

ALERTT WORKING GROUP  
RECOMMENDATIONS FOR IDENTIFYING, CLASSIFYING, AND  
DEFINING ABUSE-RELATED EVENTS IN CLINICAL TRIALS

# Classifying Abuse-Related Events: the RADARS System Experience

Richard C. Dart, MD, PhD  
Executive Director, RADARS® System  
Professor, University of Colorado Health Sciences Center

# What is Goal of Detecting Abuse-Related Events in Clinical Trials?

- Clinical: Diagnosis, Treatment = Individual
- Research, Surveillance: Safety = Population
  - To identify individuals who find the study drug to be attractive in terms of getting high.
  - **To predict the extent to which the drug is likely to be abused post-marketing**
    - Active pharmaceutical ingredient
    - Formulation
  - **To predict who and how to perform post-marketing surveillance**

# Principle of Study

The Nature of Drug Abuse Assures  
that the Individual will Attempt to  
Conceal Their Abuse  
(and the motive for their abuse)

# Mosaic Approach to Surveillance

Poison  
Center

Acute Events  
51 Centers  
47 States

Drug  
Diversion

Criminal Justice  
280 investigator  
50 states

Opioid Tx  
Program  
(OTP)

Patients in Tx  
73 programs  
33 states



Survey of Key  
Informants'  
Patients (SKIP)

Patients in Tx  
125 practices  
50 states

College  
Survey

2000 students  
50 States  
3x each year

StreetRx  
[www.StreetRx.com](http://www.StreetRx.com)

Users/Buyers  
Crowdsourcing  
50 states

# Opioid Treatment Program (OTP) / Survey of Key Informant Patients (SKIP)

- Triggering Event
  - Substance abuse leading to enrollment in methadone or other treatment program
- Definition of Abuse
  - A person presenting for treatment of dependence or addiction that endorses “Used in past month to get high”
    - Focusing on the intent and mental effect

