Today's Presentation

NORTHERN NEW ENGLAND CLINICAL & TRANSLATIONAL RESEARCH NETWORK

Designing a Randomized Clinical Trial

Experiences from the Department of Anesthesiology

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Department of Anesthesiology and Critical Care Medicine

Maine Medical Center

November 29, 2023

Project ECHO®

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Fundamental components of a Clinical Trial

- Clear importance of research question
- Randomization plan
- Intent-to-treat principles
- Blinding
- **Minimization of variation**
- Selection of control group
- Ensure study plan is feasible

Evans SR. Fundamentals of clinical trial design. J Exp Stroke Transl Med. 2010 Jan 1;3(1):19-27.

A prospective Randomized Trial of Liposomal Bupivacaine Compared to Conventional Bupivacaine on Pain Control and Postoperative Opioid Use in Adults Receiving Adductor Canal Blocks for Total Knee Arthroplasty

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In press- Journal of Arthroplasty

Why is this research question important?

Total Knee Arthroplasty is most common inpatient elective orthopedic surgical procedure performed in the United States- Inadequate postoperative analgesia associated with impaired mobility and persistent opioid use

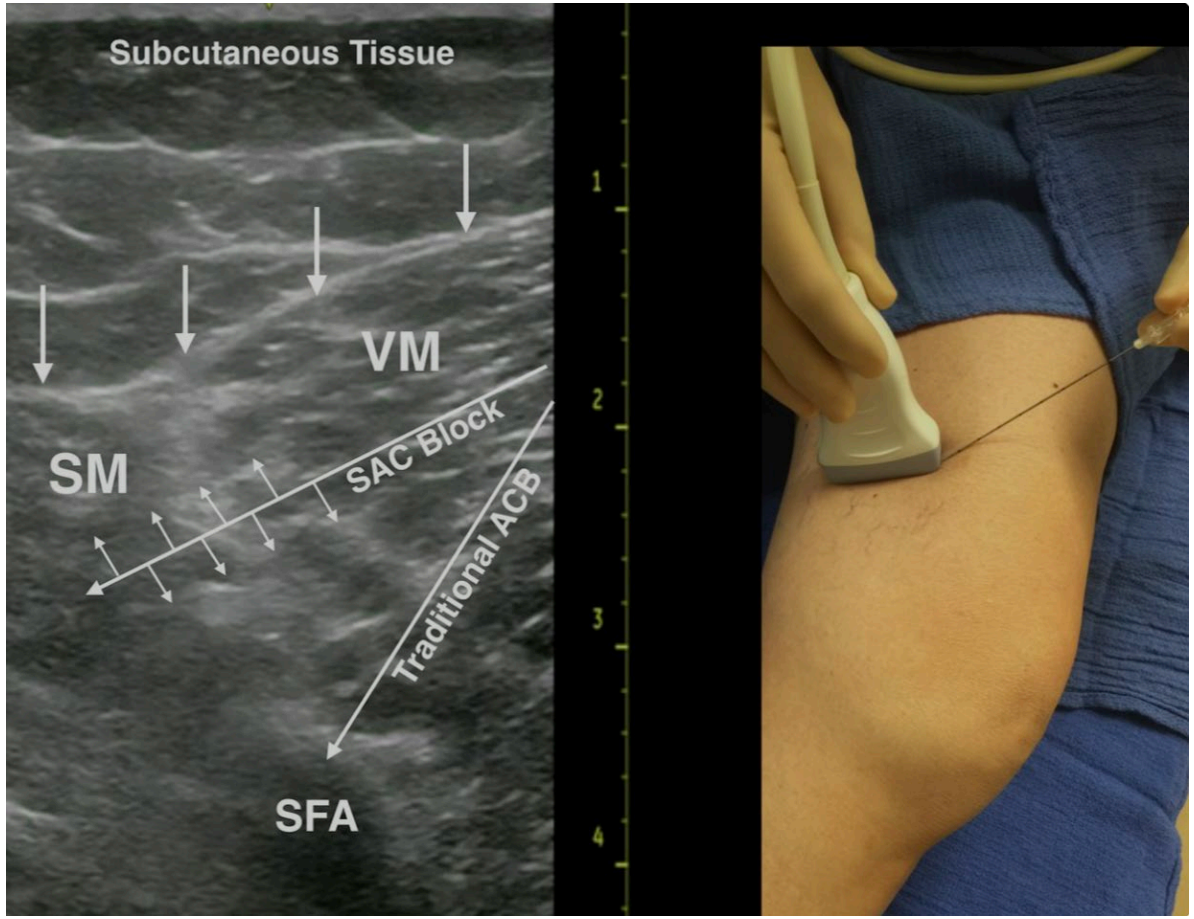
Adductor canal blocks (ACBs) improve time to participation in physical therapy and decreased opioid consumption compared to opioid use alone

