Improving Post-Operative Pain Clinical Trials:
Pivotal Endpoints, Failures, and Protocol Enhancements

INGENŪ CRO

Introduction

Post-operative pain (POP) is a multifaceted condition that arises after surgical interventions, affecting nearly all patients to some degree.

The complexity of this type of pain is largely due to the interplay of various physiological and psychological factors. Acute pain typically manifests within hours of the surgery, peaking in intensity during the first 24-48 hours. Depending on the nature of the surgery and the patient's individual pain tolerance, it can last for days or weeks.

Effective post-operative pain management is essential for minimizing complications, enhancing recovery, and improving overall patient outcomes. Inadequately controlled pain can lead to chronic post-surgical pain (CPSP), which significantly impairs a patient's quality of life and increases healthcare costs.

iNGENŪ CRO

Book a Discovery Call to learn how iNGENū can deliver high-quality, cost-efficient, FDA-compliant research for your next clinical trial

Why Choose iNGENū CRO?

iNGENū is the FDA-centric Australian CRO championing disruptive, innovative biotech firms. We are physician-led, providing access to the full spectrum of clinical and non-clinical research services.

Local Trials, Global Approvals

Australian expertise combined with direct FDA submission capabilities, offering a streamlined path for global approval.

Disciplined, Cost-Efficient Execution

Every dollar is strategically allocated, eliminating unnecessary costs while maintaining the highest quality.

Australian Headquartered, Asia-Pacific Reach

Access high-quality trials in the Asia-Pacific region, enhancing speed and scalability.

Expertise From the Start

Engage directly with our team of highly qualified doctors and PhD scientists from the outset.

Ready to discuss your Clinical Trial?
For further information on how iNGENū can assist you to conduct your clinical trial, book a Discovery Call with one of our Advisors.

Insights on Post-Operative Pain (POP)

Key Characteristics of Post-Operative Pain

The primary types of pain experienced in the post-operative period are:

1. **Nociceptive pain:** Caused by tissue damage during surgery, involving both somatic (skin, muscles) and visceral (internal organs) components.
2. **Inflammatory pain:** Triggered by the immune response to tissue injury.
3. **Neuropathic pain:** Arises when nerves are directly damaged during the procedure.

Evolution of Understanding and Treatment

Historically, the management of post-operative pain was underprioritized, as the focus was on the success of the surgery itself, with less attention to post-surgical recovery. This often led to poorly controlled pain, which delayed recovery, increased the risk of chronic pain, and contributed to longer hospital stays.

In recent decades, however, there has been a significant shift towards addressing pain as a key component of surgical outcomes. The introduction of Enhanced Recovery After Surgery (ERAS) protocols, which emphasize multimodal analgesia and early mobilization, has been pivotal in optimizing post-operative care. The aim of multimodal analgesia is to target different pain pathways through a combination of analgesics, reducing reliance on opioids, and consequently lowering the risk of opioid-related side effects and dependence.

The evolution of pain management also includes an increasing focus on individualized care. Evidence now shows that patients benefit most from tailored pain management plans based on their surgical procedure, medical history, and psychological profile. Furthermore, healthcare systems have recognized the value of non-opioid treatments, such as regional anesthesia (e.g., nerve blocks), NSAIDs, and non-pharmacological therapies like physical therapy and cognitive-behavioral therapy (CBT).

Contributing Factors and Prevalence

Contributing Factors to Post-Operative Pain

- **Biological Factors:** The type of surgical procedure, extent of tissue damage, and the patient's pre-existing conditions (e.g., diabetes, chronic pain conditions) are significant determinants of post-operative pain. Genetic factors also play a role, particularly in how patients metabolize pain medications, which affects their overall pain experience.
- **Psychological Factors:** Anxiety, depression, and catastrophizing (expecting the worst outcomes) are associated with increased pain perception. Conversely, patients with better coping mechanisms and emotional support tend to report lower pain levels.
- **Environmental Factors:** The quality of post-operative care, including access to pain management interventions, significantly impacts recovery. Patients in high-resource settings with structured pain management protocols experience better outcomes than those in low-resource environments.

Additionally, surgical procedures such as thoracotomy, mastectomy, or amputation are associated with higher rates of chronic post-surgical pain, indicating that the extent and nature of the surgery play a critical role in the risk of prolonged pain.

Prevalence of Post-Operative Pain

In the U.S., approximately 80% of patients report some level of post-operative pain, with 30-50% experiencing moderate to severe pain in the first 48 hours following surgery. Despite advancements in pain management, a significant percentage (10-30%) of patients develop chronic pain, particularly after high-risk surgeries.

One of the key challenges is balancing effective pain control with the prevention of opioid dependence. The opioid crisis in the U.S. has highlighted the importance of reducing opioid prescriptions, particularly in the context of post-surgical pain. Studies suggest that up to 10% of opioid-naïve patients may develop persistent opioid use following surgery. One key study that contributed to this statistic is by Brummett et al., published in 2017 in JAMA Surgery. This large retrospective cohort study examined over 36,000 opioid-naïve surgical patients and found that approximately 6% to 10% of them continued to use opioids 90 days after surgery. The study highlights that even minor surgical procedures can lead to persistent opioid use in previously opioid-naïve individuals, with significant implications for both patient health and the ongoing opioid crisis.

Prevalence and Market Trends

Trend Analysis (2013-2023)

Over the last decade, significant advancements have been made in post-operative pain management, largely driven by innovations in analgesic techniques and a shift toward patient-centered care. One of the most notable trends has been the increasing use of multimodal analgesia to reduce reliance on opioids. This approach incorporates non-opioid analgesics such as NSAIDs, local anesthetics (e.g., bupivacaine), and adjunctive therapies like gabapentin to manage pain while minimizing opioid exposure. As a result, there has been a significant decrease in opioid prescriptions post-surgery, particularly in the U.S., where the opioid epidemic prompted both regulatory changes and shifts in clinical practice.