Principal Investigators

OTP: M. Parrino, A. Rosenblum

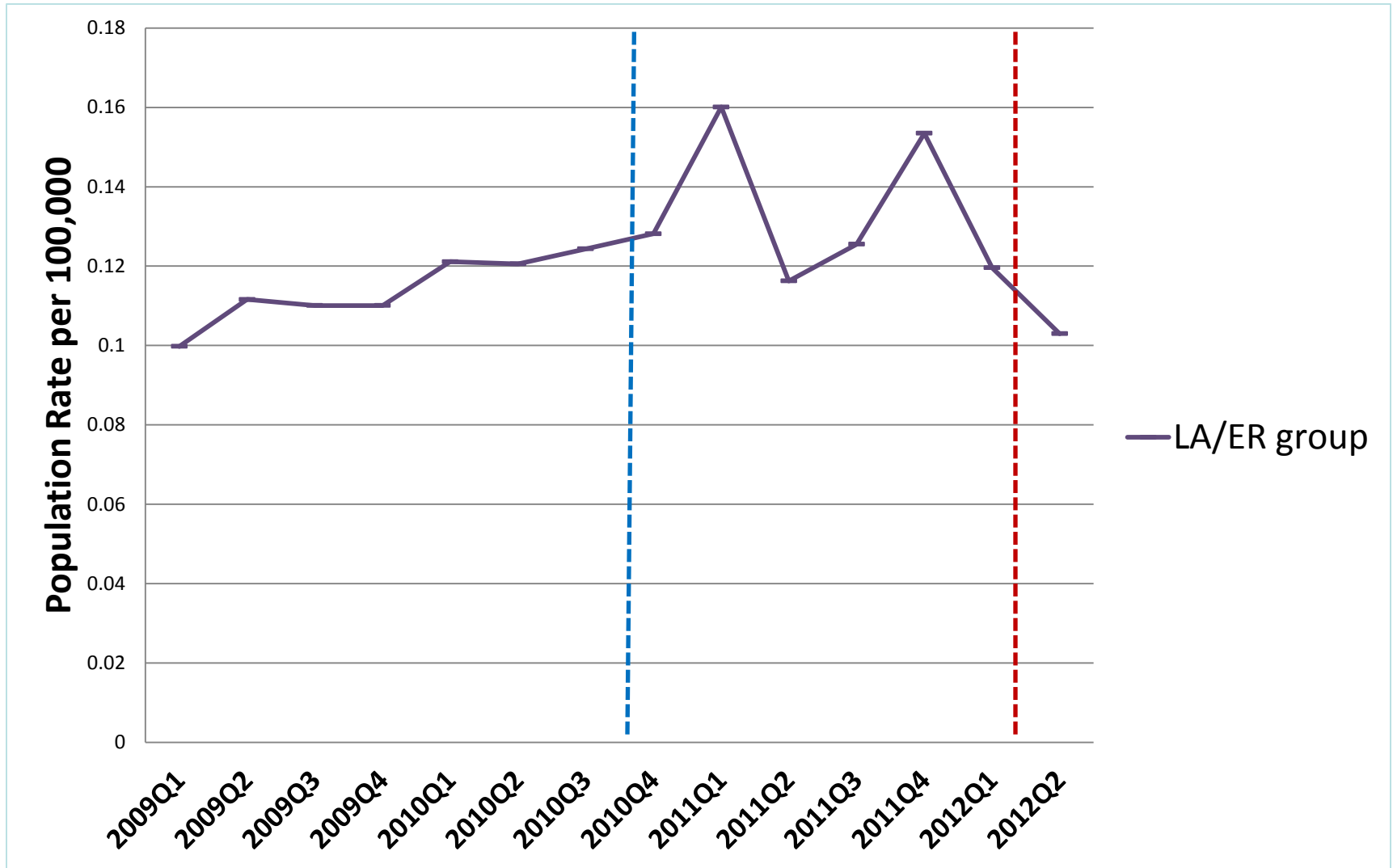
SKIP: T. Cicero

# Poison Center Program

- Triggering Event
  - Acute health event that results in a call to poison center
- Definition of Abuse
  - An exposure resulting from 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.
  - Intent is very hard to determine
    - Setting, context, dosage, h/o abuse, other history? concomitant meds, etc.
  - Misuse: intentional improper or incorrect use of a substance for reasons other than the pursuit of a psychotropic effect
    - Setting, context, dosage, history of abuse, concomitant meds, etc.
- Ultimately, there are always cases in the gray zone