Standard of care conventional bupivacaine nerve blocks provide 24 hours of pain relief with significant rebound pain after block resolution

Liposomal bupivacaine (LB) is an extended-release local anesthetic that can provide up to 72 hours of pain relief. Conflicting evidence on utility in ACBs. LB is over 300x more costly than conventional bupivacaine

Research Question

Does Liposomal bupivacaine lead to decreased pain scores and opioid consumption compared to conventional bupivacaine in ACBs for Total Knee Arthroplasty?



INTERVENTION: 10cc 13.3% liposomal bupivacaine + 10cc 0.25% bupivacaine
ACTIVE CONTROL: 20cc 0.5% bupivacaine **within one hour following surgery**

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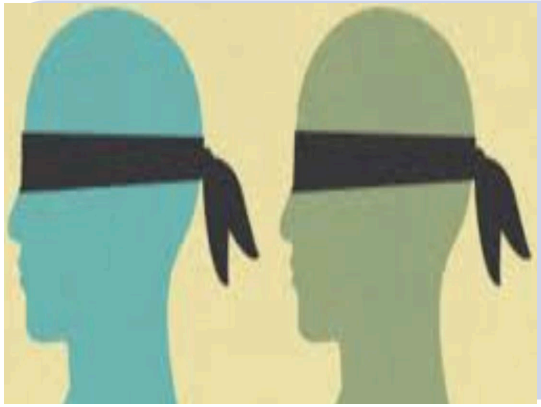
Randomization plan: control for bias associated with treatment selection

Two treatment arms 1:1 ratio using Nquery software concealed in opaque envelopes

Intent-to-Treat analysis: data analyzed according to randomization plan regardless of treatment adherence



Blinding: preventing bias by concealing intervention assignments to minimize unintentional influence