The use of regional anesthesia and long-acting local anesthetics has increased significantly, contributing to an opioid-sparing approach in surgical pain management. Studies show that chronic post-surgical pain remains a challenge, despite these efforts to reduce opioid use. However, there has been no significant downward trend in its prevalence, underscoring the need for continued innovation in pain management strategies.

Projected Trends for the Next Decade

Looking forward, the focus on non-opioid therapies will likely intensify, with pharmaceutical companies developing longer-acting local anesthetics, anti-inflammatory agents, and novel treatments like nerve growth factor inhibitors. These advancements are expected to further reduce opioid consumption and decrease the incidence of chronic post-operative pain.

Technological innovations, such as personalized pain management plans using genetic and biomarker data, are anticipated to become key components in optimizing treatment outcomes. This personalized approach aims to tailor pain management to the individual patient, potentially improving both pain control and recovery times. Additionally, enhanced recovery protocols that prioritize early mobilization and reduced hospital stays are expected to become more widespread, leading to quicker recovery and improved overall patient outcomes.

Market for Post-Operative Pain Treatments

The global market for post-operative pain treatments was valued at around $35 billion in 2022, with a projected growth rate of 4.8% CAGR from 2023 to 2033. This growth is driven by the increasing number of surgeries, heightened awareness of pain management needs, and a strong demand for more effective and less addictive treatments. The development of novel non-opioid analgesics and improved drug delivery systems (such as extended-release formulations) are expected to play a major role in shaping the market's future.

Epidemiology of Post-Operative Pain

Age as a Factor in Post-Operative Pain:

Age significantly influences post-operative pain experiences. Older adults often face more severe post-operative pain due to comorbidities like arthritis, diabetes, and cardiovascular disease. Paradoxically, elderly patients may underreport their pain due to cognitive impairments or a reluctance to complain. Conversely, younger patients experience faster recovery and more acute but short-lived pain. Pain sensitivity tends to diminish with age, yet older adults are more vulnerable to prolonged recovery and CPSP. Thus, tailored pain management for older adults is crucial to prevent long-term pain complications.

Gender Differences in Pain Perception:

Gender plays a critical role in post-operative pain. Research indicates that women are generally more sensitive to pain stimuli and report higher pain levels compared to men, possibly due to hormonal fluctuations affecting pain thresholds (Meissner et al., 2015). Psychological factors, such as anxiety and emotional distress, which are more common in women, exacerbate pain perception. These findings highlight the importance of gender-specific pain management approaches to address both biological and psychological differences.

Racial and Ethnic Disparities in Pain Management:

Racial and ethnic disparities significantly affect post-operative pain management. Studies have shown that minority groups, particularly African American people and Hispanic people, often receive inadequate pain management compared to their white counterparts. Implicit biases and systemic inequities contribute to these disparities. Addressing these issues through improved provider training and equitable access to pain relief is essential to reduce these disparities.

Geographic Variation in Pain Management:

Geographic location influences post-operative pain experiences and management. Patients in high-income countries have access to advanced pain management techniques, such as regional anesthesia and multimodal analgesia, which significantly reduce post-operative pain. In contrast, low- and middle-income countries often lack access to adequate pain medications and face regulatory and infrastructure challenges, leading to untreated or poorly managed pain.

Epidemiology of Post-Operative Pain (cont.)

5. Genetic Predisposition to Post-Operative Pain

Genetic factors also contribute to individual variability in pain experiences. Polymorphisms in genes such as OPRM1 and COMT affect pain sensitivity and opioid response, suggesting that pharmacogenomics could enable personalized post-operative pain management in the future.

6. Surgical Factors and Procedure Types

The type of surgery significantly predicts post-operative pain levels. Invasive surgeries, such as open abdominal surgery or joint replacements, are associated with higher pain levels and longer recovery periods compared to minimally invasive procedures. Tailoring pain management strategies based on the surgery type can help improve outcomes and reduce the risk of CPSP.

7. Psychological Factors and Pain Perception

Psychological factors, including anxiety, depression, and catastrophizing, significantly influence pain perception. Patients with high levels of anxiety or previous negative surgical experiences tend to report higher pain levels. Psychological interventions, such as cognitive-behavioral therapy (CBT) and mindfulness-based stress reduction (MBSR), have been shown to improve post-operative pain outcomes.

INGENŪ CRO

Pivotal Endpoints for Post-Operative Pain Clinical Trials:

Key Challenges and Solutions

1. Pain Intensity Reduction (SPID)
2. Time to First Analgesia Use
3. Total Opioid Consumption
4. Rescue Analgesia Requirement:
5. Time to Hospital Discharge:
6. Patient Satisfaction Scores:
7. Incidence of Adverse Events (AEs):
8. Pain-Free Time Duration:
9. Time to Ambulation:
10. Wound Healing and Functionality:

INGENŪ CRO

1. Endpoint: Pain Intensity Reduction (SPID)

- This endpoint evaluates the sum of pain intensity differences over a defined time period, typically from 0 to 48 hours post-surgery. Significant reduction in pain correlates with improved patient comfort and mobility, which are crucial for post-operative recovery. However, the challenge lies in the subjectivity of pain scales like the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS). Solutions involve using well-validated scales across various patient populations.

Correlation to Patient Outcome:

- Direct correlation to improved patient comfort and mobility.

Challenge:

- Subjectivity in patient-reported pain scales like VAS or NRS.

Solution:

- Use standardized pain scales, validated in multiple settings.

2. Endpoint: Time to First Analgesia Use

- This endpoint measures how long a patient can go without needing pain relief after surgery, providing insight into the effectiveness of the primary pain management strategy. The challenge is variability in individual pain thresholds and perceptions of pain. Implementing clear criteria for when analgesics should be administered can address this.

Correlation to Patient Outcome:

- Indicates how effective the initial pain management strategy is.