# Poison Center Program

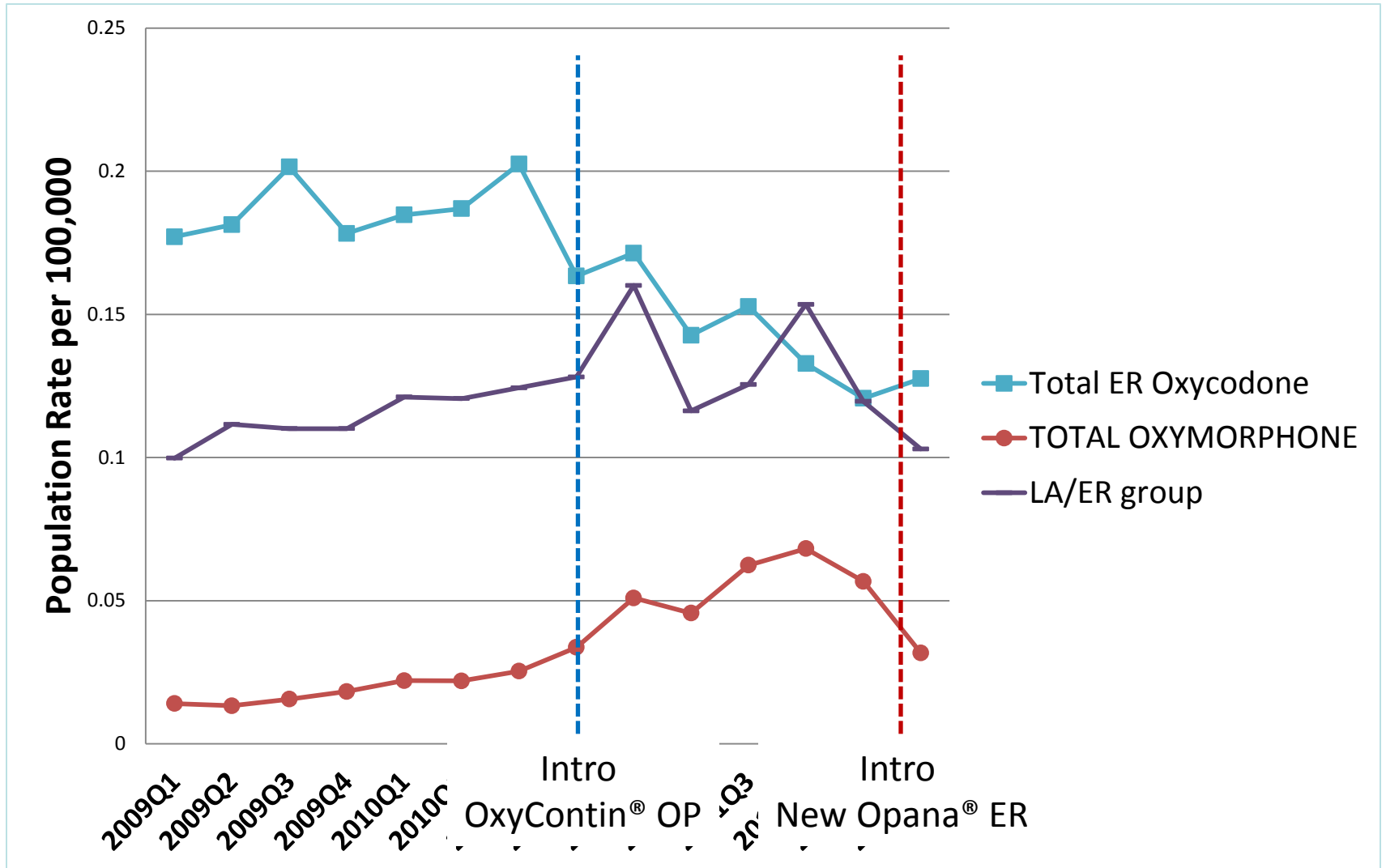
## Population Rate, 2009 Q1 to 2012 Q2



LA/ER group = extended release opioids + methadone