Single blind

Double-blind

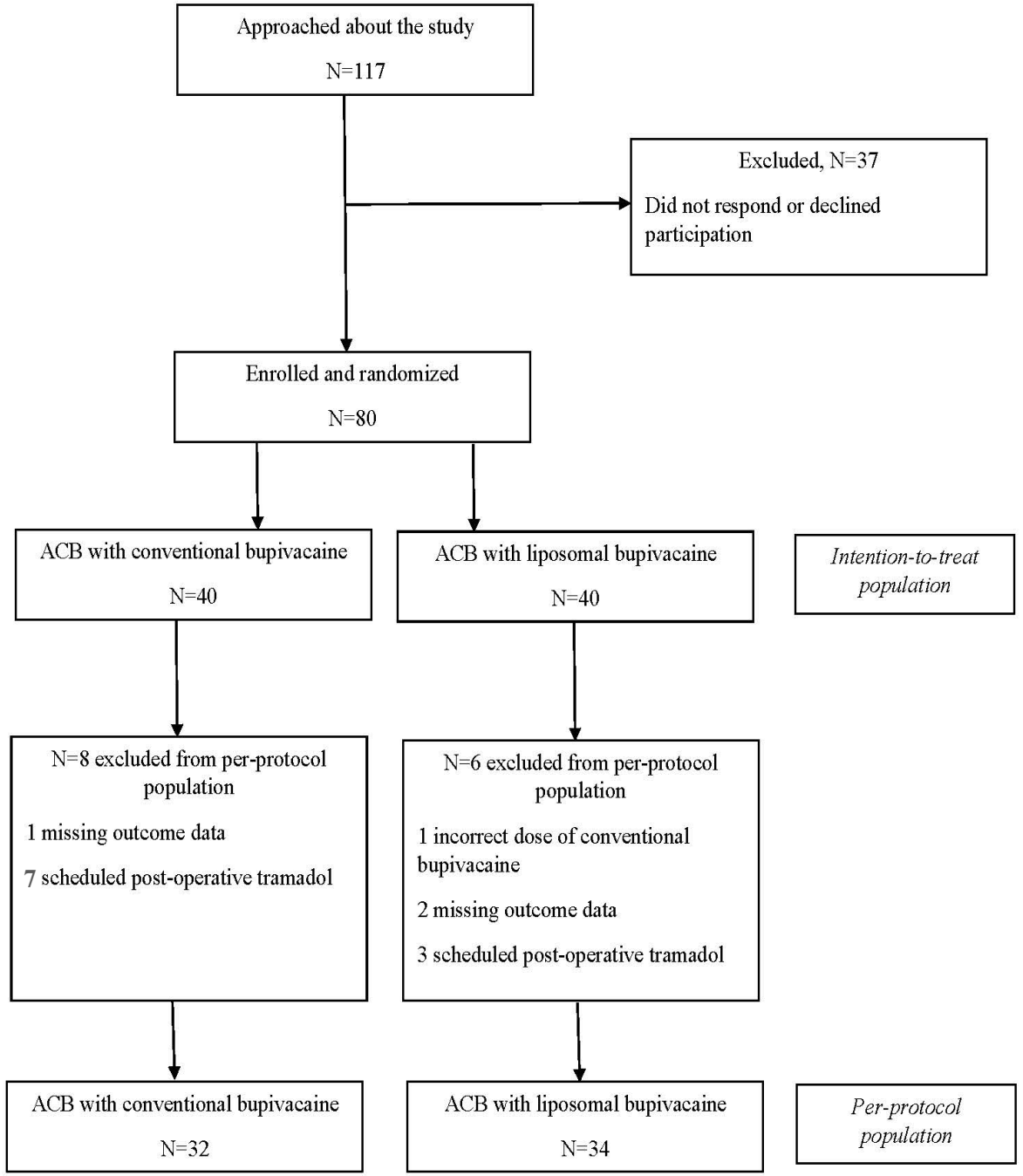
Triple-blind

Selection of control group: baseline for comparison to ensure accurate assessment of treatment effects

