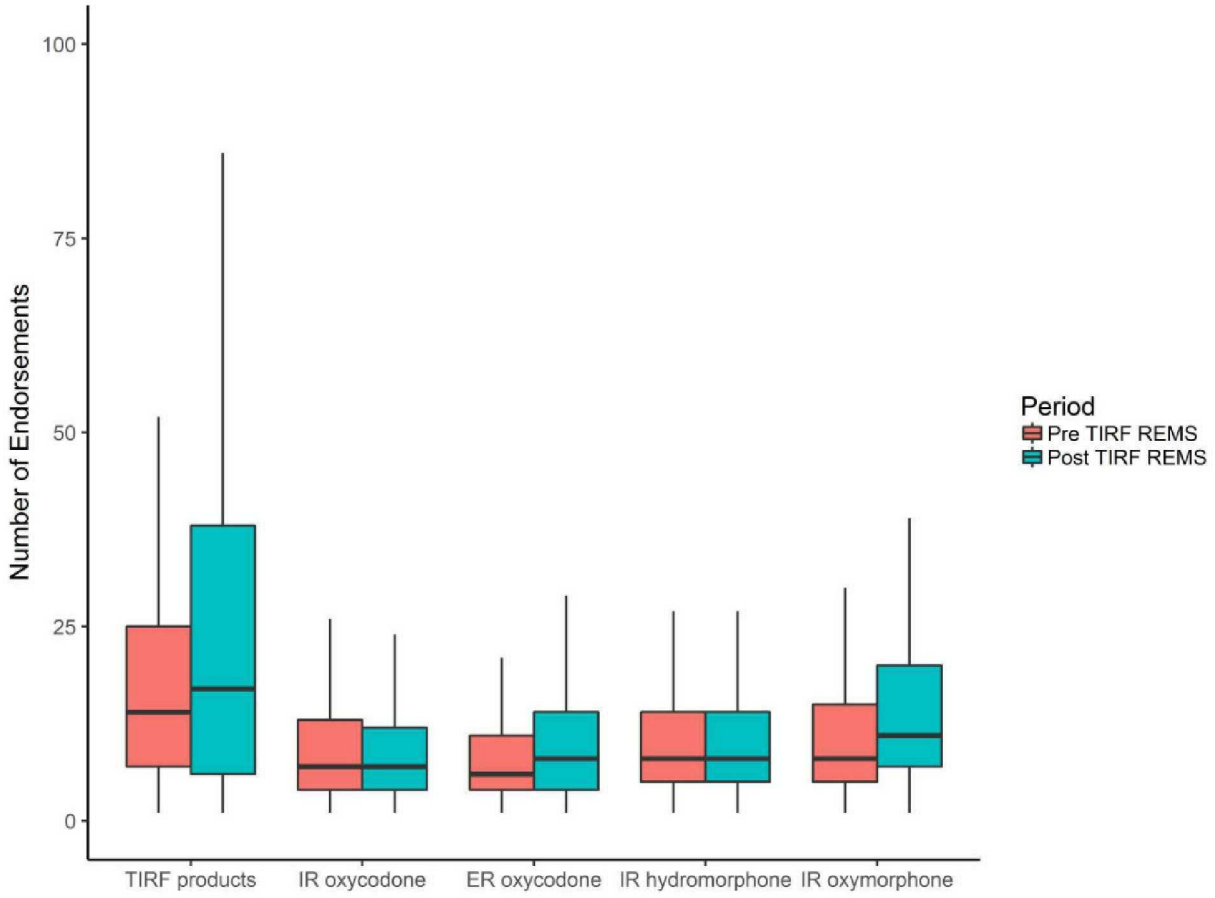
Treatment Centers: Median Number of Endorsements by Drug



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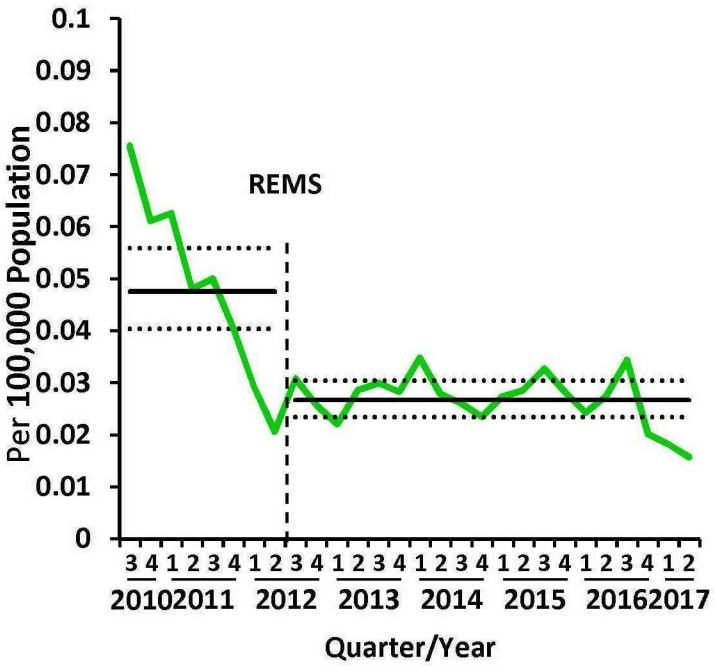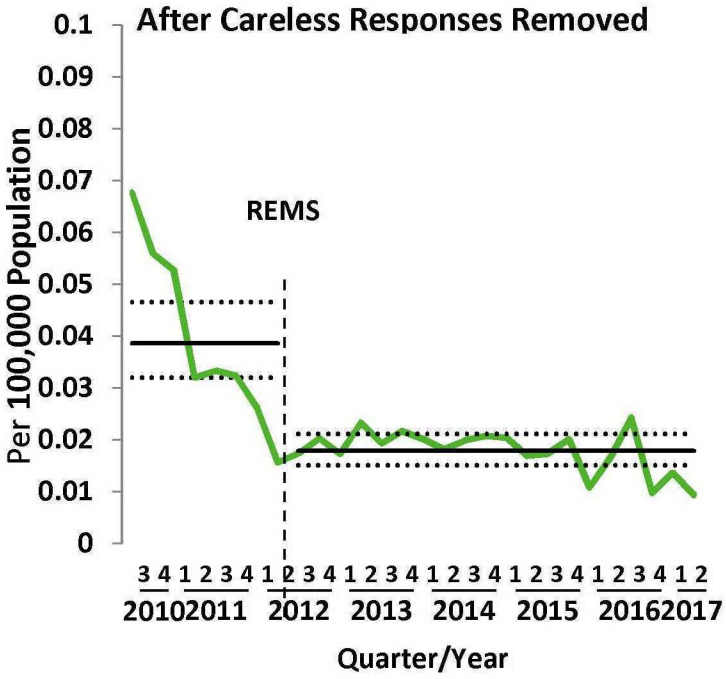
Treatment Centers: Rate of Abuse with and without Careless Responses