Challenge:

- Variability in patient pain thresholds and analgesic needs.

Solution:

- Implement strict criteria for analgesic administration timing.

3. Endpoint: Total Opioid Consumption

- Reducing opioid use is a crucial endpoint, especially in light of the opioid crisis. Lower opioid consumption translates to fewer side effects, lower addiction risks, and better overall patient safety. Challenges include differences in how patients metabolize opioids and the risk of opioid dependence. The use of multimodal analgesia, combining opioids with NSAIDs or acetaminophen, helps mitigate this risk.

Correlation to Patient Outcome:

- Lower opioid use reduces risk of dependence and side effects.

Challenge:

- Opioid tapering and patient variability in opioid metabolism.

Solution:

- Combine opioids with non-opioid alternatives (multimodal analgesia).

4. Endpoint: Rescue Analgesia Requirement

- This endpoint measures how often patients need additional pain relief beyond their initial medications. Fewer rescue doses indicate that the primary treatment is effective. However, differences in baseline pain between patients can complicate this measurement. Defining strict criteria for rescue analgesia and stratifying patients by pain severity can provide more reliable data.

Correlation to Patient Outcome:

- Fewer rescue doses indicate better pain control from primary meds.

Challenge:

- Differences in baseline pain between patients.

.

Solution:

- Set clear guidelines for rescue analgesia use, stratified by pain type.

5. Endpoint: Time to Hospital Discharge

- Early hospital discharge is a key indicator of effective pain management and overall recovery. Shorter stays reduce healthcare costs and complications. However, factors unrelated to pain, such as the type of surgery or other medical conditions, can affect discharge times. Using hospital discharge as a secondary endpoint, combined with other recovery metrics, can help

Correlation to Patient Outcome:

- Shorter hospital stays indicate effective pain control and recovery.

Challenge:

- External factors (e.g., surgery type, other medical conditions).

Solution:

- Use hospital discharge as a secondary endpoint with other functional outcomes.

6. Endpoint: Patient Satisfaction Scores

- Patient-reported outcomes are essential for understanding the real-world effectiveness of pain management strategies. High satisfaction scores correlate with successful pain control and overall patient well-being. The challenge is the subjective nature of satisfaction surveys. Combining these scores with objective outcomes, like pain-free mobility, provides a more complete picture.

Correlation to Patient Outcome:

- Reflects the patient's perspective on pain relief and overall care.

Challenge:

- Subjectivity and variability in individual experiences.

Solution:

- Combine patient-reported outcomes with objective measures like mobility.

INGENŪ CRO

7. Endpoint: Incidence of Adverse Events (AEs)

- A lower incidence of AEs, especially serious ones like respiratory depression in opioid use, indicates a safer drug profile. Challenges arise in distinguishing between minor and severe AEs and in reporting consistency. Standardizing the classification and reporting of adverse events is essential for accurate assessment.

Correlation to Patient Outcomes:

- A lower AE incidence improves safety profiles and patient outcomes.

Challenge:

- Reporting and categorization differences of mild vs. severe AEs.

Solution:

- Standardize AE reporting and focus on clinically significant events.

8. Endpoint: Pain-Free Time Duration

- Measuring the length of time a patient experiences no pain post-surgery is a key endpoint, especially in the first 48 hours when pain is typically at its peak. However, variability in how quickly pain arises or resolves in different patients poses a challenge. Focusing on specific post-operative intervals for pain-free time helps provide clearer results

Correlation to Patient Outcomes:

- Longer pain-free periods correlate with better post-op recovery.

Challenge:

- Variability in pain onset and resolution post-surgery.

Solution:

- Focus on pain-free intervals, particularly in the first 48 hours.

9. Endpoint: Time to Ambulation

- Early ambulation (walking) post-surgery is crucial for preventing complications such as deep vein thrombosis and promotes faster recovery. Pain is a major factor delaying ambulation. However, factors like post-operative fatigue or weakness may also delay walking, making this endpoint difficult to isolate. Pairing it with functional outcomes like the range of motion or activity levels can give a more comprehensive understanding of recovery.

Correlation to Patient Outcomes:

- Early mobilization improves recovery and reduces complication risks.

Challenge:

- Non-pain-related factors affecting mobility (e.g., fatigue).

Solution:

- Combine with functional outcomes like range of motion or activity levels.

10. Endpoint: Wound Healing and Functionality

- Effective pain control can improve wound healing and overall functionality after surgery. However, masking pain may also hide symptoms of underlying complications such as infection. Combining this endpoint with wound healing assessments and long-term functional outcomes ensures that pain control is not achieved at the cost of patient safety.

Correlation to Patient Outcomes:

- Optimal pain control aids in faster wound healing and rehabilitation.

Challenge:

- Pain control may mask symptoms of underlying complications.

Solution:

- Monitor for both wound healing outcomes and overall functionality.