Placebo controls

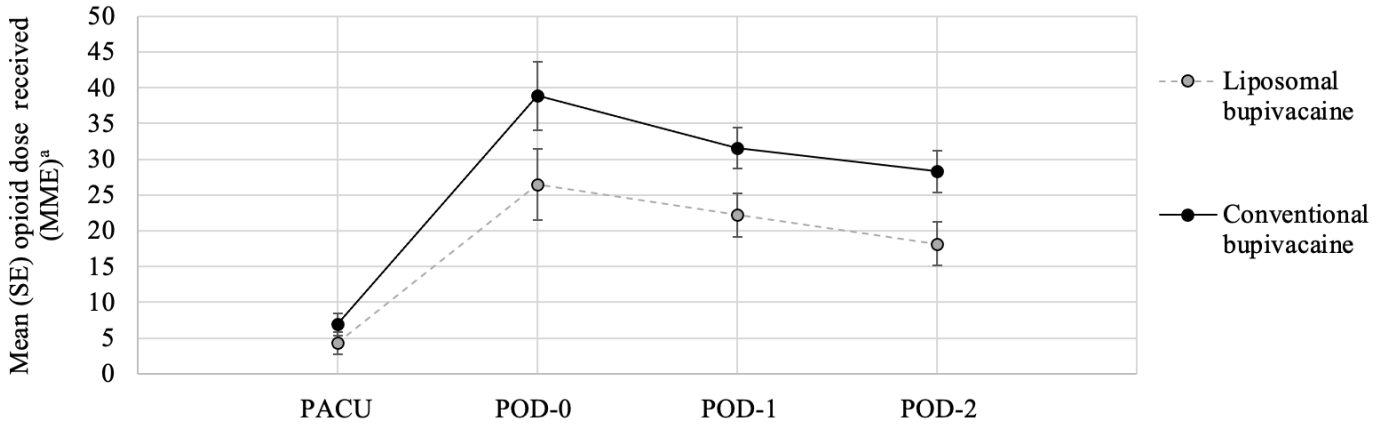
Active controls

Enrollment Outcomes



Results

Variable[a]	Bupivacaine type used in adductor canal block (treatment arm)		
	Liposomal	Conventional	p-value
Pain scores over time			
PACU			
N	40	40	
Average pain score	0 [0-3.1]	0 [0-2.0]	0.94[b]
Maximum pain score	0 [0-6.5]	0 [0-4.0]	0.94[b]
POD-0			
N	40	40	
Average pain score	3.2 [2.5-4.4]	3.9 [2.6-4.8]	0.36[b]
Maximum pain score	6 [5-7]	7 [5.1-8]	0.25[b]
POD-1			
N	36	35	
Average pain score	4.5 [3.0-5.7]	5 [3.6-6.0]	0.43[b]
Maximum pain score	6.7 [4-7]	7 [5-7.5]	0.61[b]
POD-2			
N	34	34	
Average pain score	4 [1.9-5.8]	4.2 [3.0-5.6]	0.54[b]
Maximum pain score	4.5 [2-7]	5.5 [4-7]	0.27[b]
Post-operative hospitalization			
Total time in PACU (hours)	1.7 ± 0.5	2.0 ± 0.7	0.14[c]
Time, anesthesia start to discharge (hours)	25 [7.3-28.9]	23.7 [21.5-27.1]	0.478[b]



Liposomal bupivacaine associated with reduced opioid consumption with no difference in pain scores

Feasibility of Study Plan

- Research question important to institution/collaborating group
- Research question interesting to anesthesia department
  - Attending anesthesiologists performed nerve blocks
  - Medical students and residents assisted with patient calls
  - Nurse Practitioner collected data from EMR
- Viable consenting plan given limitations inherent to Anesthesia
- Low budget study strategy
- Active control arm identical to current standard of care
- Intervention study arm with minimal risk

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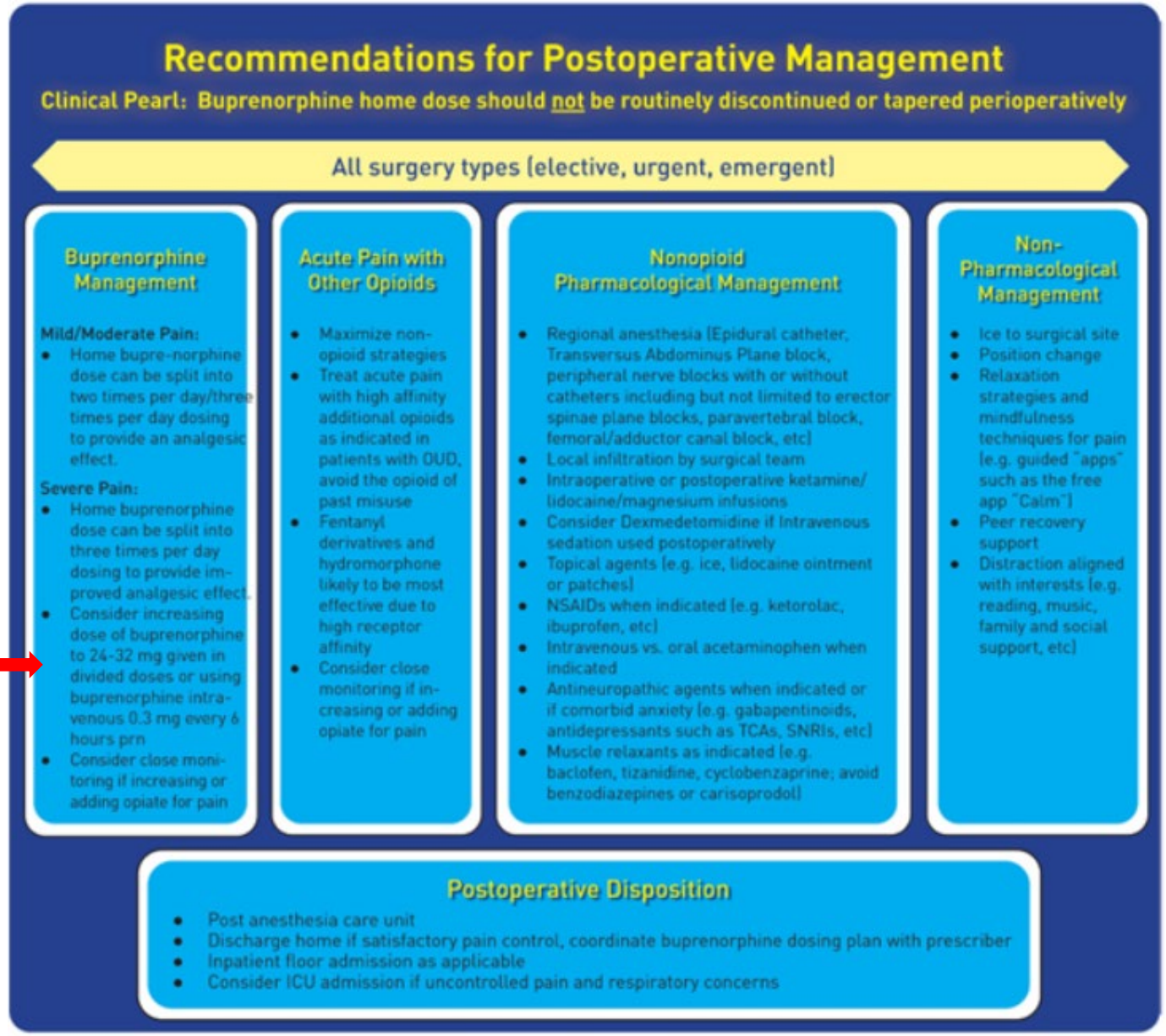
Buprenorphine and Acute Pain Management