# Poison Center Program

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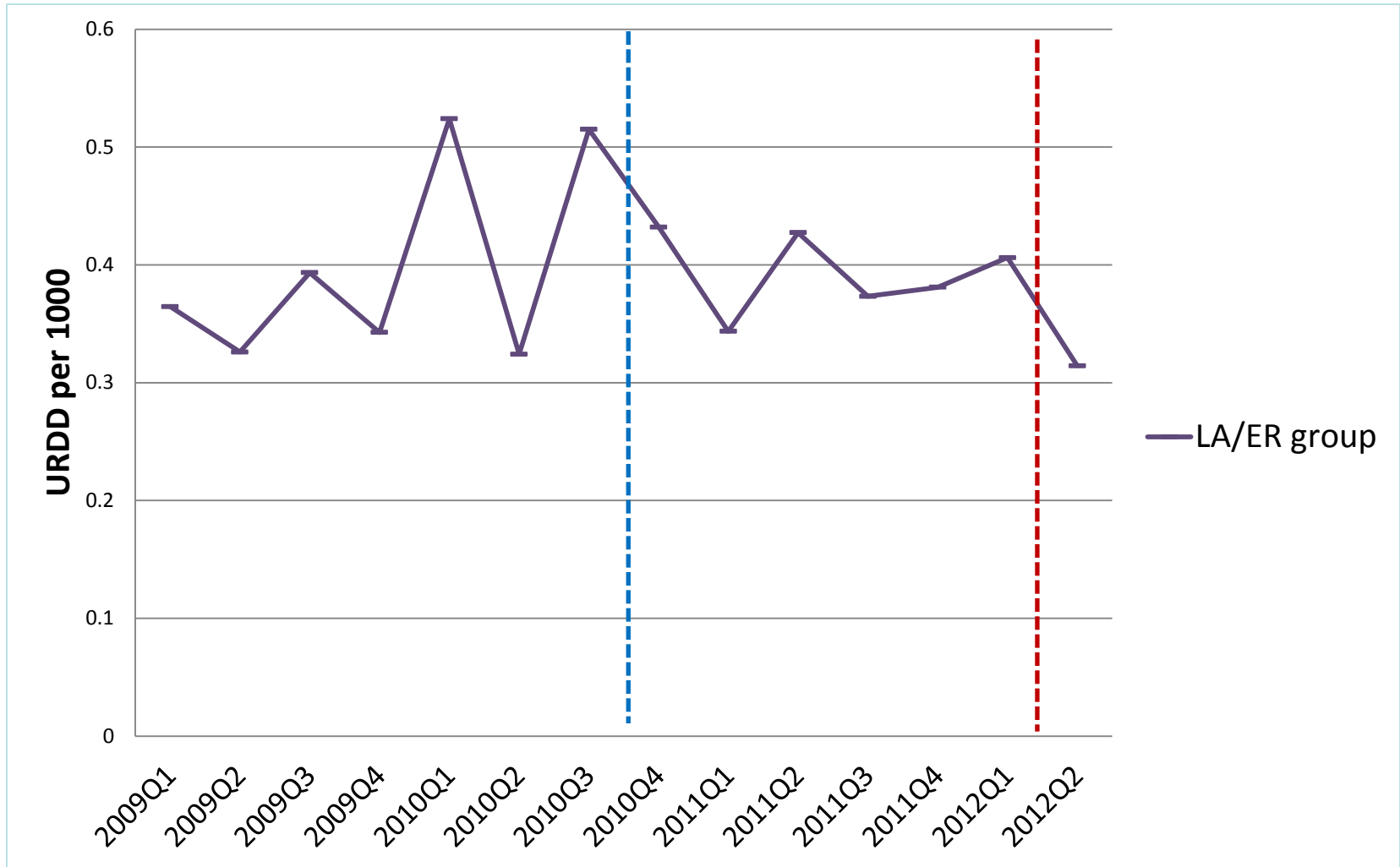