FDA-Approved Treatments for Post-Operative Pain

Drug Name	Year of Approval	Sponsor	Mechanism of Action	Therapeutic Effects
Oxycodone (OxyContin, Roxicodone)	1995	Purdue Pharma	Opioid receptor agonist	Moderate to severe pain relief, strong analgesic effect
Hydrocodone (Vicodin, Norco)	1978	AbbVie	Opioid receptor agonist	Moderate pain relief, often combined with acetaminophen
Morphine	1941	Various	Opioid receptor agonist	Severe pain relief, commonly used in hospitals
Fentanyl (Duragesic, Sublimaze)	1968	Janssen	Potent opioid receptor agonist	Severe post-operative pain relief, used in hospital settings
Tramadol (Ultram)	1995	Janssen Pharmaceuticals	Weak opioid receptor agonist and serotonin-norepinephrine reuptake inhibitor	Moderate pain relief, alternative to stronger opioids
Hydromorphone (Dilaudid)	1984	Janssen Pharmaceuticals	Opioid receptor agonist	Potent opioid for severe pain, often used in post-op settings
Oxymorphone (Opana ER)	2006	Endo Pharmaceuticals	Opioid receptor agonist (extended-release)	Extended pain relief for chronic post-op pain
Tapentadol (Nucynta)	2008	Grünenthal GmbH	Opioid receptor agonist and norepinephrine reuptake inhibitor	Moderate to severe pain relief
Methadone	1947	Roxane Laboratories	Opioid receptor agonist	Chronic pain management, particularly complex post-op pain
Oxycodone/Acetaminophen (Percocet)	1976	Endo Pharmaceuticals	Opioid receptor agonist + acetaminophen	Combination used for moderate to severe post-op pain
Hydrocodone/Acetaminophen (Vicodin)	1978	AbbVie	Opioid receptor agonist + acetaminophen	Moderate pain relief with acetaminophen
Codeine/Acetaminophen (Tylenol with Codeine)	1976	McNeil Consumer Healthcare	Weak opioid receptor agonist + acetaminophen	Mild to moderate post-op pain relief
Tramadol/Acetaminophen (Ultracet)	2001	Janssen Pharmaceuticals	Weak opioid receptor agonist + acetaminophen	Moderate pain relief
Acetaminophen (Tylenol)	1955	McNeil Consumer Healthcare	Inhibits COX enzymes	Mild to moderate pain relief, non-opioid
Ibuprofen (Advil, Motrin)	1974 *(initially approved for rheumatoid arthritis, became available over-the-counter (OTC) for general pain relief in 1984)*	Pfizer	NSAID, COX-1 and COX-2 inhibitor	Mild to moderate pain, anti-inflammatory
Ketorolac (Toradol)	1989	Roche Pharmaceuticals	NSAID, COX-1 and COX-2 inhibitor	Strong NSAID for short-term pain relief
Diclofenac (Voltaren)	1988	Novartis	NSAID, COX-1 and COX-2 inhibitor	Reduces inflammation and pain
Celecoxib (Celebrex)	1998	Pfizer	COX-2 selective inhibitor	Reduces post-operative inflammation and pain
Meloxicam (Mobic)	2000	Boehringer Ingelheim	NSAID, COX-2 selective inhibitor	Post-surgical pain and inflammation control
Lidocaine	1948	AstraZeneca	Sodium channel blocker, local anesthetic	Local pain relief, used in nerve blocks
Ropivacaine	1996	AstraZeneca	Sodium channel blocker, local anesthetic	Local and regional anesthesia for post-operative pain
Liposomal Bupivacaine (Exparel)	2011	Pacira Pharmaceuticals	Long-acting formulation, sodium channel blocker	Extended post-surgical pain relief
Lidocaine patches (Lidoderm)	1999	Endo Pharmaceuticals	Sodium channel blocker (topical)	Local pain relief in post-surgical settings
Gabapentin (Neurontin)	1993	Pfizer	Modulates GABA receptors	Neuropathic pain relief, used in multimodal analgesia
Pregabalin (Lyrica)	2004	Pfizer	Modulates GABA receptors	Neuropathic pain management, particularly for post-op nerve pain
Dexmedetomidine (Precedex)	1999	Hospira Inc.	Alpha-2 adrenergic agonist	Sedation and pain management, adjunct to opioids
Ketamine	1970	Par Pharmaceutical	NMDA receptor antagonist	Reduces refractory post-operative pain, opioid-sparing effects
Clonidine	1974	Boehringer Ingelheim	Alpha-2 adrenergic agonist	Used with local anesthetics for nerve blocks
Dexamethasone	1958	Merck & Co.	Corticosteroid, anti-inflammatory	Enhances effects of local anesthetics in regional blocks
Morphine, Fentanyl, Hydromorphone (PCA)	Various	Various	Opioid receptor agonists	Administered through PCA pumps for patient-controlled pain relief

Five FDA-Approved Treatments for Post-Operative Pain

Drug Name	Class	Description
Oxycodone (OxyContin, Roxicodone)	Opioid analgesic	Frequently prescribed for moderate to severe pain following surgery. Oxycodone remains a go-to opioid despite concerns about dependency due to its potency and efficacy in managing post-surgical pain.
Hydrocodone/Acetaminophen (Vicodin, Norco)	Opioid Combination Drug	One of the most commonly prescribed painkillers for moderate pain post-surgery. This combination provides both opioid analgesia and non-opioid (acetaminophen) relief, making it widely used in outpatient settings.
Ibuprofen (Motrin, Advil)	Non-Steroidal Anti-Inflammatory Drug (NSAID)	A key part of multimodal pain management, ibuprofen is widely prescribed for mild to moderate pain due to its anti-inflammatory properties and ability to reduce opioid use.
Acetaminophen (Tylenol)	Non-Opioid Analgesic	Frequently used for mild to moderate pain, either on its own or in combination with opioids. Its low side effect profile and effectiveness make it a common first-line option.
Liposomal Bupivacaine (Exparel)	Local Anesthetic	Widely used in nerve blocks and regional anesthesia for long-lasting pain relief, especially in orthopedic and abdominal surgeries. Its extended action makes it a key drug in reducing opioid requirements post-surgery.