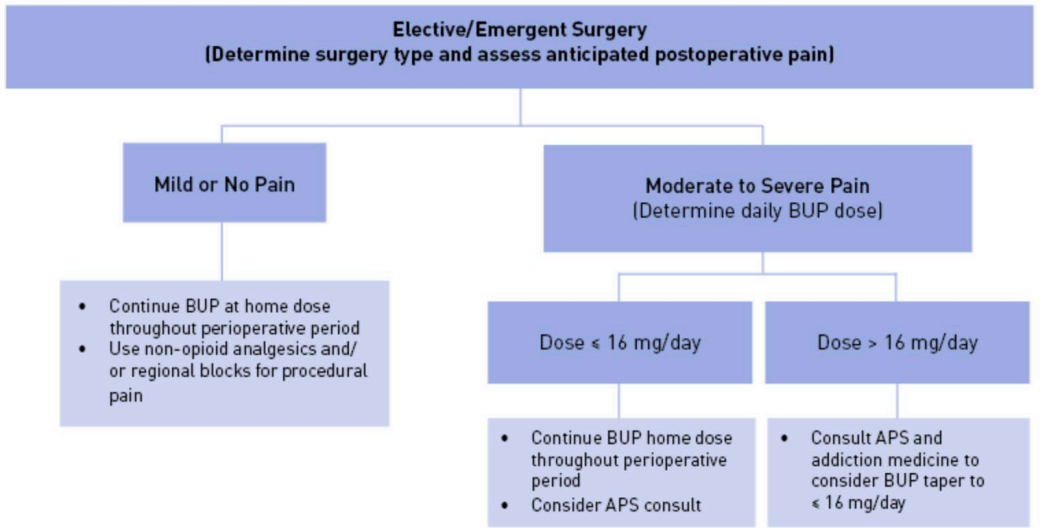
- **Partial opioid agonist antagonist used to treat opioid use disorder**
- **No consensus on optimal management to facilitate analgesia**
- Substance Abuse and Mental Health Services Administration (SAMHSA) Recommendations:
  - **Continue** buprenorphine with agonist opioids
    - DOWNSIDE: elevated opioid doses required for adequate analgesia
  - **Discontinue** buprenorphine with agonist opioids for analgesia and withdrawal prevention
    - DOWNSIDE: premature discontinuation of BUP associated with increased rates of illicit opioid use
- **Duration required to for long-term opioid abstinence unknown**
  - Discontinuation of MAT for OUD associated with increased rates of illicit opioid use
  - 82% of subjects relapsed 1-month post BUP cessation (Weiss, 2011)

Treatment Improvement Protocol 63. Medications for Opioid Use Disorder. Substance Abuse and Mental Health Services Administration. 2020



Kohan L, Barreveld AM*, et al* Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel *Regional Anesthesia & Pain Medicine* 2021;46:840-859