# Drug Diversion Program

- Triggering Event
  - Attempt to sell or purchase prescription drugs
- Definition of Abuse
  - “Diversion cases” are defined as new cases in which a prescription drug was diverted, allegedly diverted, or where the attempt to divert was evident, based on some written document, such as stolen, forged, or otherwise illegal prescriptions, physician or pharmacy reports of prescriptions written or filled, empty prescription bottles, drugs seized, or other verifiable means.”

# Drug Diversion

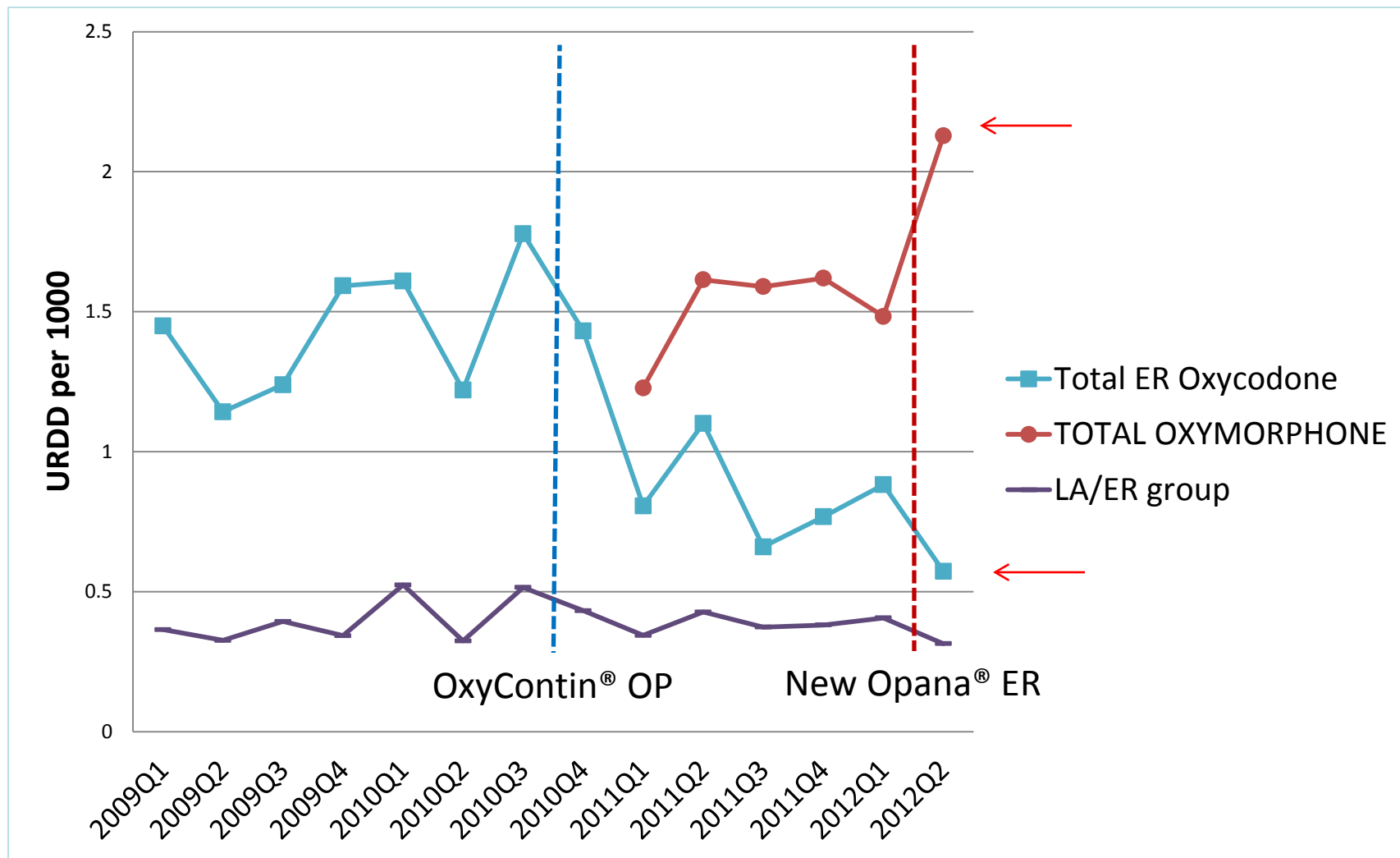
URDD Rate per 1000, 2009 Q1 to 2012 Q2



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LA/ER group = extended release opioids + methadone

# College Survey & StreetRx

- Triggering Event
  - Respond to anonymous survey on drug abuse
- Definition of Abuse:
  - College Survey (push)
    - Self-reported nonmedical use of a prescription medication to get high or for other psychotropic effect.
    - “Please indicate if you took any of these prescription drugs without a doctor's prescription or for any reason other than what was recommended by your prescribing doctor during the last three months, even if just once.”
  - StreetRx (pull)
    - Enter price for prescriptions they purchased without a prescription

StreetRx: N. Dasgupta

College Survey: R. Dart

# Potential Applications of RADARS System to Clinical Trials

- Triggering Events
  - Acute health event (PC)
    - Adverse events c/w drug effect
    - Withdrawal symptoms, decreased mental status, others
  - Enrollment in substance abuse program (OTP, SKIP)
  - Patient admits to diversion or abuse (CS, StreetRx)
    - Would there be value in simply asking patients at the end of the trial?
  - For highly attractive substances, atypical use = abuse, but for non-attractive substances atypical use may not equal abuse

# Potential Applications of RADARS System to Clinical Trials

- Interpreting “events”
  - Can we assess the context?
    - PMP?
    - Route of abuse? Alternate route must be abuse?
    - Who, what, where, how, how much?
    - H/o law enforcement record? Previous treatment program?
  - What is the threshold (e.g. 1 dosage unit?)
  - What is the role of withdrawal?

# Questions

- Should we allow subjects that have risk factors for drug abuse into a trial?
  - Presence of patients at risk could be good indicator of true abusability of a drug.
  - H/o calling poison center, law enforcement record? Previous substance abuse treatment?
  - What about measures that indicate risk factors for abuse (increase pre-test probability)
    - DAST or similar indices
    - Prescription monitoring plans
    - Abuse of non-study drugs while in study, e.g. “Vicodin”

# Questions

- What is the role of alternate routes of administration
  - IV – must be abuse
  - Snort – must be abuse?
  - For the purposes of indicating drugs that must be monitored closely in post-marketing surveillance, they should be automatic.
- Would a PMP be a useful tool to use during trial?
  - Concomitant use of controlled substance indicates treatment failure? Lack of “abusability of study drug”?
- Would there be value in simply asking patients about abuse at the end of the trial? Anonymously?



# Summary

- Exciting opportunity to glean information from clinical studies.
- Can we predict abuse in general population during a clinical trial?
- Mosaic strategy
  - Optimize conditions of trial for relevant information
  - Clinical trial data combined with other sources

# The End