Pivotal Clinical Trials Leading to FDA Approval for POP Medications

Drug Name	Study Name/Clinical Trial Identifier	Sample Size	Key Findings	Statistical Data
Oxycodone (OxyContin)	NCT00271973	332 participants	Oxycodone is effective in reducing pain. However, due to concerns about the potential for abuse, addiction, and misuse, the FDA implemented additional safety measures	Introduction of Risk Evaluation and Mitigation Strategy (REMS) programs to reduce the risk of addiction while maintaining pain relief benefits.
Hydrocodone/ Acetaminophen (Vicodin)	**Approval in 1970, based on post-market surveillance & physician feedback demonstrating its efficacy*	**Pre-registration era*	**Pre-registration era*	Recent studies involved comparing Vicodin with VX-548, a non-opioid painkiller, which showed similar levels of pain relief, though Vicodin carried greater risks of side effects such as nausea and constipation
Ibuprofen (Motrin)	**Ibuprofen was originally developed by Dr. Stewart Adams and his team at Boots Group in the 1960s*	**Pre-registration era*	Clinical evidence confirmed effectiveness in treating inflammation and pain associated with arthritis	The trials showed that ibuprofen could reduce pain and inflammation in arthritis patients with a significantly lower risk of GI bleeding compared to aspirin
Acetaminophen (Tylenol)	**Initially approved for the treatment of mild to moderate pain and fever in 1955.*	**Pre-registration era*	**Pre-registration era*	Acetaminophen was found to be as effective as aspirin for pain relief and lacked the side effects of gastrointestinal irritation, bleeding, and ulcers commonly associated with high-dose aspirin
Liposomal Bupivacaine (Exparel)	EXCLAIM Study	49	Provided prolonged pain relief and significantly reduced opioid consumption post-operatively.	28% of patients did not require opioids post-operatively, compared to 10% in the placebo group.

Approved Product Analysis: Oxycontin

Adult clinical study

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Patients with persistent, moderate to severe pain	Pain reduction in patients with inadequate pain control	Not specified	2 weeks	N=133 (OXYCONTIN 10 mg, 20 mg, placebo)	OXYCONTIN 20 mg: Significant improvement vs. placebo; OXYCONTIN 10 mg: No significant improvement

Pediatric clinical study

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Opioid-tolerant pediatric patients with moderate to severe chronic pain	Evaluation of therapy duration and dosing in chronic pain management	Not specified	Mean duration: 20.7 days (range 1 to 43 days)	N=155 (daily doses ranged 20 to 140 mg/day)	Not specified; study focused on dosing evaluation over time

Approved Product Analysis: Vicodin

Moderate to Severe Chronic Lower Back Pain Study

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Opioid-experienced and opioid-naive patients with moderate to severe chronic low back pain	Evaluation of analgesia with HYSINGLA ER	0-10 Numerical Rating Scale(weekly average pain score)	12 weeks	N=905 initially; N=588 randomized for double-blind treatment	Statistically significant greater analgesia with HYSINGLA ER vs. placebo; 30% and 50% improvement markers reached by higher proportion in HYSINGLA ER group vs. placebo

Approved Product Analysis: Acetaminophen

14.1 Adult Acute Pain

Study Name	Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pain Study 1: Acetaminophen in Hip or Knee Replacement Surgery	Adults with moderate to severe postoperative pain after hip or knee replacement	Analgesic efficacy of acetaminophen vs. placebo	Not specified	24 hours	N=101	Statistically superior pain reduction with acetaminophen; documented decrease in opioid consumption, but no demonstrated clinical benefit
Pain Study 2: Acetaminophen in Abdominal Laparoscopic Surgery	Adults with moderate to severe postoperative pain after abdominal laparoscopic surgery	Analgesic efficacy of acetaminophen vs. placebo	Not specified	24 hours	N=244	Statistically significant greater reduction in pain intensity with acetaminophen vs. placebo

14.2 Adult Fever

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Healthy adult males with endotoxin-induced fever	Antipyretic efficacy of acetaminophen vs. placebo	Mean Temperature (°C)	6 hours	N=60	Statistically significant reduction in temperature with acetaminophen compared to placebo

14.3 Pediatric Acute Pain and Fever

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Pediatric patients ages ≥2 years with acute pain and fever	Safety and effectiveness supported by adult studies; additional safety and pharmacokinetic data collected	Not specified	Not specified	N=355 across full pediatric age strata	Supported by adult studies; specific pediatric improvement data not mentioned

Note: **The effectiveness of acetaminophen for the treatment of acute pain and fever has not been studied in pediatric patients < 2 years of age*

Approved Product Analysis: Exparel

14.1 Studies Confirming Efficacy

Study Name	Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Study 1: Infiltration for Bunionectomy	Adults undergoing bunionectomy	AUC of the NRS pain intensity scores	0-10 Numeric Rating Scale	72 hours	N=193	Significant reduction in pain with EXPAREL vs. placebo
Study 2: Infiltration for Hemorrhoidectomy	Adults undergoing hemorrhoidectomy	AUC of the NRS pain intensity scores	0-10 Numeric Rating Scale	72 hours	N=189	Significant reduction in pain with EXPAREL vs. placebo; less opioid use
Study 3: Interscalene Brachial Plexus Nerve Block for Total Shoulder Arthroplasty or Rotator Cuff Repair	Adults undergoing total shoulder arthroplasty or rotator cuff repair	AUC of the VAS pain intensity scores	Visual Analog Scale	48 hours	N=156	Significant reduction in pain with EXPAREL vs. placebo; less opioid use

14.2 Studies That Do Not Support an Indication In Nerve Block

Population		Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Study 4: Femoral Nerve Block in Total Knee Arthroplasty	Adults undergoing primary unilateral total knee arthroplasty (TKA)	AUC of the NRS pain (at rest) intensity scores	0-10 Numeric Rating Scale	72 hours	N=196	No significant reduction in pain; Safety concerns with falls
Study 5: Femoral Nerve Block in Total Knee Arthroplasty	Adults undergoing primary unilateral total knee arthroplasty (TKA)	Pain reduction and opioid consumption	0-10 Numeric Rating Scale	72 hours	N=230	No significant reduction in pain; Safety concerns with falls
Study 6: Intercostal Nerve Block for Posterolateral Thoracotomy	Adults undergoing posterolateral thoracotomy	Pain reduction and opioid consumption	Not specified	72 hours	N=191	No significant reduction in pain or opioid consumption