ASRA 2023 Recommendations for Perioperative Management



- Consider splitting BUP dose into Q6-8 h to provide improved analgesia
- Titrate short acting full agonist opioids to effect as needed and consider close monitoring
- Anticipate opioid tolerance and higher doses of short acting full agonist compared to opioid naive patients
- Use multimodal analgesia to optimize pain control*
- Consider IV opioids or PCAs if patient not tolerating orals

*Multimodal analgesia includes but are not limited to regional techniques, scheduled acetaminophen, NSAIDS if not contraindicated, calcium channel blockers like gabapentin or pregabalin, topical lidocaine, oral and parenteral opioids, intravenous ketamine infusion etc.

BUP —buprenorphine; APS — acute pain service; PCA — patient-controlled analgesia

Figure 1: Perioperative Buprenorphine Management Algorithm

Selvamani BJ, et. al. Perioperative Management of Patients on Buprenorphine for Opioid Use Disorder. *ASRA Pain Medicine News.* 2023

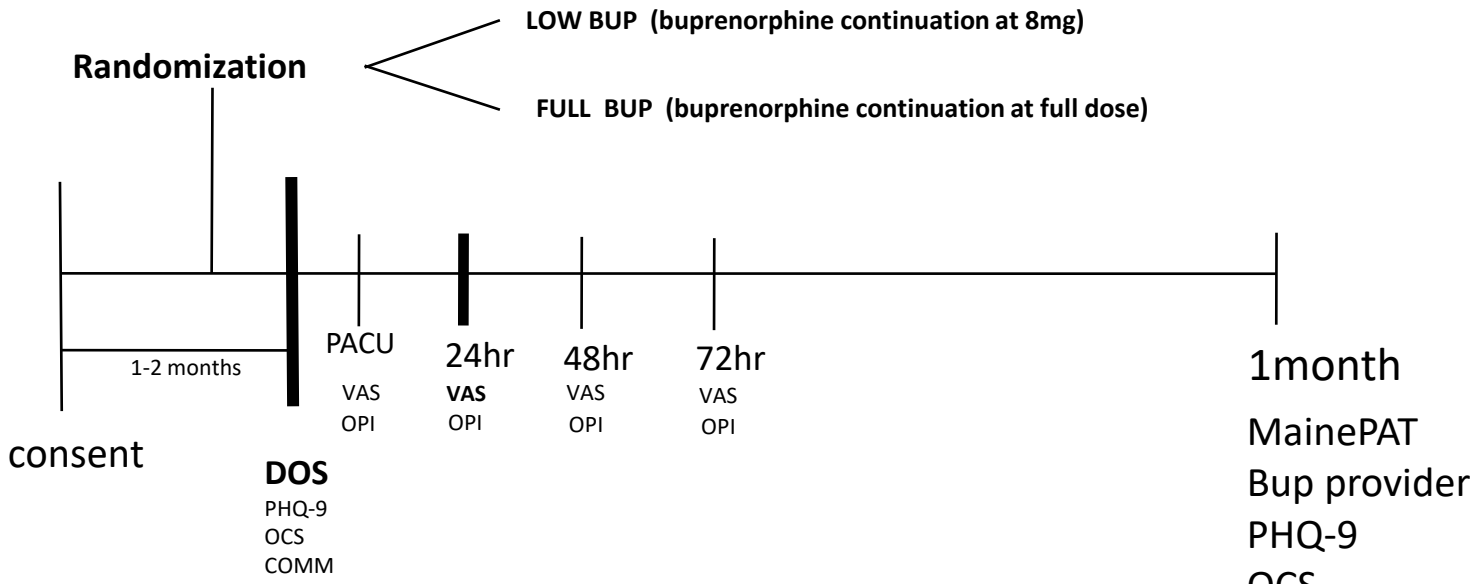
Prospective, Randomized Trial of the Effect of Buprenorphine Continuation on Pain Control and Post-Operative Opioid Use

Aim 1: To compare pain control efficacy of perioperative buprenorphine continuation to low dose reduction in adults maintained on buprenorphine for OUD.

Aim 2: To compare postoperative opioid consumption in adults maintained on buprenorphine for OUD, measured as morphine milligram equivalents (MME) at 24, 48 and 72 hours postoperatively.