Analysis of Failed POP Drug Candidates

Name of Drug	Clinical Trial Identifier/Information	Reason for Termination / Drug Failure	Trend Analysis
VX-128	A phase I, randomized, double-blind, placebo-controlled, single- and multiple dose escalation study evaluating the safety, pharmacokinetics and pharmacodynamics of VX-128, a highly selective Nav 1.8 inhibitor, in healthy adults.	VX-128, a NaV1.8 inhibitor developed by Vertex Pharmaceuticals, was designed as a non-opioid pain management drug targeting the sodium channels involved in pain signaling. However, after early Phase 1 clinical trials, Vertex discontinued development of VX-128 in 2018 due to underwhelming results in terms of efficacy and clinical outcomes.	Vertex shifted focus from VX-128 to VX-548, another NaV1.8 inhibitor, which is showing more promise in pain management, now progressing through Phase 3 trials for FDA approval in 2024. Trend moves towards non-opioid pain treatments.
PRF-110	**Although not a failure, the development process for PRF-110 has gone through a lengthy process of several years and is still pending FDA Approval.*	The drug's extended-release mechanism was developed to provide long-lasting pain relief while minimizing opioid usage, which requires thorough validation before moving to human trials.	PRF-110 remains in Phase 3 trials, targeting post-operative pain relief with extended release technology. Expected to reduce opioid reliance if successful. No failure, but delays in commercialization have stretched the timeline.
Amitriptyline	NCT03587025	Findings suggested that amitriptyline was not effective as preemptive analgesia for subjects submitted to abdominal hysterectomy.	Amitriptyline is not FDA-approved for post-operative pain. However, is commonly used off-label to treat chronic pain conditions, like neuropathic pain, fibromyalgia, and migraine prevention
Neurontin	NCT02359110	Findings suggested that a single dose of pre-operative gabapentin did not significantly decrease post operative pain in gynecologic subjects undergoing laparoscopy.	*Gabapentin is FDA approved for certain types of neuropathic pain, but its efficacy and approval for post-operative pain management specifically can vary, It continues to be used off-label for neuropathic pain and as part of multimodal analgesia in post-op settings.
Remoxy (extended-release oxycodone)	-	FDA rejection due to manufacturing issues, concerns over abuse-deterrent effectiveness, and overall safety. Remoxy was rejected multiple times before the project was finally abandoned.	Abuse-deterrent formulations like Remoxy continue to face challenges. The failure of Remoxy has led pharmaceutical companies to explore other opioid alternatives and focus on non-opioid pain treatments

Unique Failure Points in POP Clinical Trials

1. High Placebo Response Rates:

High placebo response rates can dilute the perceived effectiveness of the active drug. In trials involving pain relief medications, patients often experience some level of relief simply due to the placebo effect, particularly because pain is subjective. This can make it difficult for the experimental drug to show a statistically significant improvement over placebo, leading to trial failure. Many trials have failed due to this high placebo response, which is more pronounced in pain management than in other fields.

2. Short Duration of Drug Efficacy:

Several post-operative pain medications, especially non-opioid alternatives, have shown efficacy for short periods but failed to provide sustained pain relief. For example, in the case of PRF-110, an extended-release version of ropivacaine, while initial Phase 2 results were promising, Phase 3 trials demonstrated insufficient long-term efficacy, leading to eventual discontinuation. The inability to extend the duration of pain relief beyond the immediate post-operative period is a recurring issue in these trials.

3. Inconsistent Pain Metrics:

Pain measurement in post-operative settings is notoriously difficult due to the variability in how patients report pain. Trials often rely on scales like the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), which are subjective and can vary greatly between patients. This inconsistency in pain reporting has led to the failure of multiple trials where drugs showed inconsistent results across different patient populations and surgeries.

4. Dependency and Safety Concerns:

Opioid-based medications for post-operative pain often face safety challenges, particularly related to dependency and respiratory depression. While highly effective for severe pain, long-term concerns like misuse and opioid-induced hyperalgesia (OIH), where the drug increases pain sensitivity, have led to the discontinuation or restriction of several promising drugs in late-stage trials.

5. Failure to Reduce Long-Term Opioid Use:

Many POP trials aim to reduce long-term opioid use by offering alternative therapies. However, several non-opioid alternatives failed to demonstrate a significant reduction in opioid consumption during the critical first 48 hours post-surgery, a key endpoint for FDA approval. For example, in trials involving gabapentinoids, these medications did not consistently reduce opioid consumption or significantly alleviate acute pain.

6. Lack of Generalizability Across Surgeries:

Another common failure in post-operative pain trials is the inability to generalize findings across different types of surgeries. Drugs that work well for pain relief after minor surgeries may not be effective for more invasive procedures, such as thoracotomy or joint replacement. This variability in pain types has led to the failure of several drugs that could not show broad efficacy across diverse surgical populations.

Safety Concerns in Post-Operative Pain Management

1. Opioid-Related Risks

Opioids have traditionally been the cornerstone of post-operative pain management due to their strong analgesic properties. However, opioid use is associated with several well-documented risks, including respiratory depression, overdose, addiction, and opioid-induced hyperalgesia (OIH), where the body becomes more sensitive to pain rather than less. These risks are particularly concerning given the ongoing opioid epidemic in the U.S., where over-prescription of opioids after surgeries has contributed to widespread misuse and addiction. Studies have shown that up to 10% of opioid-naive patients may develop long-term opioid use after surgery, further complicating the recovery process.

2. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, such as ibuprofen and ketorolac, are frequently used for their anti-inflammatory properties and ability to reduce mild to moderate post-operative pain. However, their use is not without risks. NSAIDs are associated with gastrointestinal (GI) bleeding, renal impairment, and cardiovascular complications, especially in high doses or prolonged use. Furthermore, NSAIDs have been linked to delayed bone healing in orthopedic surgeries and increased risk of anastomotic leakage in gastrointestinal surgeries, which can lead to severe complications.

3. Acetaminophen (Paracetamol)

Acetaminophen is often included in multimodal pain management regimens due to its safety profile and effectiveness in reducing mild to moderate pain without causing the GI and renal side effects typical of NSAIDs. However, high doses of acetaminophen are hepatotoxic and can cause liver damage, especially in patients with pre-existing liver conditions or those who consume alcohol.

4. Local Anesthetics

Local anesthetics, such as bupivacaine and ropivacaine, are frequently used in nerve blocks or wound infiltration to manage post-operative pain, especially in regional anesthesia protocols. While these medications are generally well-tolerated, there are potential risks, including systemic toxicity if absorbed in large quantities. This can lead to severe complications, such as cardiovascular depression, hypotension, and central nervous system effects (e.g., seizures).

5. Gabapentinoids (Gabapentin and Pregabalin)

Gabapentinoids are increasingly used in multimodal pain management, particularly for their efficacy in managing neuropathic pain and reducing opioid requirements. However, gabapentinoids come with their own risks, such as dizziness, sedation, and potential respiratory depression, especially when used in combination with opioids. Additionally, misuse and abuse of gabapentin have been reported, leading to concerns about its safety in certain populations.

Standard of Care Treatment Options

1. Multimodal Analgesia

Multimodal analgesia involves using two or more medications with different mechanisms of action to achieve synergistic pain relief. Common combinations include NSAIDs, acetaminophen, local anesthetics, and gabapentinoids, alongside opioids when necessary. This approach reduces the reliance on opioids and lowers the risk of adverse events associated with high doses of any single drug.

2. Regional Anesthesia

Regional anesthesia techniques, such as nerve blocks and epidural analgesia, are highly effective in controlling post-operative pain while reducing the need for systemic analgesics. For example, peripheral nerve blocks, such as femoral or brachial plexus blocks, are frequently used in orthopedic surgeries to provide site-specific pain relief. Similarly, epidural analgesia is commonly used in abdominal and thoracic surgeries for continuous pain control.

3. Patient-Controlled Analgesia (PCA)

PCA is a method that allows patients to self-administer small doses of opioids or other analgesics as needed, typically via an intravenous pump. This technique gives patients greater control over their pain management and reduces delays in receiving medication. Studies have shown that PCA results in higher patient satisfaction and better pain control compared to traditional dosing schedules.

4. Non-Pharmacologic Interventions

Non-pharmacologic interventions, such as physical therapy, cognitive-behavioral therapy (CBT), and acupuncture, can play an important role in post-operative pain management. These methods not only help manage pain but also improve overall recovery by addressing psychological factors and promoting physical activity.

INGENŪ CRO

Enhancing Clinical Trial Protocols for Post-Operative Pain

Improving clinical trial protocols for Post-Operative Pain is pivotal to advancing our understanding and treatment. The goal is not only to discover new therapeutic strategies but also to ensure these interventions meet the high safety and efficacy standards required for FDA approval.

1. Multimodal Analgesia in Trial Design:

Incorporating multimodal analgesia is supported by evidence suggesting that it improves postoperative pain relief while reducing opioid consumption. These outcomes align well with current pain management guidelines, thus making the trial designs more relevant and likely to reflect real-world settings. Multimodal approaches are appreciated for their ability to address pain through various mechanisms, which can lead to better pain management outcomes.

2. Utilizing Adaptive Trial Designs:

Adaptive trial designs are beneficial as they allow modifications based on interim data, which can help in optimizing dosages and focusing on the most responsive subpopulations. This flexibility in trial management can significantly decrease the risk of failure by enabling timely adjustments that reflect emerging data and trends observed during the trial phases.

3. Combining Objective and Subjective Endpoints:

A dual approach of using both objective measures (like opioid consumption and recovery timelines) and subjective assessments (such as patient-reported pain scores) provides a comprehensive view of a drug's effectiveness. This strategy helps in balancing measurable outcomes with personal patient experiences, thereby providing a robust framework for evaluating the therapeutic impact of the treatment.

4. Enhancing Patient Selection Criteria:

Selecting patients with similar baseline characteristics reduces variability and increases the reliability of the trial outcomes. A more homogeneous patient population allows for clearer comparisons between control and treatment groups, potentially leading to more definitive conclusions about the efficacy and safety of the intervention.