Aim 3: To compare OUD symptom severity and depressive symptoms; measured preoperatively and 30 days postoperatively using the Patient Health Questionnaire-9 (PHQ-9), Current Opioid Misuse Measure (COMM), and Opioid Craving Scale (OCS) instruments.

Aim 4: To compare the number of opioid prescriptions and quantity (in MME) of opioid medications dispensed, up to 30 days following surgery



Randomization based on surgical type
DOS: Day of Surgery
PACU: Post Anesthesia Care Unit
VAS: Visual analog pain scores VAS 0-10
PHQ-9: Patient Health Questionnairre-9
OCS: Opioid Craving Scale
OPI: opioid consumption in milligram morphine equivalents (MME)
COMM: current opioid misuse measure
MainePAT: prescription awareness tool tracking opioid prescriptions 30 days post-surgery in MME
Bup provider: Phone call to buprenorphine provider to identify postoperative OUD treatment adherence

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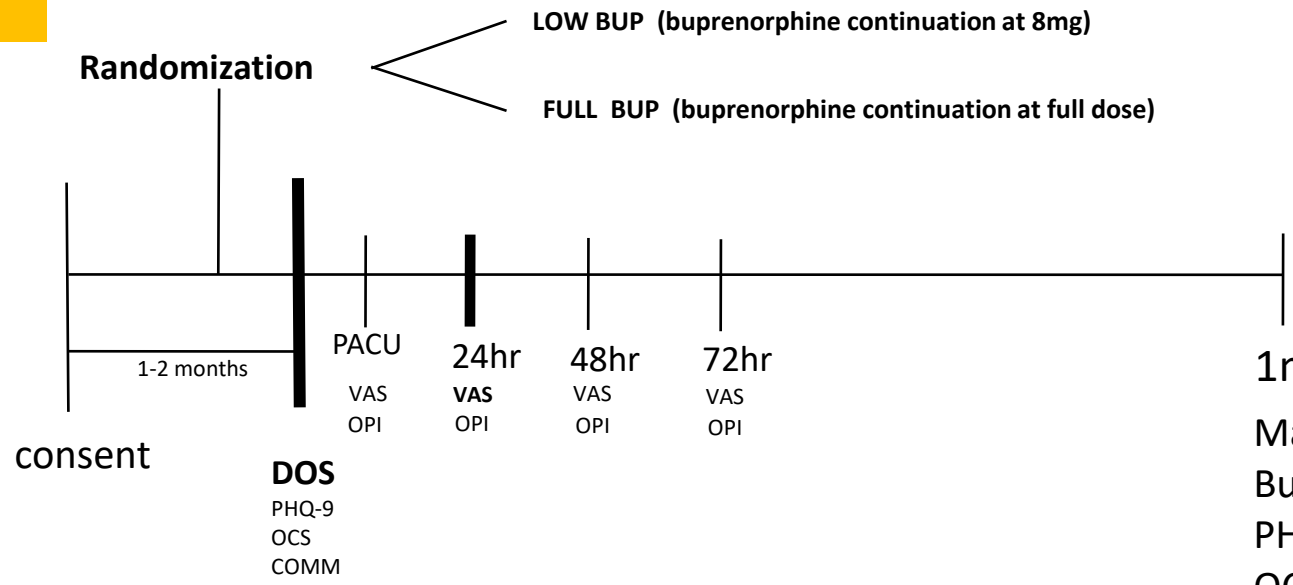
Challenging consent/randomization process prior to surgery

Multiple service lines to coordinate with

Control group low dose continuation-discontinuation was prior standard



Subjects not blinded to treatment-opportunities for dropout

Randomization based on surgical type
PHQ-9: Patient Health Questionnairre-9
OCS: Opioid Craving Scale
COMM: current opioid misuse measure

Many opportunities for missing data
Due to subject heterogeneity and various instruments administered

BUPRENORPHINE STUDY- LESSONS LEARNED

- Very challenging to recruitment opioid tolerant patients pre-operatively
- Complexity of study required multiple sites of recruitment to minimize surgical types

OUTCOMES IDENTIFIED

- All patients on their full buprenorphine dose one month following surgery
- No patients with evidence of opioid relapse (provider and patient report)

- **NEXT STEPS:** Use registry data to execute retrospective analysis for buprenorphine full dose continuation vs low dose continuation