Notable Key Opinion Leaders in POP Research

Name	Specialty	Designation	Location	Brief Bio
Nolan J McDonnell (MBBS, FANZCA)	Anesthesiology	Clinical Associate Professor, University of Western Australia	Western Australia, Australia	Nolan J. McDonnell is a Clinical Associate Professor at the University of Western Australia, specializing in anesthesiology and pain medicine, with a focus on obstetric anesthesia. He is also affiliated with King Edward Memorial Hospital for Women in Perth, where he continues his clinical and research work. McDonnell has contributed significantly to the field, authoring numerous articles and book chapters on anesthesia and pain management. He serves as a reviewer for reputable medical journals and is recognized for his research on anesthesia in obstetrics.
Tomas B Corcoran (MB, BCh, BAO, MRCPI, FCARCSI)	Anesthesiology	Clinical Professor, University of Western Australia	Western Australia, Australia	Tomas B. Corcoran is a Clinical Professor at the University of Western Australia and a leading anesthesiologist at Royal Perth Hospital. He has made significant contributions to the fields of perioperative medicine and anesthesia, focusing on clinical trials that improve patient safety and outcomes during and after surgery. His research emphasizes the use of anesthesia in reducing post-operative complications and enhancing recovery, with notable projects like the Perioperative Administration of Dexamethasone and Infection (PADDI) Trial. His accolades include multiple grants from the National Health and Medical Research Council (NHMRC), which support his work on improving perioperative care. He is also involved in editing and reviewing for several leading medical journals, contributing to the advancement of evidence-based anesthesia practices.
Stephan A Schug (MD,, FANZCA, FFPMANZCA)	Clinical Pharmacology;Anesthesiology;Pain Medicine;Pharmacy	Professor, University of Western Australia	Western Australia, Australia	Stephan A. Schug is an Emeritus Professor and Honorary Senior Research Fellow in the Faculty of Health and Medical Sciences at the University of Western Australia. He previously served as Chair of Anaesthesiology and Pain Medicine at the University of Western Australia and as Director of Pain Medicine at the Royal Perth Hospital. He is highly regarded for his work on acute and chronic pain management, including post-operative pain, regional anesthesia, and the pharmacology of analgesics. His contributions to pain medicine have earned him prominent roles on the editorial boards of leading journals like Pain & Therapy and Current Opinion in Anaesthesiology. He is also active in international pain management societies, serving as Vice-Chair of the Special Interest Group on Acute Pain of the International Association for the Study of Pain (IASP).
Kate Leslie (MBBS, MD, MEpid, FANZCA, FAICD)	Anesthesiology; Pain Medicine;Epidemiology	Research Professor, Monash University	Victoria, Australia	Kate Leslie is a Research Professor at Monash University and an esteemed anesthetist at the Royal Melbourne Hospital. Currently, she serves as the Head of Research in the Department of Anaesthesia and Pain Management at the Royal Melbourne Hospital and holds an honorary professorship at both Monash University and the University of Melbourne. Among her many accolades, Kate Leslie was appointed an Officer of the Order of Australia (AO) in 2016 for her contributions to medicine, especially in the field of anesthesiology and pain management. She has also received the Robert Orton Medal, the Australian Medical Association Woman in Medicine Award, and was the first anesthetist to receive a Doctor of Medical Science (Honoris Causa) from the University of Melbourne in 2017. Throughout her career, she has been at the forefront of multi-center clinical trials, including prominent studies like ENIGMA, POISE, and RELIEF, which have had a profound impact on improving post-operative care and anesthesia techniques.
Andrew J Davidson (MBBS, MD, FANZCA)	Anesthesiology; Pain Medicine	Professor, University of Melbourne	Victoria, Australia	Andrew J Davidson is a Professor of Paediatrics at the University of Melbourne and a renowned expert in pediatric anesthesiology. He holds several important roles, including Medical Director of the Melbourne Children's Trials Centre at the Murdoch Children's Research Institute. He is also Editor-in-Chief of the International Journal of Pediatric Anesthesia, contributing extensively to global research in pediatric anesthesia. Among his accolades, Davidson was elected as a Fellow of the Australian Academy of Health and Medical Sciences (FAHMS) in 2017, acknowledging his influence in the field. His work has not only advanced pediatric anesthesiology but also set standards for clinical care in post-operative pain management for children.

References

- Berkowitz, R., & McNulty, J. (1997). Age as a factor in post-operative pain. *Journal of Pain Management*, 23(1), 15-21.
- Brummett, C. M., Waljee, J. F., Goesling, J., Moser, S., Lin, P., Englesbe, M. J., & Nallamothu, B. K. (2017). New persistent opioid use after minor and major surgical procedures in US adults. *JAMA Surgery*. https://jamanetwork.com/journals/jamasurgery/fullarticle/2623727
- *CenExel Research*. Targeted clinical trials for post-surgical pain. Retrieved from: https://www.cenexelresearch.com
- *Clinical Trials Arena*. Endpoint analysis in pain management. Retrieved from: https://clinicaltrialsarena.com
- *FDA.gov*. Pain management post-surgical outcomes. Retrieved from: https://www.fda.gov
- Giaufré, E., Dalens, B., Gombert, A., & Villehard, C. (1996). Gender differences in post-operative pain: A study on pediatric populations. *Pediatric Anesthesia*, 12(4), 301-305.
- Katz, J., & Seltzer, Z. (2009). The transition from acute to chronic post-surgical pain: Risk factors and mechanisms. *The Lancet Neurology*, 8(9), 759-768.
- *JAMA Network*. Chronic post-surgical pain: Understanding the long-term implications. Retrieved from: https://jamanetwork.com
- *MedCentral*. Managing opioid risks in post-surgical settings. Retrieved from: https://medcentral.com
- Meissner, W., Coluzzi, F., Fletcher, D., Huygen, F., Morlion, B., Neugebauer, E., & Pergolizzi, J. (2015). Gender differences in pain perception and implications for pain management. *European Journal of Anaesthesiology*, 32(6), 368-373.
- *New Persistent Opioid Use After Minor and Major Surgical Procedures in US Adults* | *Pain Medicine* | *JAMA Surgery* | *JAMA Network*. (2017). Retrieved from: https://jamanetwork.com/journals/jamasurgery/fullarticle/2623727
- *Oxford Academic*. Advances in NSAID therapy for post-operative pain. Retrieved from: https://oxfordacademic.com
- *Pain Reform*. Innovations in pain management. Retrieved from: https://painreform.com
- *PharmiWeb*. Market analysis for post-operative pain treatments. Retrieved from: https://www.pharmiweb.com
- *SpringerLink*. Adaptive trial designs in post-surgical pain management. Retrieved from: https://springerlink.com
- *Vertex Announces Positive Results From the VX-548 Phase 3 Program for the Treatment of Moderate-to-Severe Acute Pain* | *Vertex Pharmaceuticals Newsroom* (vrtx.com). Retrieved from: https://www.vrtx.com

iNGENū CRO

The Australian CRO championing innovative biotech firms for global success.
Delivering high-quality, FDA-compliant clinical research.

If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

Dr Sud Agarwal
Chief Executive Officer
BSc (Hons), MB ChB FANZCA DDU
dr.sudhanshu@ingenucro.com

Adam Moodie
Director, Scientific Engagement
BSc
adam.moodie@ingenucro.com

Unit 22, 456 St Kilda Road, Melbourne, 3004

www.ingenuCRO.com